CARECONTINUUM

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Alpha$_1$-Proteinase Inhibitor Products Utilization Management Medical Policy
- Aralast NP® (alpha$_1$-proteinase inhibitor [human] intravenous infusion – Shire)
- Glassia® (alpha$_1$-proteinase inhibitor [human] intravenous infusion – Shire)
- Prolastin®-C and Prolastin®-C Liquid (alpha$_1$-proteinase inhibitor [human] intravenous infusion – Grifols Therapeutics)
- Zemaira® (alpha$_1$-proteinase inhibitor [human] intravenous infusion – CSL Behring)

REVIEW DATE: 12/06/2023

OVERVIEW

Alpha$_1$-proteinase inhibitor (also known as alpha$_1$-antitrypsin [AAT]), is indicated for **alpha$_1$-proteinase deficiency** as a chronic augmentation and maintenance therapy in adults with clinical evidence of emphysema.[1-5] The following products are available commercially in the US: Prolastin-C (also available as Prolastin-C Liquid), Aralast NP, Zemaira, and Glassia. The products vary in their availability and in some of their purification and viral inactivation processes.

Disease Overview

AAT deficiency is a rare, chronic, hereditary, autosomal co-dominant disorder marked by low concentrations of AAT which leads to progressive, severe emphysema that often does not manifest until the third to fourth decades of life.[1] Diagnosis of AAT deficiency begins with quantitative measurement of AAT levels in the plasma.[6] Treatment is aimed at raising serum levels of AAT above a theoretical protective threshold of 11 mcM (mcmol/L), which is equivalent to the tenth percentile of the AAT range of PI*SZ individuals; epidemiological data suggest lower probability of chronic obstructive pulmonary disease (COPD) above this level.[7] A variety of techniques have been used to measure serum AAT concentration.[8] The most commonly used technique today is nephelometry. Using this technique, a serum AAT concentration < 57 mg/dL is usually associated with AAT deficiency with lung disease. Of note, older laboratory techniques (e.g., radial immunodiffusion) measured non-purified levels of AAT, which tend to overestimate the concentration by 35% to 40%.[9] An AAT level of 80 mg/dL measured by radial immunodiffusion corresponds to a plasma AAT level of 11 mcM.

Guidelines

A European Respiratory Society (ERS) statement addresses diagnosis and treatment of pulmonary disease in AAT deficiency (2017).[6] It is noted that augmentation therapy has been shown to reduce progression of emphysema in severe AAT deficiency. There is no evidence to support efficacy of AAT augmentation therapy for current smokers of any phenotype. These guidelines support earlier American Thoracic Society (ATS)/ERS guidelines (2003) which state that intravenous augmentation therapy is recommended for individuals with established airflow obstruction from AAT deficiency.[10]

The Canadian Thoracic Society updated its guidelines (2012) regarding AAT deficiency testing and augmentation therapy.[11] The guidelines state that evidence supports the consideration of AAT augmentation therapy in non-smoking or ex-smoking patients with COPD due to emphysema and a documented AAT deficiency (level ≤ 11 mcM). Patients should also be receiving other pharmacological and non-pharmacologic therapies, including comprehensive case management and pulmonary rehabilitation.

The Medical and Scientific Advisory Committee of the Alpha-1 Foundation guidelines (2016) provide similar recommendations.[12] Intravenous AAT augmentation is strongly recommended in non-smoking or ex-smoking patients with forced expiratory volume (FEV_1) 30 to 65% of predicted due to well-documented benefit in this group. Weaker recommendations also support treatment of patients with FEV_1 below 30% of predicted or above 65% of predicted. Usual management of COPD should also be provided, with strong emphasis on facilitating tobacco cessation. Of note, AAT replacement therapy is not recommended for patients who continue to smoke.

Other Uses with Supportive Evidence

In the ATS/ERS 2003 guidelines, it is stated that AAT replacement therapy is a reasonable option for AAT deficiency-associated panniculitis.[10] Although no controlled trials provide a clear treatment recommendation, augmentation therapy with purified human alpha$_1$-proteinase inhibitor or fresh frozen plasma to restore plasma and local tissue levels of AAT appears to be rational, safe, and effective. In a review of treatment options for panniculitis in AAT deficiency, augmentation therapy with alpha$_1$-proteinase inhibitor was noted to be the most successful medical treatment.[13]

Dosing Considerations

For AAT deficiency-associated panniculitis, limited dosing is available. A dose of 60 mg/kg once weekly is recommended in product labeling for all alpha$_1$-proteinase inhibitors for the labeled indication.[1-5]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of alpha$_1$-proteinase inhibitor. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of alpha$_1$-proteinase inhibitor (e.g., Aralast NP, Glassia, Prolastin-C, Prolastin-C Liquid, Zemaira) is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **Alpha$_1$-Antitrypsin Deficiency with Emphysema (or Chronic Obstructive Pulmonary Disease).** Approve for 1 year if the patient meets the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has a baseline (pretreatment) alpha$_1$-antitrypsin serum concentration of 11 mcM (11 mcmol/L) [< 80 mg/dL if measured by radial immunodiffusion or < 57 mg/dL if measured by nephelometry]; AND
   - **C)** According to the prescriber, the patient is a current non-smoker.

   Dosing. Approve a dose of 60 mg/kg intravenously once weekly.

Other Uses with Supportive Evidence

2. **Alpha$_1$-Antitrypsin Deficiency-Associated Panniculitis.** Approve for 1 year if the patient is ≥ 18 years of age.

   Dosing. Approve a dose of 60 mg/kg intravenously once weekly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of alpha$_1$-proteinase inhibitor is not recommended in the following situations:

1. **Alpha$_1$-Antitrypsin Deficiency without Lung Disease, even if Deficiency-Induced Hepatic Disease is Present**. The ATS/ERS standards for the diagnosis and management of individuals with AAT deficiency (2003) state that the pathophysiology of liver disease in AAT deficiency is different from that of lung disease, and the use of alpha$_1$-proteinase inhibitor is not discussed for these patients.[10] There is an absence of information that suggests alpha$_1$-proteinase inhibitor is useful in patients with AAT deficiency-related liver disease.

2. **Bronchiectasis (without alpha$_1$-antitrypsin deficiency).** Studies have not demonstrated alpha$_1$ proteinase inhibitor to be effective for this condition. The ATS/ERS standards for the diagnosis and management of individuals with AAT deficiency (2003) state that despite the well-recognized association between AAT deficiency and the early development of emphysema, only a limited number of studies have assessed the association between AAT deficiency and bronchiectasis.[10] Studies suggest that bronchiectasis is more a result of emphysematous changes in the parenchyma than of AAT deficiency.

3. **Chronic Obstructive Pulmonary Disease (COPD) without Alpha$_1$-Antitrypsin Deficiency.** The Global Initiative for Chronic Obstructive Lung Disease guidelines for the diagnosis, management, and prevention of COPD (updated 2023) state that never or ex-smokers with an FEV_1 of 35 to 60% of predicted may be most suitable for AAT deficiency augmentation therapy; newer evidence suggests that individuals with higher FEV_1 values may also be candidates.[14] However, this therapy is not recommended for COPD that is unrelated to AAT deficiency.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Aralast NP® intravenous infusion [prescribing information]. Lexington, MA: Shire; December 2022.
2. Zemaira® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; September 2022.
3. Prolastin®-C intravenous infusion [prescribing information]. Research Triangle Park, NC: Grifols Therapeutics; January 2021.
4. Prolastin®-C Liquid intravenous infusion [prescribing information]. Research Triangle Park, NC: Grifols Therapeutics; May 2020.
5. Glassia® intravenous infusion [prescribing information]. Lexington, MA: Shire; September 2022.
6. Miravitlles M, Dirksen A, Ferrarotti I, et al. European Respiratory Society statement: diagnosis and treatment of pulmonary disease in alpha1-antitrypsin deficiency. *Eur Respir J.* 2017;50(5).
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9. Miravitlles M, Herr C, Ferrarotti I, et al. Laboratory testing of individuals with severe alpha1-antitrypsin deficiency in three European centres. *Eur Respir J.* 2010 May;35(5):960-968.
10. American Thoracic Society and the European Respiratory Society. Standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med.* 2003;168:818-900.
11. Marciniuk DD, Hernandez P, Balter M, et al. Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: A Canadian Thoracic Society clinical practice guideline. *Can Respir J.* 2012;19:109-116.
12. Sandhaus RA, Turino G, Brantly ML, et al. The diagnosis and management of alpha-1 antitrypsin deficiency in the adult. *Chronic Obstr Pulm Dis.* 2016;3(3):668-682.
13. Sabbagh DK, Barmayehvar B, Nguyen T, Edgar RG, Turner AM. Managing panniculitis in alpha-1 antitrypsin deficiency: systematic review of evidence behind treatment. *World J Dermatol.* 2018;7(1):1-8.
14. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2023. Available at: https://goldcopd.org/2024-gold-report/. Accessed on November 28, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Alpha$_1$-Antitrypsin Deficiency with Emphysema (or Chronic Obstructive Pulmonary Disease):** The requirement regarding baseline (pretreatment) serum alpha$_1$-antitrypsin concentration was clarified to note that a value of < 11 mcM corresponds with a value of < 80 mg/dL if measured by radial immunodiffusion or < 57 mg/dL if measured by nephelometry. Previously, the different cutoff values for varying assay methods were not specified.	11/16/2022
Annual Revision	No criteria changes.	12/06/2023

CARECONTINUUM

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Amyloidosis – Amvuttra Management Medical Policy
- Amvuttra™ (vutrisiran subcutaneous injection – Alnyam)

REVIEW DATE: 06/28/2023; selected revision 01/03/2024

OVERVIEW

Amvuttra, a transthyretin (TTR)-directed small interfering RNA, is indicated for the treatment of **polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR)** in adults.[1] Amvuttra has not been studied in patients with prior liver transplantation.[6] hATTR is a progressive disease caused by mutations in the TTR gene leading to multisystem organ dysfunction.[2] Common neurologic manifestations include sensiomotor polyneuropathy, autonomic neuropathy, small-fiber polyneuropathy, and carpal tunnel syndrome.

Guidelines

There are no guidelines that include recommendations for Amvuttra. A scientific statement from the American Heart Association (AHA) on the treatment of the cardiomyopathy of hATTR amyloidosis (July 2020) includes recommendations related to polyneuropathy.[3] Canadian guidelines for the treatment of patients with polyneuropathy (February 2021) and recommendations from the European Society of Cardiology (ESC) [2021] include treatment recommendations for hATTR polyneuropathy as well.[2,4] In general, Onpattro® (patisiran intravenous infusion) and Tegsedi® (inotersen subcutaneous injection) are recommended for patients with hATTR polyneuropathy.

For patients with hATTR amyloidosis with polyneuropathy, the AHA recommends treatment with Onpattro or Tegsedi.[3] For patients with hATTR with polyneuropathy and cardiomyopathy, Onpattro, Tegsedi, or Vyndamax® (tafamidis meglumine capsules)/Vyndaqel™ (tafamidis capsules) are recommended. Use of combination therapy is discussed; however, it is noted that there is little data to support combination therapy.

The Canadian guidelines recommend Onpattro and Tegsedi as first-line treatment to stop the progression of neuropathy and improve polyneuropathy in early and late stage hATTR amyloidosis with polyneuropathy.[2]

The ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure note that TTR stabilization and reduction are the recommended basis of treatment for cardiomyopathy of hATTR.[4] Onpattro and Tegsedi may be considered for patients with hATTR polyneuropathy and cardiomyopathy.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Amvuttra. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Amvuttra as well as the monitoring required for adverse events and long-term efficacy, approval requires Amvuttra to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Amvuttra is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis (hATTR).** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥18 years of age; AND
   - **B)** Patient has a transthyretin mutation as confirmed by genetic testing; AND
   - **C)** Patient has symptomatic polyneuropathy; AND
     Note: Examples of symptomatic polyneuropathy include reduced motor strength/coordination, and impaired sensation (e.g., pain, temperature, vibration, touch). Examples of assessments for symptomatic disease include history and clinical exam, electromyography, or nerve conduction velocity testing.
   - **D)** Patient does not have a history of liver transplantation; AND
   - **E)** The medication is prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis.

   Dosing. Approve the following dosing regimen (A and B):
   - **A)** The dose is 25 mg by subcutaneous injection; AND
   - **B)** The dose is administered not more frequently than once every 3 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Amvuttra is not recommended in the following situations:

1. **Concomitant Use With Onpattro (patisiran intravenous infusion), Tegsedi (inotersen subcutaneous injection), Wainua (eplontersen subcutaneous injection), or a Tafamidis Product.**
   Note: Examples of tafamidis products are Vyndaqel and Vyndamax.
   There are insufficient data supporting the safety and efficacy of concurrent use of these agents for hereditary transthyretin-mediated amyloidosis with polyneuropathy. The Vyndaqel/Vyndamax pivotal trial, which took place prior to when Onpattro and Tegsedi were under investigation for amyloidosis, did not include patients who were taking investigational drugs. The pivotal trials for Amvuttra, Onpattro, Tegsedi, and Wainua did not allow concurrent use of tetramer stabilizers (e.g., tafamidis, diflunisal). The pivotal trials for Amvuttra and Wainua did not allow concurrent use of Onpattro or Tegsedi (Amvuttra was not approved when Wainua was under investigation). A Phase II open-label extension study (n = 27) included 13 patients who were treated concomitantly with Onpattro and tafamidis.[5] Following 24 months of treatment, there was no significant difference in the median serum transthyretin percent change from baseline with concomitant Onpattro and tafamidis (-80%) vs. Onpattro monotherapy (-88%). A scientific statement from the AHA notes that there is little data to support combination therapy for these products.[3]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Amvuttra™ subcutaneous injection [prescribing information]. Cambridge, MA: Alnylams; February 2023.
2. Alcantara M, Mezi MM, Baker SK, et al. Canadian guidelines for hereditary transthyretin amyloidosis polyneuropathy management. *Can J Nero Sci.* 2022;49:7-18.
3. Kittleson MM, Maurer MS, Ambardekar AV, et al; on behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology. AHA scientific statement: cardiac amyloidosis: evolving diagnosis and management. *Circulation.* 2020;142:e7-e22.
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6. Adams D, Tournev IL, Talor MS, et al. Efficacy and safety of vutrisitan for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid*. 2023; 30(1):1-9.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	06/29/2022
Annual Revision	No criteria changes.	06/28/2023
Selected Revision	Conditions Not Recommended for Approval **Concomitant Use With Onpattro (patisiran intravenous injection), Tegsedi (inotersen subcutaneous injection), Wainua (eplontersen subcutaneous injection), or a Tafamidis Product.** Wainua was added to this condition not recommended for approval.	01/03/2024

CARECONTINUUM

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Amyloidosis – Onpattro Utilization Management Medical Policy
- Onpattro® (patisiran intravenous infusion – Alnylam)

REVIEW DATE: 11/29/2023; selected revision 01/03/2024

OVERVIEW

Onpattro, a lipid nanoparticle formulated RNA interference therapeutic, is indicated for treatment of adults with **polyneuropathy of hereditary amyloid transthyretin amyloidosis (hATTR)**.[1] hATTR is a progressive disease caused by mutations in the transthyretin (TTR) gene leading to multisystem organ dysfunction.[2] Common neurologic manifestations include sensiomotor polyneuropathy, autonomic neuropathy, small-fiber polyneuropathy, and carpal tunnel syndrome.

Clinical Efficacy

The pivotal trial for Onpattro did not include patients with liver transplantation, which has historically been a treatment modality for hATTR.[1,6] A Phase IIIb, open-label trial evaluated the efficacy of Onpattro in adults with hATTR polyneuropathy progression post liver transplant (n = 23).[6] Patients received Onpattro at the FDA-approved dose for 12 months. The average of Month 6 and Month 12 serum TTR reduction was 91%. In addition, improvements in neuropathy, quality of life, autonomic symptoms from baseline to Month 12, and stabilized disability and nutritional status were noted. The prescribing information for Onpattro notes that age, race (non-Caucasian vs. Caucasian), sex, and prior liver transplantation had no impact on the steady state pharmacokinetics of Onpattro or TTR reduction.[1]

APOLLO-B was a Phase III, double-blind, trial that randomized patients with hATTR cardiac amyloidosis to receive Onpattro or placebo for 12 months (n = 360).[7] The primary endpoint was a change from baseline in the distance walked on 6-minute walk test. The first secondary endpoint was the change from baseline to Month 12 in the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score. A composite of death from any cause, cardiovascular events, and change from baseline in the 6-minute walk test distance over 12 months, was a secondary endpoint. A third secondary endpoint assessed the composite of death from any cause, hospitalization for any cause, and urgent heart failure visits. At Month 12, the magnitude of decline in 6-minute walk distance was significantly lower in the Onpattro group (-8.15 meters) vs. placebo (-21.35 meters) [median difference 14.69 meters; 95% confidence interval [CI]: 0.69, 28.69; P = 0.02). The KCCQ-OS score was slightly improved with Onpattro (+0.3 points), but reduced with placebo (-3.4 points), leading to a statistically significant between group difference (3.7 points; 95% CI: 0.2, 7.2; P = 0.04). The secondary composite endpoints were not significant between groups. Based on these findings, the FDA cited insufficient evidence of clinical meaningfulness for the treatment of cardiomyopathy of hATTR and issued a complete response letter to the manufacturer of Onpattro for the treatment of cardiomyopathy of hATTR.[8]

Guidelines

A scientific statement from the American Heart Association (AHA) on the treatment of cardiomyopathy of hATTR amyloidosis (July 2020) includes recommendations related to polyneuropathy.[3] Canadian guidelines for the treatment of patients with polyneuropathy (February 2021) and recommendations from the European Society of Cardiology (ESC) [2021] include treatment recommendations for hATTR polyneuropathy as well.[2,4] The American College of Cardiology (ACC) expert consensus decision pathway on comprehensive multidisciplinary care for patients with cardiac amyloidosis (2023) mention Onpattro for polyneuropathy of hATTR; but, it is noted that the product is not indicated for cardiomyopathy of hATTR

amyloidosis (APOLLO-B trial results are acknowledged).[9] In general, Onpattro and Tegsedi® (inotersen subcutaneous injection) are recommended for patients with hATTR polyneuropathy.

For patients with hATTR amyloidosis with polyneuropathy, the AHA recommends treatment with Onpattro or Tegsedi.[3] For patients with hATTR with polyneuropathy and cardiomyopathy, Onpattro, Tegsedi, or Vyndamax™ (tafamidis capsules)/Vyndaqel® (tafamidis meglumine capsules) are recommended. Use of combination therapy is discussed; however, it is noted that there is little data to support combination therapy.

The Canadian guidelines recommend Onpattro and Tegsedi as first-line treatment to stop the progression of neuropathy and improve polyneuropathy in early and late stage hATTR amyloidosis with polyneuropathy.[2]

The ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure note that TTR stabilization and reduction are the recommended basis of treatment for cardiomyopathy of ATTR.[4] Onpattro and Tegsedi may be considered for patients with hATTR polyneuropathy and cardiomyopathy.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Onpattro. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Onpattro as well as the monitoring required for adverse events and long-term efficacy, approval requires Onpattro to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Onpattro is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis (hATTR).** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Patient is ≥18 years of age; AND
   - **B)** Patient has a transthyretin mutation as confirmed by genetic testing; AND
   - **C)** Patient has symptomatic polyneuropathy; AND
     Note: Examples of symptomatic polyneuropathy include reduced motor strength/coordination, and impaired sensation (e.g., pain, temperature, vibration, touch). Examples of assessments for symptomatic disease include history and clinical exam, electromyography, or nerve conduction velocity testing.
   - **D)** The medication is prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis.

Dosing. Approve the following dosing (A and B):
A) The dose is up to 0.3 mg/kg given intravenously up to a maximum dose of 30 mg; AND
B) The dose is administered not more frequently than once every 3 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Onpattro is not recommended in the following situations:

1. **Concomitant Use With Amvuttra (vutrisiran subcutaneous injection), Tegsedi (inotersen subcutaneous injection), Wainua (eplontersen subcutaneous injection), or a Tafamidis Product.**
   Note: Examples of tafamidis products are Vyndaqel and Vyndamax.
   There are insufficient data supporting the safety and efficacy of concurrent use of these agents for hATTR with polyneuropathy. The Vyndaqel/Vyndamax pivotal trial, which took place prior to when Onpattro and Tegsedi were under investigation for amyloidosis, did not include patients who were taking investigational drugs. The pivotal trials for Amvuttra, Onpattro, Tegsedi, and Wainua did not allow concurrent use of tetramer stabilizers (e.g., tafamidis, diflunisal). The pivotal trials for Amvuttra and Wainua did not allow concurrent use of Onpattro or Tegsedi (Amvuttra was not approved when Wainua was under investigation). A Phase II open-label extension study (n = 27) included 13 patients who were treated concomitantly with Onpattro and tafamidis.[5] Following 24 months of treatment, there was no significant difference in the median serum TTR percent change from baseline with concomitant Onpattro and tafamidis (-80%) vs. Onpattro monotherapy (-88%). A scientific statement from the American Heart Association notes that there is little data to support combination therapy for these products.[3]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Onpattro® [prescribing information]. Cambridge, MA: Alnylam; January 2023.
2. Alcantara M, Mezi MM, Baker SK, et al. Canadian guidelines for hereditary transthyretin amyloidosis polyneuropathy management. *Can J Nero Sci.* 2022;49:7-18.
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4. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42:3599-3726.
5. Lin H, Merkel M, Hale C, Marantz JL. Experience of patisiran with transthyretin stabilizers in patients with hereditary transthyretin-mediated amyloidosis. *Neurodegener Dis Manag*. 2020;10(5):289-300.
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7. Maurer MS, Kale P, Fontanta M, et al; for the APOLLO-B Trial Investigators. Patisiran treatment in patients with transthyretin cardiac amyloidosis. *N Engl J Med.* 2023;389(17); 1553-1565.
8. Alnylam announces receipt of complete response letter from U.S. FDA for supplemental new drug application for patisiran for the treatment of the cardiomyopathy of ATTR amyloidosis [press release]. Cambridge, MA: Alnylam; October 6, 2023. Available at: https://investors.alnylam.com/press-release?id=27741. Accessed on: November 16, 2023.
9. Kittleson M, Ruberg FL, Ambardekar AV, et al. A report of the American College of Cardiology Solution Set Oversight Committee. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis. *JACC*. 2023;81(11):1076-1126.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis (hATTR):** The criterion requiring the patient did not have a history of liver transplantation was removed.	11/30/2022
Annual Revision	No criteria changes.	11/29/2023
Selected Revision	Conditions Not Recommended for Approval **Concomitant Use With Amvuttra (vutrisiran subcutaneous injection), Tegsedi (inotersen subcutaneous injection), Wainua (eplontersen subcutaneous injection) or a Tafamidis Product.** Wainua was added to this condition not recommended for approval.	01/03/2024

CARECONTINUUM

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Amyloidosis – Tegsedi Utilization Management Medical Policy
- Tegsedi® (inotersen subcutaneous injection – Ionis/Akcea Therapeutics)

REVIEW DATE: 11/29/2023; selected revision 01/03/2024

OVERVIEW

Tegsedi, an antisense oligonucleotide, is indicated for treatment of adults with **polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR)**.[1] Tegsedi has not been studied in patients with a history of liver transplantation. hATTR is a progressive disease caused by mutations in the transthyretin (TTR) gene leading to multisystem organ dysfunction.[2] Common neurologic manifestations include sensiomotor polyneuropathy, autonomic neuropathy, small-fiber polyneuropathy, and carpal tunnel syndrome.

Guidelines

A scientific statement from the American Heart Association (AHA) on the treatment of cardiomyopathy of hATTR treatment of patients with polyneuropathy (February 2021) and recommendations from the European Society of Cardiology (ESC) [2021] include treatment recommendations for hATTR polyneuropathy as well.[2,4] The American College of Cardiology (ACC) expert consensus decision pathway on comprehensive multidisciplinary care for patients with cardiac amyloidosis (2023) mention Tegsedi for polyneuropathy of hATTR.[5] In general, Onpattro® (patisiran intravenous infusion) and Tegsedi are recommended for patients with hATTR polyneuropathy.

For patients with hATTR with polyneuropathy, the AHA recommends treatment with Onpattro or Tegsedi.[3] For patients with hATTR with polyneuropathy and cardiomyopathy, Onpattro, Tegsedi, or Vyndamax/Vyndaqel are recommended. Use of combination therapy is discussed; however, it is noted that there is little data to support combination therapy.

The Canadian guidelines recommend Onpattro and Tegsedi as first-line treatment to stop the progression of neuropathy and improve polyneuropathy in early and late stage hATTR with polyneuropathy.[2]

The ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure note that TTR stabilization and reduction are the recommended basis of treatment for cardiomyopathy of hATTR.[4] Onpattro and Tegsedi may be considered for patients with hATTR polyneuropathy and cardiomyopathy.

Safety

Tegsedi has a Boxed Warning regarding sudden and unpredictable thrombocytopenia which may be life-threatening.[1] It is contraindicated in patients with a platelet count less than 100 x 10^9/L. Based on monitoring, Tegsedi may need to be interrupted or discontinued. Following discontinuation, continue to monitor platelet counts for 8 weeks (or longer if platelet count is less than 100 x 10^9/L). Tegsedi also has a Boxed Warning regarding glomerulonephritis, which may require immunosuppressive treatment and may lead to dialysis-dependent renal failure. Due to the risks and frequent monitoring for both serious bleeding caused by severe thrombocytopenia and because of glomerulonephritis, Tegsedi is only available through a restricted distribution program under the Tegsedi REMS (Risk Evaluation and Mitigation Strategy).

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Tegsedi. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tegsedi as well as the monitoring required for adverse events and long-term efficacy, approval requires Tegsedi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tegsedi is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Polyneuropathy of Hereditary Transthyretin–Mediated Amyloidosis (hATTR).** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has a transthyretin mutation as confirmed by genetic testing; AND
   - **C)** Patient has symptomatic polyneuropathy; AND
     Note: Examples of polyneuropathy include reduced motor strength/coordination, and impaired sensation (e.g., pain, temperature, vibration, touch). Examples of assessments for symptomatic disease include history and clinical exam, electromyography, or nerve conduction velocity testing.
   - **D)** Patient does not have a history of liver transplantation; AND
   - **E)** The medication is prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis.

   Dosing. Approve 284 mg subcutaneously once weekly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tegsedi is not recommended in the following situations:

1. **Concomitant Use With Amvuttra (vutrisiran subcutaneous injection), Onpattro (patisiran lipid complex intravenous infusion), Wainua (eplontersen subcutaneous injection), or a Tafamidis Product.**
   Note: Examples of tafamidis products are Vyndaqel and Vyndamax.
   There are insufficient data supporting the safety and efficacy of concurrent use of these agents for hATTR with polyneuropathy. The Vyndaqel/Vyndamax pivotal trial, which took place prior to when Onpattro and Tegsedi were under investigation for amyloidosis, did not include patients who were taking investigational drugs. The pivotal trials for Amvuttra, Onpattro, Tegsedi, and Wainua did not allow concurrent use of tetramer stabilizers (e.g., tafamidis, diflunisal). The pivotal trials for Amvuttra and Wainua did not allow concurrent use of Onpattro or Tegsedi (Amvuttra was not approved when Wainua was under investigation). A scientific statement from the American Heart Association notes that there is little data to support combination therapy for these products.[3]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Tegsedi® injection [prescribing information]. Waltham, MA: Sobi/Akcea; June 2022.
2. Alcantara M, Mezi MM, Baker SK, et al. Canadian guidelines for hereditary transthyretin amyloidosis polyneuropathy management. *Can J Nero Sci.* 2022;49:7-18.
3. Kittleson MM, Maurer MS, Ambardekar AV, et al; on behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology. AHA scientific statement: cardiac amyloidosis: evolving diagnosis and management. *Circulation.* 2020;142:e7-e22.
4. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42:3599-3726.
5. Kittleson M, Ruberg FL, Ambardekar AV, et al. A report of the American College of Cardiology Solution Set Oversight Committee. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis. *JACC.* 2023;81(11):1076-1126.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/16/2022
Annual Revision	No criteria changes.	11/29/2023
Selected revision	Conditions Not Recommended for Approval **Concomitant Use With Amvuttra (vutrisiran subcutaneous injection), Onpattro (patisiran lipid complex intravenous infusion), Wainua (eplontersen subcutaneous injection), or a Tafamidis Product.** Wainua was added to this condition not recommended for approval.	01/03/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Amyloidosis – Wainua Utilization Management Medical Policy
- Wainua™ (eplontersen subcutaneous injection – AstraZeneca)

REVIEW DATE: 01/03/2024

OVERVIEW

Wainua, a transthyretin (TTR)-directed antisense oligonucleotide, is indicated for the treatment of the **polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR)** in adults.[1] Wainua has not been studied in patients with prior liver transplantation. hATTR is a progressive disease caused by mutations in the TTR gene leading to multisystem organ dysfunction.[2] Common neurologic manifestations include sensiomotor polyneuropathy, autonomic neuropathy, small-fiber polyneuropathy, and carpal tunnel syndrome.

Guidelines

There are no guidelines that include recommendations for Wainua. A scientific statement from the American Heart Association (AHA) on the treatment of the cardiomyopathy of hATTR amyloidosis (July 2020) includes recommendations related to polyneuropathy.[3] Canadian guidelines for the treatment of patients with polyneuropathy (February 2021) and recommendations from the European Society of Cardiology (ESC) [2021] include treatment recommendations for hATTR polyneuropathy as well.[2,4] In general, Onpattro® (patisiran intravenous infusion) and Tegsedi® (inotersen subcutaneous injection) are recommended for patients with hATTR polyneuropathy.

For patients with hATTR amyloidosis with polyneuropathy, the AHA recommends treatment with Onpattro or Tegsedi.[3] For patients with hATTR with polyneuropathy and cardiomyopathy, Onpattro, Tegsedi, or Vyndamax® (tafamidis meglumine capsules)/Vyndaqel™ (tafamidis capsules) are recommended. Use of combination therapy is discussed; however, it is noted that there is little data to support combination therapy.

The Canadian guidelines recommend Onpattro and Tegsedi as first-line treatment to stop the progression of neuropathy and improve polyneuropathy in early and late stage hATTR amyloidosis with polyneuropathy.[2]

The ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure note that TTR stabilization and reduction are the recommended basis of treatment for cardiomyopathy of hATTR.[4] Onpattro and Tegsedi may be considered for patients with hATTR polyneuropathy and cardiomyopathy.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Wainua. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Wainua as well as the monitoring required for adverse events and long-term efficacy, approval requires Wainua to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Wainua is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. **Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis (hATTR).** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥18 years of age; AND
   - **B)** Patient has a transthyretin mutation as confirmed by genetic testing; AND
   - **C)** Patient has symptomatic polyneuropathy; AND
     Note: Examples of symptomatic polyneuropathy include reduced motor strength/coordination, and impaired sensation (e.g., pain, temperature, vibration, touch). Examples of assessments for symptomatic disease include history and clinical exam, electromyography, or nerve conduction velocity testing.
   - **D)** Patient does not have a history of liver transplantation; AND
   - **E)** The medication is prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis.

   Dosing. Approve 45 mg subcutaneously once monthly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Wainua is not recommended in the following situations:

1. **Concomitant Use With Amvuttra (vutrisiran subcutaneous injection), Onpattro (patisiran intravenous infusion), Tegsedi (inotersen subcutaneous injection), or a Tafamidis Product.**
   Note: Examples of tafamidis products are Vyndaqel and Vyndamax.
   There are insufficient data supporting the safety and efficacy of concurrent use of these agents for hereditary transthyretin-mediated amyloidosis with polyneuropathy. The Vyndaqel/Vyndamax pivotal trial, which took place prior to when Onpattro and Tegsedi were under investigation for amyloidosis, did not include patients who were taking investigational drugs. The pivotal trials for Amvuttra, Onpattro, Tegsedi, and Wainua did not allow concurrent use of tetramer stabilizers (e.g., tafamidis, diflunisal). The pivotal trials for Amvuttra and Wainua did not allow concurrent use of Onpattro or Tegsedi (Amvuttra was not approved when Eplontersen was under investigation). A Phase II open-label extension study (n = 27) included 13 patients who were treated concomitantly with Onpattro and tafamidis.[5] Following 24 months of treatment, there was no significant difference in the median serum transthyretin percent change from baseline with concomitant Onpattro and tafamidis (-80%) vs. Onpattro monotherapy (-88%). A scientific statement from the AHA notes that there is little data to support combination therapy for these products.[3]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Wainua™ subcutaneous injection [prescribing information]. Wilmington, DE: AstraZeneca; December 2023.
2. Alcantara M, Mezi MM, Baker SK, et al. Canadian guidelines for hereditary transthyretin amyloidosis polyneuropathy management. *Can J Nero Sci.* 2022;49:7-18.
3. Kittleson MM, Maurer MS, Ambardekar AV, et al; on behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology. AHA scientific statement: cardiac amyloidosis: evolving diagnosis and management. *Circulation.* 2020;142:e7-e22.
4. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42:3599-3726.
5. Lin H, Merkel M, Hale C, Marantz JL. Experience of patisiran with transthyretin stabilizers in patients with hereditary transthyretin-mediated amyloidosis. *Neurodegener Dis Manag*. 2020;10(5):289-300.
6. Coelho T, Ando Y, Benson MD, et al. Design and rationale of the global Phase 3 NEURO-TTransform Study of antisense oligonucleotide AKCEA-TTR-L_{rx} (ION-682884-CS3) in hereditary transthyretin-mediated amyloid polyneuropathy. *Neurol Ther.* 2021;10:375-389.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/03/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Antibiotics – Synercid Utilization Management Medical Policy
- Synercid® (quinupristin and dalfopristin intravenous infusion – Pfizer)

REVIEW DATE: 07/12/2023

OVERVIEW

Synercid is indicated in adults for the treatment of **complicated skin and skin structure infections** caused by *Staphylococcus aureus* (methicillin-susceptible) or *Streptococcus pyogenes*.[1] To reduce the development of drug-resistant bacteria and maintain effectiveness of Synercid, it should only be used to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

Guidelines

According to the Infectious Diseases Society of America (IDSA) guidelines for the diagnosis and management of skin and soft tissue infections (SSTIs) [2014], oral antibiotics such as penicillin VK, cephalosporin, dicloxacillin, and clindamycin can be used for mild nonpurulent SSTI (i.e., necrotizing infection, cellulitis, erysipelas).[2] For moderate nonpurulent SSTI, intravenous (IV) antibiotics such as penicillin, ceftriaxone, cefazolin, and clindamycin are recommended. For moderate purulent SSTIs, empiric treatment can be started with trimethoprim/sulfamethoxazole (TMP/SMX) or doxycycline. For methicillin-resistant *Staphylococcus aureus* (MRSA) infections, TMP/SMX is the recommended therapy. Cephalexin or dicloxacillin are usually effective for methicillin-susceptible *Staphylococcus aureus* (MSSA) infections. For severe purulent SSTI, empiric therapy with vancomycin (IV), daptomycin, linezolid, Vibativ® (telavancin intravenous infusion), or Teflaro® (ceftaroline intravenous infusion) are recommended. All of these agents are active against MRSA strains. For severe purulent SSTI caused by MSSA, therapy can be switched to nafcillin, cefazolin, or clindamycin. Synercid is recommended as an alternative in patients with severe penicillin hypersensitivity for the treatment of necrotizing infections of the skin, fascia, and muscle.

Dosing Information

The recommended dosage (per prescribing information) for the treatment of complicated SSTI is 7.5 mg/kg every 12 hours.[1] In pooled data from two prospective, emergency-use studies conducted simultaneously, the safety and efficacy of Synercid was assessed in the treatment of patients (n = 396) with infections caused by vancomycin-resistant *Enterococcus faecium* infection and other gram-positive bacteria.[3] The most common types of infection were intra-abdominal, bacteremia, and urinary tract infections. Patients received Synercid 7.5 mg/kg IV once every 8 hours for a mean of 14.5 ± 10.7 days (range, 1 day to 108 days). The clinical success rate was 73.6% and the microbiologic success rate was 70.5% in the evaluable population. In another prospective, emergency-use study, the safety and efficacy of Synercid was assessed in the treatment of patients (n = 396) with infections caused by vancomycin-resistant *Enterococcus faecium* infection.[4] Bacteremia, intra-abdominal, and skin and skin-structure infections were the most common types of infection. Patients received Synercid 7.5 mg/kg IV every 8 hours for a mean of 13.7 ± 11 days. In the evaluable population, the clinical response rate was 68.8% and the microbiologic response rate was 68.0%. In an open-label trial, patients with nosocomial pneumonia caused by gram-positive bacteria were randomized to Synercid 7.5 mg/kg IV every 8 hours (n = 150) for a mean of 10.1 ± 4.0 days or vancomycin 1 gm every 12 hours (n = 148) for a mean of 9.5 ± 4.1 days.[5] In the bacteriologically evaluable group, clinical success was achieved by 56.3% of the patients receiving Synercid and in 58.3% of the patients receiving vancomycin (difference -2.0%; 95% confidence interval [CI]: -16.8%, 12.8%).

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Synercid. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Synercid is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **Skin and Skin Structure Infections, Complicated.** Approve for 1 month if the patient meets the following (A and B):
   - **A)** Patient has an infection that is proven or strongly suspected to be caused by *Staphylococcus aureus* (methicillin-susceptible) or *Streptococcus pyogenes*; AND
   - **B)** Patient has severe penicillin hypersensitivity.

   Dosing. Approve up to 7.5 mg/kg administered intravenously no more frequently than three times daily.

Other Uses with Supportive Evidence

2. **Treatment of an Infection Caused by a Susceptible Microorganism**. Approve for 1 month if the patient meets the following (A and B):
   - **A)** The microorganism is resistant to two other antibiotics; AND
   - **B)** The microorganism is sensitive to Synercid.

   Dosing. Approve up to 7.5 mg/kg administered intravenously no more frequently than three times daily.

3. **Continuation of Synercid Therapy.** Approve for 1 month if the patient meets the following (A and B):
   - **A)** Patient was started on Synercid; AND
   - **B)** Patient is continuing a course of therapy.

   Dosing. Approve up to 7.5 mg/kg administered intravenously no more frequently than three times daily.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Synercid is not recommended in the following situation:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Synercid for injection [prescribing information]. New York, NY: Pfizer; July 2018.
2. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59:e10-e52.
3. Moellering RC, Linden PK, Reinhardt J, et al. The efficacy and safety of quinupristin/dalfopristin for the treatment of infections caused by vancomycin-resistant *Enterococcus faecium*. *J Antimicrob Chemother*. 1999;44:251-261.
4. Linden PK, Moellering RC, Wood CA, et al. Treatment of vancomycin-resistant *Enterococcus faecium* infections with quinupristin/dalfopristin. *Clin Infect Dis*. 2001;33:1816-1823.
5. Fagon JY, Patrick H, Haas DW, et al. Treatment of gram-positive nosocomial pneumonia. Prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. *Am J Respir Crit Care Med*. 2000;161:753-762.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	06/29/2022
Annual Revision	No criteria changes	07/12/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Antiemetics – Palonosetron Intravenous Utilization Management Medical Policy
- Palonosetron intravenous infusion (generic only)

REVIEW DATE: 05/01/2024

OVERVIEW

Palonosetron intravenous (IV) [brand name: Aloxi®], a serotonin-3 (5-HT_3) receptor antagonist, is indicated for the **prevention** of the following:[1]

- **Acute nausea and vomiting**, associated with initial and repeat courses of emetogenic chemotherapy, including highly emetogenic cancer chemotherapy, in patients ≥ 1 month of age.
- **Delayed nausea and vomiting**, associated with initial and repeat courses of moderately emetogenic cancer chemotherapy in adults.
- **Postoperative nausea and vomiting (PONV)**, in adults for up to 24 hours following surgery. The efficacy of palonosetron IV in PONV beyond 24 hours has not been demonstrated.

Disease Overview

Palonosetron has strong affinity for the 5-HT_3 receptor and little or no affinity for other receptors.[1] Chemotherapy-induced nausea and vomiting (CINV) is thought to be mediated by release of serotonin from the small intestine, which then activates 5-HT_3 receptors located on vagal afferent nerves in the gastrointestinal tract and chemoreceptor trigger zone of the brain. PONV is influenced by multiple patient, surgical, and anesthesia related factors leading to release of serotonin in the central nervous system and periphery. By blocking the 5-HT_3 receptor, palonosetron inhibits the serotonin-stimulated emetic response.

Guidelines

The 5-HT_3 receptor antagonists feature prominently in National Comprehensive Cancer Network (NCCN) antiemesis guidelines for CINV. In these guidelines (version 1. 2024 – December 13, 2023), palonosetron is supported as part of a combination regimen for both acute and delayed emesis CINV prevention.[2] American Society of Clinical Oncology (ASCO) antiemetic guidelines (2020) provide similar recommendations for the prevention of CINV.[3] The American Society of Pediatric Hematology/Oncology (ASPHO) guidelines for the prevention of acute and delayed CINV (2022) recommend palonosetron treatment strategies in selected pediatric patients requiring CINV prevention.[4]

Consensus guidelines for management of PONV (2020) support 5-HT_3 receptor antagonists as one strategy for prevention of PONV in selected patients and note that palonosetron has been found to be more effective than low doses of granisetron or ondansetron in several meta-analyses.[5]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of palonosetron IV. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. An approval duration of one month is sufficient in cases where approval is listed as one dose.

Automation: None.
*Indications and/or approval conditions noted with **[eviCore]** are managed by eviCore healthcare for those clients who use eviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to eviCore at www.eviCore.com.*

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of palonosetron IV is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Chemotherapy-Induced Nausea and Vomiting, Prevention.** ***[eviCore]*** Approve for 1 year.

   Dosing. Approve ONE of the following dosing regimens (A or B):
   A) Adults: Approve up to a dose of 0.25 mg administered intravenously for one dose per cycle of chemotherapy; OR
   B) Pediatrics (less than 18 years of age): Approve up to a dose of 20 mcg/kg (maximum dose 1.5 mg) administered intravenously for one dose per cycle of chemotherapy.

2. **Postoperative Nausea and Vomiting, Prevention.** Approve for one dose if the patient is ≥ 18 years of age.

   Dosing. Approve up to a dose of 0.075 mg intravenously for one dose.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of palonosetron IV is not recommended in the following situations:

1. **Radiation-Induced Nausea and Vomiting.** Ondansetron and granisetron are the recommended 5-HT_3 receptor antagonists by NCCN (version 1.2024 – December 13, 2023) and ASCO (2020).[2,3] The guidelines note insufficient evidence for use of palonosetron IV.
   Note: For patients also receiving chemotherapy in addition to radiation, refer to FDA-Approved Indication #1, Chemotherapy-Induced Nausea and Vomiting, Prevention.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Aloxi® intravenous injection or infusion [prescribing information]. Iselin, NJ: Helsinn; April 2020.
2. The NCCN Antiemesis Clinical Practice Guidelines in Oncology (version 1.2024 – December 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: www.nccn.org. Accessed on April 26, 2024.
3. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2020 Aug 20; 38(24):2782-2797.
4. Patel P, Robinson PD, Cohen M, et al. Prevention of acute and delayed chemotherapy-induced nausea and vomiting in pediatric cancer patients: A clinical practice guideline. *Pediatr Blood Cancer*. 2022;69(12):e30001.
5. Gan T, Belani K, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2020; 131:411-448.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	05/03/2023
Annual Revision	**Title**: Updated from "Antiemetics – Aloxi Intravenous" to "Antiemetics – Palonosetron Intravenous". No criteria changes.	05/01/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Bone Modifiers – Evenity Utilization Management Medical Policy
- Evenity® (romosozumab-aqqg subcutaneous injection – Amgen)

REVIEW DATE: 05/24/2023

OVERVIEW

Evenity, a sclerostin inhibitor, is indicated for the treatment of **osteoporosis** in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.[1] It is recommended to adequately supplement with calcium and vitamin D during treatment with Evenity. According to the Evenity prescribing information, the anabolic effect of Evenity wanes after 12 monthly doses of therapy. Therefore, limit the duration of use to 12 monthly doses. If osteoporosis therapy remains warranted, continued therapy with an anti-resorptive therapy (e.g., alendronate) should be considered.

Guidelines

Evenity is cited guidelines that discusses the management of postmenopausal osteoporosis.[2,3]

- **Postmenopausal Osteoporosis:** The Endocrine Society (2020) issued a guideline update regarding the pharmacological management of osteoporosis in postmenopausal women which addressed Evenity.[2] In postmenopausal women with osteoporosis at very high risk of fractures such as patients with severe osteoporosis (i.e., low T-score < -2.5 and fractures) or multiple fractures, Evenity therapy is recommended for up to 1 year for the reduction of vertebral, hip, and nonvertebral fractures. The recommended dose is 210 mg monthly by subcutaneous injection for 12 months. In postmenopausal women with osteoporosis who have completed a course of Evenity, antiresorptive osteoporosis therapy is recommended to maintain bone density gains and reduce fracture risk.
- **Treatment and Prevention of Osteoporosis:** In 2022, the Bone Health and Osteoporosis Foundation updated a guideline for the prevention and treatment of osteoporosis (2022).[3] In the 12-month FRAME trial involving women with postmenopausal osteoporosis, Evenity, compared with placebo, reduced the risk of new vertebral fracture by 73% and clinical fractures by 36%. In the ARCH trial, high-risk postmenopausal women experienced significantly fewer fractures when given Evenity compared with alendronate for 12 months (48% fewer new vertebral fractures, 19% fewer non-vertebral fractures, and 38% fewer hip fractures). However, the Boxed Warning that Evenity has regarding an increased risk for myocardial infarction, stroke, and cardiovascular death was concerning.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Evenity. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Coverage is limited to 12 monthly doses during the therapy course. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Evenity is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. **Osteoporosis Treatment of a Postmenopausal Patient.** Approve for 1 year if the patient meets ALL of the following criteria (A, B, and C):
   - **A)** The patient meets ONE of the following conditions (i, ii, or iii):
     - **i.** Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist); OR
     - **ii.** Patient has had an osteoporotic fracture or a fragility fracture; OR
     - **iii.** Patient meets both of the following (a and b):
       - **a)** Patient has low bone mass; AND
         Note: Examples of a low bone mass include a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one third) radius (wrist).
       - **b)** According to the prescriber, the patient is at high risk for fracture; AND
   - **B)** The patient meets ONE of the following (i, ii, iii, or iv):
     - **i.** Patient has tried ibandronate injection (Boniva IV) or zoledronic acid injection (Reclast); OR
     - **ii.** Patient has tried one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a or b):
       Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).
       - **a)** According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR
         Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.
       - **b)** Patient has experienced significant intolerance to an oral bisphosphonate; OR
         Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, or a femoral fracture.
     - **iii.** Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):
       - **a)** Patient cannot swallow or has difficulty swallowing; OR
       - **b)** Patient cannot remain in an upright position post oral bisphosphonate administration; OR
       - **c)** Patient has a pre-existing gastrointestinal medical condition; OR
         Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).
     - **iv.** Patient meets one of the following conditions (a, b, or c):
       - **a)** Severe renal impairment; OR
         Note: An example of severe renal impairment is a creatinine clearance < 35 mL/min.
       - **b)** Chronic kidney disease; OR
       - **c)** Patient has had an osteoporotic fracture or a fragility fracture; AND
   - **C)** Patient has received no more than 12 monthly doses during this therapy course.

Dosing. Approve 210 mg of Evenity subcutaneously once every month for no more than 12 monthly doses during a therapy course.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Evenity is not recommended in the following situations:

1. **Osteoporosis Prevention.** Evenity is not indicated for the prevention of osteoporosis.

2. **Concurrent Use of Other Medications for Osteoporosis.**
   Note: Examples of medications for osteoporosis that Evenity should not be given with include oral bisphosphonates (e.g., alendronate, risedronate, ibandronate), intravenous bisphosphonates (zoledronic acid injection [Reclast], intravenous ibandronate), Prolia (denosumab subcutaneous injection), Forteo (teriparatide subcutaneous injection, generic), Tymlos (abaloparatide subcutaneous injection), and calcitonin nasal spray (Miacalcin/Fortical). However, this does NOT exclude use of calcium and/or vitamin D supplements in combination with Evenity.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Evenity® subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; April 2020.
2. Shoback D, Rosen CJ, Black DM, et al. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society guideline update. *J Clin Endocrinol Metab*. 2020;105(3):587-594.
3. LeBoff MS, Greenspan SL, Insogna KL, et al. The clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. 2022;33:2049-2102.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Conditions Not Recommended for Approval:** To the Note which lists the medications that should not be used with Evenity, it was clarified that this does NOT exclude use of calcium and/or vitamin D supplements in combination with Evenity.	05/18/2022
Annual Revision	**Osteoporosis – Treatment for a Postmenopausal Patient:** The exception that the patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy was removed. Instead, this exception was incorporated into a Note that lists osteoporotic fracture or a fragility fracture as an example of inadequate efficacy or significant intolerance to a trial of an oral bisphosphonate or an oral bisphosphonate-containing product.	05/24/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Bone Modifiers – Ibandronate Intravenous Utilization Management Medical Policy
- ibandronate intravenous infusion – generic

REVIEW DATE: 03/13/2024

OVERVIEW
Ibandronate injection is indicated for the treatment of **osteoporosis** in postmenopausal women.[1]

POLICY STATEMENT
Prior Authorization is recommended for medical benefit coverage of ibandronate injection. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of ibandronate injection is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Osteoporosis – Treatment for a Postmenopausal Patient.** Approve for 1 year if the patient meets BOTH of the following criteria (A and B):
   - **A)** Patient meets ONE of the following (i, ii, or iii):
     - **i.** Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist); OR
     - **ii.** Patient has had an osteoporotic fracture or a fragility fracture; OR
     - **iii.** Patient meets BOTH of the following (a and b):
       - **a)** Patient has low bone mass; AND
         Note: An example of low bone mass includes a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist).
       - **b)** According to the prescriber, patient is at high risk for fracture; AND
   - **B)** Patient meets ONE of the following (i, ii, iii, or iv):
     - **i.** Patient has tried ibandronate injection (Boniva) or zoledronic acid injection (Reclast); OR
     - **ii.** Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets ONE of the following (a or b):
       Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).
       - **a)** According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR

Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.

b) Patient has experienced significant intolerance to an oral bisphosphonate; OR
Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, or a femoral fracture.

iii. Patient cannot take an oral bisphosphonate due to ONE of the following (a, b, or c):
- **a)** Patient cannot swallow or has difficulty swallowing; OR
- **b)** Patient cannot remain in an upright position post oral bisphosphonate administration; OR
- **c)** Patient has a pre-existing gastrointestinal medical condition in which intravenous bisphosphonate therapy may be warranted; OR
  Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient has had an osteoporotic fracture or a fragility fracture.

Dosing. Approve 3 mg intravenously no more frequently than once every 3 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of ibandronate injection is not recommended in the following situations:

1. **Osteoporosis Prevention.** Ibandronate injection is not indicated for the prevention of osteoporosis and supporting data are limited.

2. **Concurrent Use of Ibandronate Injection with Other Medications for Osteoporosis.**
   Note: Examples of medications for osteoporosis that ibandronate injection should not be given with include oral bisphosphonates (e.g., alendronate, risedronate, ibandronate), other intravenous bisphosphonates (e.g., zoledronic acid injection [Reclast]), Prolia (denosumab subcutaneous injection), Evenity (romosozumab-aqqg subcutaneous injection), Forteo (teriparatide subcutaneous injection, generic), Tymlos® (abaloparatide subcutaneous injection), and calcitonin nasal spray. However, this does NOT exclude use of calcium and/or vitamin D supplements in combination with ibandronate injection.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Boniva® intravenous infusion [prescribing information]. South San Francisco, CA: Genentech/Roche; January 2022.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	The brand name of Boniva was removed from the title of the policy. **Osteoporosis – Treatment of a Postmenopausal Patient:** The requirement that the patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy was removed. Instead, this requirement was incorporated into a Note that lists osteoporotic fracture or a fragility fracture as an example of inadequate efficacy or significant intolerance to a trial of an oral bisphosphonate or an oral bisphosphonate-containing product. **Concurrent Use of Ibandronate Injection with Other Medications for Osteoporosis:** To the Note which lists the medications that should not be used with ibandronate injection, it was clarified that this does NOT exclude use of calcium and/or vitamin D supplements in combination with ibandronate injection.	03/22/2023
Annual Revision	No criteria changes.	03/13/2024
Update	03/31/2024: No criteria changes. Removed the brand name of Boniva from the policy and noted that ibandronate intravenous infusion is available only as a generic.	NA

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Bone Modifiers – Prolia Utilization Management Medical Policy
- Prolia® (denosumab subcutaneous injection – Amgen)

REVIEW DATE: 09/27/2023

OVERVIEW

Prolia, a receptor activator of nuclear factor kappa-B ligand inhibitor, is indicated for the following uses:[1]

- **Bone loss (treatment to increase bone mass), in men with nonmetastatic prostate cancer** at high risk for fracture receiving androgen deprivation therapy.
- **Bone loss (treatment to increase bone mass), in women with breast cancer** at high risk for fracture receiving adjuvant aromatase inhibitor therapy.
- **Glucocorticoid-induced osteoporosis** (treatment), in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months.
- **Osteoporosis,** treatment of **postmenopausal women** at high risk of fracture.
- **Osteoporosis,** treatment to **increase bone mass in men** at high risk for fracture.

In general, high risk of fractures is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.[1] Of note, denosumab subcutaneous injection is also available under the brand name Xgeva®, and is indicated for the prevention of skeletal-related events in patients with multiple myeloma, as well as in patients with bone metastases from solid tumors, giant cell tumor of bone, and hypercalcemia of malignancy.[2]

Dosing Information

For all indications, the dose is 60 mg once every 6 months as a subcutaneous injection.[1]

Guidelines

Several guidelines address Prolia.

- **Breast Cancer/Prostate Cancer:** The National Comprehensive Cancer Network guidelines for breast cancer (version 4.2023 – March 23, 2023)[6] and prostate cancer (version 4.2023 – September 7, 2023)[7] note that if patients are receiving agents that impact bone mineral density (BMD), bisphosphonates (oral/intravenous), as well as Prolia, should be considered to maintain or improve BMD and/or reduce the risk of fractures.
- **Glucocorticoid-Induced Osteoporosis (GIO):** In 2017, the American College of Rheumatology updated guidelines for the prevention and treatment of GIO.[5] In various clinical scenarios, oral bisphosphonates are preferred, followed by intravenous bisphosphonates (e.g., zoledronic acid intravenous infusion [Reclast]).
- **Postmenopausal Osteoporosis:** Prolia is prominently featured in guidelines for postmenopausal osteoporosis by the Endocrine Society (2019)[3] and the American Association of Clinical Endocrinologists and the American College of Endocrinology (2020).[4] Prolia is one of several agents cited as an alternative for patients at high risk for fractures. The Bone Health and Osteoporosis Foundation clinician's guide for prevention and treatment of osteoporosis (2022) cites Prolia as robustly reducing vertebral and non-vertebral fractures in studies involving women with postmenopausal osteoporosis.[8]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Prolia. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In the approval indication, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: None.

*Indications and/or approval conditions noted with **[eviCore]** are managed by eviCore healthcare for those clients who use eviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to eviCore at www.eviCore.com.*

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Prolia is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Bone Loss (Treatment to Increase Bone Mass) in Patients with Breast Cancer at High Risk for Fracture Receiving Adjuvant Aromatase Inhibitor Therapy.** Approve for 1 year if the patient meets the following (A and B): ***[eviCore]***
   - **A)** Patient has breast cancer that is not metastatic to bone; AND
   - **B)** Patient is receiving aromatase inhibitor therapy.
     Note: Examples of aromatase inhibitor therapy are anastrozole, letrozole, or exemestane.

   Dosing. Approve 60 mg subcutaneously once every 6 months.

2. **Bone Loss (Treatment to Increase Bone Mass) in Patients with Nonmetastatic Prostate Cancer at High Risk for Fracture Receiving Androgen Deprivation Therapy.** Approve for 1 year of the patient meets the following (A and B): ***[eviCore]***
   - **A)** Patient has prostate cancer that is not metastatic to bone; AND
   - **B)** Patient meets ONE of the following conditions (i or ii):
     - **i.** Patient is receiving androgen deprivation therapy; OR
       Note: Examples of androgen deprivation therapy are Lupron Depot (leuprolide depot suspension injection), Eligard (leuprolide acetate suspension injectable), Trelstar (triptorelin pamoate suspension injection), and Zoladex (goserelin implant).
     - **ii.** Patient has undergone bilateral orchiectomy.

   Dosing. Approve 60 mg subcutaneously once every 6 months.

3. **Glucocorticoid-Induced Osteoporosis – Treatment.** Approve for 1 year of the patient meets the following (A and B):
   - **A)** Patient is either initiating or continuing systemic glucocorticoids; AND

Note: An example of a systemic glucocorticoid is prednisone.

B) Patient meets ONE of the following (i, ii, iii, or iv):
- **i.** Patient has tried zoledronic acid intravenous infusion (Reclast); OR
- **ii.** Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a or b):
  Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).
  - **a)** According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR
    Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.
  - **b)** Patient has experienced significant intolerance to an oral bisphosphonate; OR
    Note: Examples of significant intolerance include severe gastrointestinal related adverse events and/or severe musculoskeletal related adverse events.
- **iii.** Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):
  - **a)** Patient cannot swallow or has difficulty swallowing; OR
  - **b)** Patient cannot remain in an upright position post oral bisphosphonate administration; OR
  - **c)** Patient has a pre-existing gastrointestinal medical condition; OR
    Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).
- **iv.** Patient meets one of the following conditions (a, b, or c):
  - **a)** Severe renal impairment; OR
    Note: An example of severe renal impairment is a creatinine clearance < 35 mL/min.
  - **b)** Chronic kidney disease; OR
  - **c)** Patient has had an osteoporotic fracture or a fragility fracture.

Dosing. Approve 60 mg subcutaneously once every 6 months.

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4. Osteoporosis Treatment for a Postmenopausal Patient. Approve for 1 year if the patient meets the following (A and B):

A) Patient meets ONE of the following conditions (i, ii, or iii):
- **i.** Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist); OR
- **ii.** Patient has had an osteoporotic fracture or a fragility fracture; OR
- **iii.** The patient meets both of the following (a and b):
  - **a)** Patient has low bone mass; AND
    Note: An example of low bone mass includes a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist).
  - **b)** According to the prescriber, patient is at high risk for fracture; AND

B) Patient meets ONE of the following (i, ii, iii, or iv):
- **i.** Patient has tried ibandronate intravenous injection (Boniva) or zoledronic acid intravenous infusion (Reclast); OR

ii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a or b):
Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).
a) According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR
Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.
b) Patient has experienced significant intolerance to an oral bisphosphonate; OR
Note: Examples of significant intolerance include severe gastrointestinal related adverse events and/or severe musculoskeletal related adverse events.

iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):
a) Patient cannot swallow or has difficulty swallowing; OR
b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR
c) Patient has a pre-existing gastrointestinal medical condition; OR
Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient meets one of the following conditions (a, b, or c):
a) Severe renal impairment; OR
Note: An example of severe renal impairment is a creatinine clearance < 35 mL/min.
b) Chronic kidney disease; OR
c) Patient has had an osteoporotic fracture or a fragility fracture.

Dosing. Approve 60 mg subcutaneously once every 6 months.

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5. Osteoporosis Treatment (to Increase Bone Mass) for Men*. Approve for 1 year of the patient meets the following (A and B):

A) Patient meets ONE of the following conditions (i, ii, or iii):
i. Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, or total hip, and/or 33% (one-third) radius (wrist); OR
ii. Patient has had an osteoporotic fracture or a fragility fracture; OR
iii. The patient meets both of the following (a and b):
a) Patient has low bone mass; AND
Note: An example of low bone mass includes a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist).
b) According to the prescriber, patient is at high risk for fracture; AND

B) Patient meets ONE of the following (i, ii, iii, or iv):
i. Patient has tried zoledronic acid intravenous infusion (Reclast); OR
ii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and has had one of the following (a or b):
Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).

a) According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR
Note: Example of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.

b) Patient has experienced significant intolerance to an oral bisphosphonate; OR
Note: Examples of significant intolerance include severe gastrointestinal related adverse events and/or severe musculoskeletal related adverse events.

iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):

a) Patient cannot swallow or has difficulty swallowing; OR

b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR

c) Patient has a pre-existing gastrointestinal medical condition; OR
Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient meets one of the following conditions (a, b, or c):

a) Severe renal impairment; OR
Note: An example of severe renal impairment is a creatinine clearance < 35 mL/min.

b) Chronic kidney disease; OR

c) Patient has had an osteoporotic fracture or a fragility fracture.

***** Refer to the Policy Statement

Dosing. Approve 60 mg subcutaneously once every 6 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Prolia is not recommended in the following situations:

1. **Concurrent Use with Other Medications for Osteoporosis.**
Note: Examples of medications for osteoporosis that Prolia should not be given with include teriparatide subcutaneous injection (Forteo), Tymlos (abaloparatide subcutaneous injection), oral bisphosphonates (e.g., alendronate, risedronate, ibandronate), intravenous bisphosphonates (zoledronic acid intravenous infusion [Reclast], ibandronate intravenous infusion), calcitonin nasal spray (Miacalcin/Fortical), and Evenity (romosozumab-aqqg subcutaneous injection). However, this does NOT exclude use of calcium and/or vitamin D supplements in combination with Prolia.

2. **Giant Cell Tumor of Bone.** *[eviCore]*
Studies with denosumab in giant cell tumor of the bone used dosing for Xgeva® (denosumab subcutaneous injection), which is indicated for the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.[2]

3. **Osteoporosis Prevention.** Prolia is not indicated for the prevention of osteoporosis.[1]

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Prolia® subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; January 2023.
2. Xgeva® subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; June 2020.
3. Eastell R, Rosen CJ, Black DM, et al. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2019;104(5):1595-1622.
4. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update. *Endocrin Pract*. 2020;26(Suppl 1):1-46.
5. Buckley L, Guyatt G, Fink HA, et al. 2017 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Rheumatol*. 2017;69(8):1521-1537.
6. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – March 23, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 19, 2023.
7. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – September 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September, 19, 2023.
8. LeBoff MS, Greenspan SL, Insogna KL, et al. The clinician's guide to prevention and treatment of osteoporosis. *Osteoporosis Int*. 2022;33(10):2049-2102.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Concurrent Use with Other Medications for Osteoporosis:** To the Note which lists the medications that should not be used with Prolia, it was clarified that this does NOT exclude use of calcium and/or vitamin D supplements in combination with Prolia.	09/07/2022
Annual Revision	To comply with standard wording, the phrase "as determined by the prescriber" was replaced with "according to the prescriber. In addition, the following changes were made: **Glucocorticoid-Induced Osteoporosis – Treatment:** The exception that the patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy was removed. Instead, this exception was incorporated into a Note that lists osteoporotic fracture or a fragility fracture as an example of inadequate efficacy or significant intolerance to a trial of an oral bisphosphonate or an oral bisphosphonate-containing product. Femoral fracture was removed as an example of significant intolerance to an oral bisphosphonate. **Osteoporosis Treatment for Men:** The exception that the patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy was removed. Instead, this exception was incorporated into a Note that lists osteoporotic fracture or a fragility fracture as an example of inadequate efficacy or significant intolerance to a trial of an oral bisphosphonate or an oral bisphosphonate-containing product. Femoral fracture was removed as an example of significant intolerance to an oral bisphosphonate. **Osteoporosis Treatment for a Postmenopausal Patient:** The exception that the patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy was removed. Instead, this exception was incorporated into a Note that lists osteoporotic fracture or a fragility fracture as an example of inadequate efficacy or significant intolerance to a trial of an oral bisphosphonate or an oral bisphosphonate-containing product. Femoral fracture was removed as an example of significant intolerance to an oral bisphosphonate.	09/27/2023

CARECONTINUUM

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Bone Modifiers – Xgeva Utilization Management Medical Policy
- Xgeva® (denosumab subcutaneous injection – Amgen)

REVIEW DATE: 03/13/2024

OVERVIEW

Xgeva, a receptor activator of nuclear factor kappa-B ligand inhibitor, is indicated for the following uses:[1]

- **Giant cell tumor of bone**, treatment of adults and skeletally mature adolescents, with disease that is unresectable or where surgical resection is likely to result in severe morbidity.
- **Hypercalcemia of malignancy**, treatment of, that is refractory to bisphosphonate therapy.
- **Skeletal-related events**, prevention of, in patients with multiple myeloma and in those with bone metastases from solid tumors.

Another injectable formulation of denosumab is available, Prolia® (denosumab subcutaneous injection), but it is not included in this policy.[2]

Guidelines

Several guidelines address Xgeva.

- **Cancer:** Various guidelines from the National Comprehensive Cancer Network (e.g., breast cancer, prostate cancer, lung cancer, multiple myeloma) recommend Xgeva for the prevention of skeletal related adverse events.[3-6]
- **Hypercalcemia of Malignancy:** Guidelines from the Endocrine Society for the treatment of hypercalcemia of malignancy in adults (2023) have several recommendations.[7] In adults with hypercalcemia of malignancy, treatment with Xgeva over an intravenous bisphosphonate is recommended.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Xgeva. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Xgeva as well as the monitoring required for adverse events and long-term efficacy, approval requires Xgeva to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xgeva is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Bone Metastases from Solid Tumors – Prevention of Skeletal-Related Events.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   Note: Some examples of cancer in this clinical scenario include breast cancer, prostate cancer, and non-small cell lung cancer.
   A) Patient is ≥ 18 years of age; AND
   B) Patient has bone metastases; AND
   C) Patient with prostate cancer must have castration-resistant prostate cancer; AND
   Note: This includes patients who have progressed after treatment with hormonal therapy or after surgical castration (e.g., bilateral orchiectomy). Examples of hormonal therapies for prostate cancer include Lupron Depot (leuprolide for depot suspension), Eligard (leuprolide acetate for injectable suspension), Trelstar (triptorelin pamoate for injectable suspension), or Zoladex (goserelin implant).
   D) Medication is prescribed by or in consultation with a hematologist or an oncologist.

   Dosing. Approve 120 mg administered as a subcutaneous (SC) injection up to once every 4 weeks.

2. **Giant Cell Tumor of Bone.** Approve for 1 year.

   Dosing. Approve 120 mg subcutaneous (SC) up to once every 4 weeks with loading doses on Day 8 and Day 15 of Month 1.

3. **Hypercalcemia of Malignancy.** Approve for 2 months if the patient meets BOTH of the following (A and B):
   A) Patient has a current malignancy; AND
   B) Patient has an albumin-corrected calcium (cCa) ≥ 11.5 mg/dL.

   Dosing. Approve 120 mg subcutaneous (SC) up to once every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy.

4. **Multiple Myeloma – Prevention of Skeletal-Related Events.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) The medication is prescribed by or in consultation with a hematologist or an oncologist.

   Dosing. Approve 120 mg administered as a subcutaneous (SC) injection up to once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Xgeva is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Xgeva® subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; June 2020.
2. Prolia® subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; March 2024.
3. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 2.2024 – March 5, 2024). © 2024 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 13, 2024.
4. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 1.2024 – January 25, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 13, 2024.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Hypercalcemia of Malignancy:** Requirements were deleted that the patient has tried at least one intravenous bisphosphonate therapy or that the patient has an estimated calculated creatinine clearance < 30 mL/min.	03/22/2023
Annual Revision	No criteria changes.	03/13/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Bone Modifiers – Zoledronic Acid (Reclast) Utilization Management Medical Policy
- Reclast® (zoledronic acid intravenous infusion – Novartis, generic)

REVIEW DATE: 03/13/2024

OVERVIEW

Zoledronic acid (Reclast), a bisphosphonate given intravenously, is indicated for the following uses:[1]

- **Glucocorticoid-induced osteoporosis**, for treatment and prevention in men and women who are either initiating or continuing systemic glucocorticoids (e.g., prednisone 7.5 mg or greater) and who are anticipated to remain on glucocorticoids for at least 12 months.
- **Osteoporosis, prevention in postmenopausal women**.
- **Osteoporosis, treatment in men** to increase bone mass.
- **Osteoporosis, treatment in postmenopausal women**.
- **Paget's disease of bone**, treatment in men and women.

Another zoledronic acid injection product (Zometa®) is indicated for hypercalcemia of malignancy; and for multiple myeloma and bone metastases from solid tumors.[2] Although not indicated, zoledronic acid injection (Reclast) has been used in patients, mainly children, with osteogenesis imperfecta and benefits were noted, such as increases in bone mineral density.[1,3-8]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of zoledronate acid (Reclast). Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Regarding the approval duration of one dose, the approval is for 30 days, which is an adequate duration for the patient to receive one dose. In the approval indication for zoledronic acid injection (Reclast), as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of zoledronate acid injection (Reclast) is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Glucocorticoid-Induced Osteoporosis – Prevention and Treatment.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is either initiating or continuing systemic glucocorticoids; AND

Note: An example of a systemic glucocorticoid is prednisone.

B) Patient meets ONE of the following (i, ii, iii, or iv):
- **i.** Patient has tried zoledronic acid intravenous infusion (Reclast); OR
- **ii.** Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets ONE of the following (a or b):
  Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).
  - **a)** According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR
    Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.
  - **b)** Patient has experienced significant intolerance to an oral bisphosphonate; OR
    Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, and femoral fracture.
- **iii.** Patient cannot take an oral bisphosphonate due to ONE of the following (a, b, or c):
  - **a)** Patient cannot swallow or has difficulty swallowing; OR
  - **b)** Patient cannot remain in an upright position post-oral bisphosphonate administration; OR
  - **c)** Patient has a pre-existing gastrointestinal medical condition in which intravenous bisphosphonate therapy may be warranted; OR
    Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, and abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).
- **iv.** Patient has had an osteoporotic fracture or a fragility fracture.

Dosing. Approve one 5 mg infusion given intravenously (IV) up to once every year.

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2. Osteoporosis – Prevention for a Postmenopausal Patient. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

A) Patient meets ONE of the following (i or ii):
- **i.** Patient has had a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist); OR
- **ii.** Patient has had an osteoporotic fracture or a fragility fracture; AND

B) Patient meets ONE of the following (i, ii, iii, or iv):
- **i.** Patient has tried zoledronic acid intravenous infusion (Reclast); OR
- **ii.** Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets ONE of the following (a or b):
  Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).
  - **a)** According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR
    Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.
  - **b)** Patient has experienced significant intolerance to an oral bisphosphonate; OR

Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, and femoral fracture.

iii. Patient cannot take an oral bisphosphonate due to ONE of the following (a, b, or c):
- **a)** Patient cannot swallow or has difficulty swallowing; OR
- **b)** Patient cannot remain in an upright position post oral bisphosphonate administration; OR
- **c)** Patient has a pre-existing gastrointestinal medical condition in which intravenous bisphosphonate therapy may be warranted; OR
  Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, and abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient has had an osteoporotic fracture or a fragility fracture; AND

C) If the patient has received Reclast previously, at least 24 months has elapsed since the last dose.

Dosing. Approve one 5 mg infusion given intravenously (IV) up to once every 2 years.

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3. Osteoporosis – Treatment for a Man*. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) The patient meets ONE of the following (i, ii, or iii):
- **i.** Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist); OR
- **ii.** Patient has had an osteoporotic fracture or a fragility fracture; OR
- **iii.** Patient meets BOTH of the following (a and b):
  - **a)** Patient has low bone mass; AND
    Note: An example of low bone mass includes a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist).
  - **b)** According to the prescriber, patient is at high risk of fracture; AND

B) Patient meets ONE of the following (i, ii, iii, or iv):
- **i.** Patient has tried zoledronic acid intravenous infusion (Reclast); OR
- **ii.** Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets ONE of the following (a or b):
  Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).
  - **a)** According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR
    Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.
  - **b)** The patient has experienced significant intolerance to an oral bisphosphonate; OR
    Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, and femoral fracture.
- **iii.** Patient cannot take an oral bisphosphonate due to ONE of the following (a, b, or c):
  - **a)** Patient cannot swallow or has difficulty swallowing; OR
  - **b)** Patient cannot remain in an upright position post oral bisphosphonate administration; OR
  - **c)** Patient has a pre-existing gastrointestinal medical condition in which intravenous bisphosphonate therapy may be warranted; OR

Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, and abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient has had an osteoporotic fracture or a fragility fracture.

* Refer to the Policy Statement.

Dosing. Approve one 5 mg infusion given intravenously up to once every year.

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4. Osteoporosis – Treatment for a Postmenopausal Patient. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient meets ONE of the following (i, ii, or iii):

i. Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist); OR

ii. Patient has had an osteoporotic fracture or a fragility fracture; OR

iii. Patient meets BOTH of the following (a and b):

a) Patient has low bone mass; AND

Note: An example of low bone mass includes a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist).

b) According to the prescriber, patient is at high risk for fracture; AND

B) Patient meets ONE of the following (i, ii, iii, or iv):

i. Patient has tried ibandronate intravenous infusion (Boniva IV) or zoledronic acid intravenous infusion (Reclast); OR

ii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets ONE of the following (a, b, or c):

Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).

a) According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR

Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.

b) Patient has experienced significant intolerance to an oral bisphosphonate; OR

Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, and femoral fracture.

iii. Patient cannot take an oral bisphosphonate due to ONE of the following (a, b, or c):

a) Patient cannot swallow or has difficulty swallowing; OR

b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR

c) Patient has a pre-existing gastrointestinal medical condition in which intravenous bisphosphonate therapy may be warranted; OR

Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, and abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient has had an osteoporotic fracture or a fragility fracture.

Dosing. Approve one 5 mg infusion given intravenously up to once every year.

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5. **Paget's Disease of Bone.** Approve for one dose if the patient meets ONE of the following (A, B, or C):
   - **A)** Patient has elevations in serum alkaline phosphatase of two times higher than the upper limit of the age-specific normal reference range; OR
   - **B)** Patient is symptomatic; OR
     Note: Examples of symptoms include bone pain, hearing loss, or osteoarthritis.
   - **C)** Patient is at risk for complications from their disease.
     Note: Examples of disease complications include immobilization, bone deformity, fractures, and nerve compression syndrome.

   Dosing. Approve one 5 mg intravenous (IV) infusion.

Other Uses with Supportive Evidence

6. **Osteogenesis Imperfecta.** Approve for 1 year.

   Dosing. Dosing information is limited. Approve up to 0.05 mg per kg intravenous (IV) given no more frequently than once every 3 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of zoledronic acid injection (Reclast) is not recommended in the following situations:

1. **Concurrent Use of Zoledronic Acid Intravenous Infusion (Reclast) with Other Medications for Osteoporosis.**
   Note: Examples of medications for osteoporosis that zoledronic acid intravenous infusion (Reclast) should not be given with include oral bisphosphonates (alendronate, risedronate, ibandronate), other intravenous bisphosphonates (e.g., intravenous ibandronate [Boniva]), Evenity (romosozumab-aqqg subcutaneous injection), Prolia (denosumab subcutaneous injection), Forteo (teriparatide subcutaneous injection, generic), Tymlos (abaloparatide subcutaneous injection), and calcitonin nasal spray. This applies only to osteoporosis-related indications. However, this does NOT exclude use of calcium and/or vitamin D supplements in combination with zoledronic acid intravenous infusion (Reclast). This criterion applies only to osteoporosis-related indications.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Glucocorticoid-Induced Osteoporosis – Prevention and Treatment:** The exception that the patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy was removed. Instead, this exception was incorporated into a Note that lists osteoporotic fracture or a fragility fracture as an example of inadequate efficacy or significant intolerance to a trial of an oral bisphosphonate or an oral bisphosphonate-containing product. **Osteoporosis – Prevention for a Postmenopausal Patient:** The exception that the patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy was removed. Instead, this exception was incorporated into a Note that lists osteoporotic fracture or a fragility fracture as an example of inadequate efficacy or significant intolerance to a trial of an oral bisphosphonate or an oral bisphosphonate-containing product. **Osteoporosis – Treatment for a Man:** The exception that the patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy was removed. Instead, this exception was incorporated into a Note that lists osteoporotic fracture or a fragility fracture as an example of inadequate efficacy or significant intolerance to a trial of an oral bisphosphonate or an oral bisphosphonate-containing product. **Osteoporosis – Treatment for a Postmenopausal Patient:** The exception that the patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy was removed. Instead, this exception was incorporated into a Note that lists osteoporotic fracture or a fragility fracture as an example of inadequate efficacy or significant intolerance to a trial of an oral bisphosphonate or an oral bisphosphonate-containing product. **Conditions Not Recommended for Approval:** Regarding **Concurrent Use of Zoledronic Acid Injection (Reclast) with Other Medications for Osteoporosis**, to the Note which lists the medications that should not be used with zoledronic acid injection (Reclast), it was clarified that this does NOT exclude use of calcium and/or vitamin D supplements in combination with zoledronic acid injection (Reclast).	03/22/2023
Annual Revision	No criteria changes.	03/13/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Bone Modifiers – Zoledronic Acid (Zometa) Utilization Management Medical Policy
- Zometa® (zoledronic acid intravenous infusion – generic only)

REVIEW DATE: 03/13/2024

OVERVIEW

Zoledronic acid intravenous infusion (Zometa), a bisphosphonate, is indicated for the treatment of the following:[1]

- **Hypercalcemia of malignancy**.
- **Multiple myeloma and documented bone metastases from solid tumors**, in addition to standard antineoplastic therapy.

Prostate cancer should have progressed after treatment with at least one hormonal therapy.[1] Another formulation of zoledronic acid intravenous infusion (Reclast®) is available but is not included in this policy.[2]

Data are available with zoledronic acid intravenous infusion (Zometa) regarding off-label uses. One example is to prevent bone loss in patients with breast cancer receiving aromatase inhibitor therapy. Aromatase inhibitor therapy prevents peripheral production and suppresses estrogen levels and can lead to accelerated bone loss beyond what would naturally occur in women.[3,4] This can place the patient at an increased risk for having a fracture. A review on the management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer[5] states that zoledronic acid intravenous infusion (Zometa) [4 mg every 6 months] is the preferred agent for prevention and treatment of aromatase inhibitor bone loss.[4] Zoledronic acid intravenous infusion (Zometa) has been studied and shown benefits in postmenopausal women receiving adjuvant letrozole for breast cancer.[5,6]

Zoledronic acid intravenous infusion (Zometa) has also been utilized to prevent bone loss in patients with prostate cancer who are receiving androgen deprivation therapy (ADT). ADT is associated with a variety of adverse events, including osteoporosis. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines regarding prostate cancer (version 3.2024 – March 8, 2024)[7] cite zoledronic acid as an option to increase bone density, a surrogate for fracture risk, during ADT for prostate cancer. Zoledronic acid intravenous infusion (Zometa) has led to bone mineral density increases in patients with prostate cancer who are receiving androgen deprivation therapy.[8,9] A clinical practice guideline for osteoporosis in men from the Endocrine Society[9] recommends pharmacological treatment for osteoporosis for men with prostate cancer receiving ADT who have a high risk of fracture.

Zoldedronic acid intravenous infusion (Zometa) has utility in premenopausal patients with breast cancer who have developed ovarian failure. Chemotherapy-induced ovarian failure is an adverse effect associated with some adjuvant chemotherapy and can lead to rapid bone loss.[10,11] Studies have demonstrated zoledronic acid intravenous infusion (Zometa) to be efficacious in preserving bone mineral density in premenopausal women with breast cancer who developed ovarian failure due to adjuvant chemotherapy.

The American Society of Clinical Oncology and the Cancer Care Ontario group updated guidelines for use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer. The guideline recommends adjuvant bisphosphonate therapy in postmenopausal patients with primary breast cancer who are candidates to receive adjuvant systemic therapy.[12] NCCN guidelines for breast cancer (version 1.2024 – January 25,

2024) also recommend bisphosphonates as adjuvant therapy for postmenopausal women with breast cancer.[13]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of zoledronic acid intravenous infusion (Zometa). Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with zoledronic acid intravenous infusion (Zometa) as well as the monitoring required for adverse events and long-term efficacy, approval requires zoledronic acid intravenous infusion (Zometa) to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of zoledronic acid intravenous infusion (Zometa) is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. **Bone Metastases from Solid Tumors – Prevention of Skeletal-Related Events.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   Note: Some examples of cancer in this clinical scenario include breast cancer, prostate cancer, non-small cell lung cancer, renal cell cancer, small cell lung cancer, colorectal cancer, bladder cancer, gastrointestinal cancer, genitourinary cancer, and head and neck cancer.
   A) Patient has bone metastases; AND
   B) Patient with prostate cancer must have castration-resistant prostate cancer; AND
   Note: This includes patients who have progressed after treatment with hormonal therapy or after surgical castration (e.g., bilateral orchiectomy). Examples of hormonal therapies for prostate cancer include Lupron Depot (leuprolide for depot suspension), Eligard (leuprolide acetate for injectable suspension), Trelstar (triptorelin pamoate for injectable suspension), and Zoladex (goserelin implant).
   C) The medication is prescribed by or in consultation with a hematologist or an oncologist.

   Dosing. Approve 4 mg or less by intravenous infusion administered no more frequently than once every 3 weeks.

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2. **Hypercalcemia of Malignancy.** Approve for 1 month if the patient meets BOTH of the following (A and B):
   A) Patient has a current malignancy; AND
   B) Patient has an albumin-corrected calcium (cCa) ≥ 11.5 mg/dL.

Dosing. Approve 4 mg given as a single dose intravenous (IV) infusion for up to two doses with the second dose given a minimum of 7 days from the first dose.

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3. Multiple Myeloma – Prevention of Skeletal-Related Events. Approve for 1 year if the medication is prescribed by or in consultation with a hematologist or an oncologist.

Dosing. Approve 4 mg or less by intravenous infusion administered no more frequently than once every 3 weeks.

Other Uses with Supportive Evidence

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4. Breast Cancer – Adjuvant Therapy. Approve for 1 year if the patient is post-menopausal.

Dosing. Approve 4 mg or less by intravenous infusion no more frequently than once every 3 months.

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5. Prevention of Bone Loss (To Increase Bone Mass) in a Patient with Breast Cancer Receiving Aromatase Inhibitor Therapy. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient has breast cancer that is not metastatic to bone; AND

B) Patient is receiving an aromatase inhibitor therapy.
Note: Examples of aromatase inhibitor agents include anastrozole, letrozole, and exemestane.

Dosing. Approve 4 mg or less by intravenous infusion no more frequently than once every 6 months.

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6. Prevention of Bone Loss (to Increase Bone Mass) in a Patient with Prostate Cancer Who are Receiving Androgen Deprivation Therapy (ADT). Approve 1 year if the patient meets BOTH of the following (A and B):

A) Patient has prostate cancer that is not metastatic to bone; AND

B) Patient meets ONE of the following (i or ii):

i. Patient is currently receiving androgen deprivation therapy; OR
Note: Examples of androgen deprivation therapies include Lupron Depot (leuprolide for depot suspension), Eligard (leuprolide acetate for injectable suspension), Trelstar (triptorelin pamoate for injectable suspension), and Zoladex (goserelin implant).

ii. Patient has undergone bilateral orchiectomy.

Dosing. Approve 4 mg or less by intravenous infusion no more frequently than once every 3 months.

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6. Prevention of Bone Loss (to Increase Bone Mass) in a Premenopausal Patient with Breast Cancer Who Have Developed Ovarian Failure. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

A) Patient is premenopausal; AND

B) Breast cancer is not metastatic to bone; AND

C) Patient received adjuvant chemotherapy that led to ovarian failure.

Dosing. Approve 4 mg or less by intravenous infusion no more frequently than once every 3 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of zoledronic acid intravenous infusion (Zometa) is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	It was noted that Zometa (brand name) is no longer available. **Breast Cancer – Adjuvant Therapy:** This was added as a new indication of use. Criteria are to approve if the patient is postmenopausal. **Bone Metastases From Solid Tumors – Prevention of Skeletal-Related Events:** The indication was changed to as stated. Previously it was "Bone Metastases from Solid Tumors – Treatment". **Multiple Myeloma – Prevention of Skeletal-Related Events:** The indication was changed to as stated. Previously it was "Multiple Myeloma – Treatment".	03/22/2023
Annual Revision	No criteria changes.	03/13/2024

CARECONTINUUM™

MEDICAL STEP MANAGEMENT POLICY

POLICY: Bone Modifiers – Zoledronic Acid (Zometa) – Xgeva Medical Step Management Policy
- Xgeva® (denosumab subcutaneous injection – Amgen)
- Zometa® (zoledronic acid intravenous infusion – generic only)

REVIEW DATE: 03/13/2024

OVERVIEW

Zoledronic acid injection (Zometa), a bisphosphonate, is indicated for the treatment of the following:[1]
- **Hypercalcemia of malignancy**.
- **Multiple myeloma and documented bone metastases from solid tumors**, in addition to standard antineoplastic therapy.

Xgeva, a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor, is indicated for the following uses:[2]
- **Giant cell tumor of bone**, treatment of adults and skeletally mature adolescents with disease that is unresectable or where surgical resection is likely to result in severe morbidity.
- **Hypercalcemia of malignancy**, treatment of, that is refractory to bisphosphonate therapy.
- **Skeletal-related events**, prevention of, in patients with multiple myeloma and in those with bone metastases from solid tumors.

Zoledronic acid injection (Zometa) and Xgeva are used in patients with cancerous conditions. Xgeva has a unique indication for use in giant cell tumor of bone.[2] For many common indications, the place in therapy is similar.

Guidelines

Various guidelines addressed this class of medications:
- **Hypercalcemia of Malignancy:** Guidelines from the Endocrine Society for the treatment of hypercalcemia of malignancy in adults (2023) have several recommendations.[3] In adults with hypercalcemia of malignancy, treatment with Xgeva over an intravenous bisphosphonate is recommended.[3]
- **Prostate Cancer:** National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (version 3.2024 – March 8, 2024) state that if bone antiresorptive therapy is recommended, Xgeva is preferred (category 1) over zoledronic acid (Zometa) [category 2A] if bone metastases are present.[4]

POLICY STATEMENT

This Medical Step Management program has been developed to encourage the use the Preferred Product (zoledronic acid injection [Zometa]). For all medications (Preferred and Non-Preferred), the patient is required to meet the respective *Utilization Management Medical Policy* criteria. The program also directs the patient to the Preferred Product. Requests for the Non-Preferred Product will be reviewed using the exception criteria (below). All approvals are provided for a duration as directed in the respective *Utilization Management Medical Policy* criteria.

Automation: None.

Preferred Products: Zoledronic acid injection
Non-Preferred Product: Xgeva

RECOMMENDED EXCEPTION CRITERIA

Non-Preferred Product	Exception Criteria
Xgeva	**1. Bone Metastases from Solid Tumors – Prevention of Skeletal-Related Events.** Approve if the patient meets BOTH of the following (A and B): **A)** Patient meets the standard *Bone Modifiers – Xgeva Utilization Management Medical Policy* criteria; AND **B)** Patient meets ONE of the following (i, ii, iii, or iv): **i.** Patient has tried zoledronic acid injection (Zometa); OR **ii.** Patient has renal impairment (creatinine clearance < 30 mL/min); OR **iii.** Patient has a previous history of using Xgeva; OR **iv.** Patient has prostate cancer with bone metastases. **2. Giant Cell Tumor of Bone.** Approve if the patient meets the standard *Bone Modifiers – Xgeva Utilization Management Medical Policy* criteria. **3. Hypercalcemia of Malignancy.** Approve if the patient meets the standard *Bone Modifiers – Xgeva Utilization Management Medical Policy* criteria. **4. Multiple Myeloma – Prevention of Skeletal-Related Events.** Approve if the patient meets BOTH of the following (A and B): **A)** Patient meets the standard *Bone Modifiers – Xgeva Utilization Management Medical Policy* criteria; AND **B)** Patient meets ONE of the following (i, ii, or iii): **i.** Patient has tried zoledronic acid injection (Zometa); OR **ii.** Patient has renal impairment (creatinine clearance < 30 mL/min); OR **iii.** Patient has a previous history of using Xgeva.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Hypercalcemia of Malignancy:** The requirement that the patient has tried at least one intravenous bisphosphonate therapy or that the patient has an estimated calculated creatinine clearance < 30 mL/min was removed.	03/22/2023
Annual Revision	No criteria changes.	03/13/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Botulinum Toxins – Botox Utilization Management Medical Policy
- Botox® (onabotulinumtoxinA injection – Allergan/AbbVie)

REVIEW DATE: 10/11/2023; selected revision 04/10/2024

OVERVIEW

Botox (onabotulinumtoxinA) is indicated for the following uses:[1]

- **Blepharospasm** associated with dystonia, including benign essential blepharospasm or seventh (VII) nerve disorders in patients ≥ 12 years of age.
- **Cervical dystonia,** in adults to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.
- **Hyperhidrosis, severe primary axillary** which is inadequately managed with topical agents in adults.
- **Migraine headache prophylaxis (prevention),** in adults with chronic migraine (≥ 15 days per month with headache lasting 4 hours a day or longer).
- **Neurogenic detrusor overactivity** in pediatric patients ≥ 5 years of age who have had an inadequate response to or are intolerant of an anticholinergic medication.
- **Overactive bladder** with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have had an inadequate response to or are intolerant of an anticholinergic medication.
- **Spasticity** in patients ≥ 2 years of age.
- **Strabismus** in patients ≥ 12 years of age.
- **Urinary incontinence due to detrusor overactivity** associated with a neurological condition (e.g., spinal cord injury, multiple sclerosis) in adults who have had an inadequate response to or are intolerant of an anticholinergic medication.

In regard to the indication of migraine headache prophylaxis, an updated position statement for the prevention of migraines from the American Headache Society (2024) notes that specifically for prevention of chronic migraine with or without aura, Botox should be considered a first-line treatment recommendation without a requirement for prior failure of other classes of migraine preventative treatment.[4]

Other Uses with Supportive Evidence

Botulinum toxin type A has been used to treat a multitude of disorders characterized by abnormal muscle contraction.[2] The benefit of these products has also been demonstrated in the treatment of gastrointestinal, genitourinary, ocular, and autonomic nervous system disorders.[2,3]

Botulinum toxins have been studied in a variety of indications outside of FDA-approved uses. Literature is available to support use of Botox in the following conditions:

- **Achalasia:** The American College of Gastroenterology (ACG) clinical guideline for the diagnosis and management of achalasia (2020) recommends the use of botulinum toxin as first-line therapy for patients with achalasia who are unfit for definitive therapies for the treatment of achalasia such as pneumatic dilation or surgical myotomy.[5]
- **Anal Fissures:** The ACG clinical guideline for the management of benign anorectal disorders (2021) suggests that botulinum toxin A injections may be attempted for patients in whom calcium channel blockers fail or as an alternative option to calcium channel blockers (conditional recommendation; quality of evidence low).[6]

- **Chronic Facial Pain/Pain Associated with Temporomandibular Dysfunction:** Data from several open-label studies, as well as one randomized, placebo-controlled trial, support the efficacy of Botox in the treatment of chronic facial pain/chronic facial pain associated with hyperactivity of the masticatory muscles.[7-10]
- **Chronic Low Back Pain:** In one 8-week, randomized, double-blind, placebo-controlled trial in 31 patients with chronic low back pain (no causative factor identified in the majority of patients; history of disc disease in 6 patients, discectomy in 3 patients, and trauma in 4 patients), Botox in addition to their current pharmacologic treatment regimen resulted in significantly greater improvement in pain relief and degree of disability compared with placebo.[11] A 14-month, open-label, prospective study evaluated the short- and long-term effects of paraspinal muscle injections of Botox in 75 patients with refractory chronic low back pain. A total of 53% and 52% of patients reported significant pain relief at 3 weeks and 2 months, respectively.[12]
- **Dystonia, other than Cervical:** Guidelines from the American Academy of Neurology (AAN) support use of botulinum toxins in focal dystonias of the upper extremity (should be considered; Level B recommendation).[13] Botulinum toxin A is the most widely accepted treatment for spasmodic dysphonia, a focal laryngeal dystonia, viewed as the treatment of choice by the American Academy of Otolaryngology-Head and Neck Surgery.[14] Per the guideline, clinicians should offer, or refer to a clinician who can offer, botulinum toxin injections for treatment of dysphonia caused by spasmodic dysphonia and other types of laryngeal dystonia. AAN guidelines note that botulinum toxin is probably effective and should be considered for adductor type laryngeal dystonia (Level B).[13]
- **Essential Tremor:** According to the clinical practice parameter on essential tremor by the AAN, propranolol and primidone are first-line therapy in the treatment of essential tremor.[15] Second-line medication options include alprazolam, atenolol, sotalol, gabapentin, and topiramate. Botulinum toxin A may also reduce tremor. The guidelines recommend that botulinum toxin A may be considered in medically refractory cases of limb, head, and voice tremor associated with essential tremor (Level C for limb, head, and voice tremor).
- **Hemifacial Spasm:** Per the AAN, botulinum toxin (formulation not specified) may be considered in hemifacial spasm (Level C).[13] Data with Botox and Dysport® (abobotulinumtoxinA injection) are cited in the recommendations regarding hemifacial spasm.
- **Hyperhidrosis, Gustatory:** Botox is recommended as a first-line option for gustatory sweating by the International Hyperhidrosis Society.[16]
- **Hyperhidrosis, Palmar/Plantar and Facial:** The efficacy of Botox is well-established in the treatment of primary focal/palmar hyperhidrosis based on data from both randomized, double-blind, placebo-controlled studies and open-label studies.[3,18,19] Guidelines from the International Hyperhidrosis Society support use of Botox in patients who have failed to respond to topical therapy.[16,20,21]
- **Myofascial Pain:** Data from several retrospective reviews and open-label trials support the efficacy of Botox in the treatment of myofascial pain syndromes associated with various muscle groups.[7,22] In one randomized, controlled trial in 40 patients with chronic myofascial pain of various forms, Botox resulted in a significantly greater reduction in pain score from baseline compared with intramuscularly administered methylprednisolone at 30 days and 60 days post injection.[23,24]
- **Ophthalmic Disorders, other than Blepharospasm or Strabismus:** Botulinum toxin A has been successful in improving or treating many ophthalmic disorders. One retrospective review (n = 54) concluded that Botox may have a role in the treatment of esotropia in patients > 18 months of age.[25] Botox improved visual acuity in case reports and one small, open-label study in patients with acquired symptomatic nystagmus from multiple sclerosis or brain-stem hemorrhage.[26,27] Data from uncontrolled studies have shown Botox to be beneficial in the treatment of sixth nerve palsy.[28,29]

- **Plantar Fasciitis:** In one randomized, double-blind study (n = 36), botulinum toxin A exhibited more rapid and sustained improvement over the duration of the study as compared with patients who received steroid injections.[30] The clinical consensus statement on the diagnosis and treatment of heel pain (developed by the American College of Foot and Ankle Surgeons) published in 2010 list botulinum toxin injection as a Tier 2 option (Grade I); Tier 1 treatment options include: padding and strapping of the foot (Grade B), therapeutic orthotic insoles (Grade B), oral anti-inflammatory agents (Grade I), corticosteroid injections (Grade B), and Achilles and plantar fascia stretching (Grade B) [Grade B recommendations are supported by fair evidence, Grade I recommendations indicate there is insufficient evidence to make a recommendation].[31]
- **Sialorrhea, Chronic:** Botulinum toxin A has been studied in the treatment of sialorrhea associated with Parkinson's Disease, parkinsonian syndromes, cerebral palsy, head and neck carcinoma, neurodegenerative disease, stroke, and amyotrophic lateral sclerosis.[3] A review of the literature on medical treatment of sialorrhea found that Botox is probably effective for the treatment of this condition (level B evidence).[32]

Dosing Considerations

Definitive dosing has not been established for off-label uses of botulinum toxins, including Botox. In general, Botox is not recommended to be injected more frequently than once every 3 months, and botulinum toxins appear to have an approximately 3-month duration of effect or longer, depending on the site of injection. The Botox prescribing information advises that in a 3-month interval, adults should not exceed a total dose of 400 units. Pediatric patients should not exceed a total dose of the lesser of 10 units/kg or 340 units in a 3-month interval. Specific considerations by indication are noted below:

- **Achalasia:** Botox has been studied for achalasia in several trials. Doses higher than 100 units per treatment have not been shown to be more effective.[34]
- **Sialorrhea, Chronic:** Xeomin® (incobotulinumtoxinA injection) is indicated for this use.[35] Per Xeomin labeling, the maximum recommended dose for adults is 100 units (50 units per side) and for pediatric patients is 75 units (37.5 units per side), administered not more frequently than once every 16 weeks. Recommendations for maximum dosing and frequency for Botox are based on suggested relative conversion of 1:1 for Botox to Xeomin.[36,37]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Botox. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Requests for doses outside the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

Medical benefit coverage is not recommended for Botox Cosmetic or cosmetic conditions.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Botox is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Blepharospasm. Approve for 1 year if the patient is ≥ 12 years of age.

Note: This includes blepharospasm associated with dystonia, benign essential blepharospasm, seventh (VII) nerve disorders.

Dosing. Approve up to a maximum dose of 200 units, administered not more frequently than once every 3 months.

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2. Cervical Dystonia. Approve for 1 year if the patient is ≥ 18 years of age.
Note: Cervical dystonia is also referred to as spasmodic or cervical torticollis.

Dosing. Approve up to a maximum dose of 300 units, administered not more frequently than once every 3 months.

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3. Hyperhidrosis, Primary Axillary. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient is ≥ 18 years of age; AND

B) Patient has tried at least one topical agent for axillary hyperhidrosis.
Note: Examples of topical agents for the treatment of axillary hyperhidrosis include topical aluminum chloride, Qbrexza (glycopyrronium cloth 2.4% for topical use).

Dosing. Approve up to a maximum dose of 50 units per axilla, administered not more frequently than once every 3 months.

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4. Migraine Headache **Prevention.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient has ≥ 15 migraine headache days per month with headache lasting 4 hours per day or longer (prior to initiation of Botox therapy); AND

C) Botox is being prescribed by or after consultation with a neurologist or headache specialist; AND

D) If the patient is currently taking Botox for migraine headache prevention, the patient has had a significant clinical benefit from the medication as determined by the prescriber.
Note: Examples of significant clinical benefit include a reduction in the overall number of migraine days per month or a reduction in number of severe migraine days per month from the time that Botox was initiated.

Dosing. Approve up to a maximum dose of 155 units, administered not more frequently than once every 12 weeks.

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5. Neurogenic Detrusor Overactivity (NDO), Pediatric. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient is ≥ 5 years of age; AND

B) Patient has tried at least one other pharmacologic therapy for the treatment of neurogenic detrusor overactivity (NDO).
Note: Examples of other NDO pharmacologic therapies include a beta-3 adrenergic agonist or an anticholinergic medication.

Dosing. Approve up to a maximum dose of 200 units, administered not more frequently than once every 12 weeks.

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6. **Overactive Bladder with Symptoms of Urge Urinary Incontinence, Urgency, and Frequency (Adult).** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried at least one other pharmacologic therapy for the treatment of overactive bladder (OAB).
   Note: Examples of other OAB pharmacologic therapies include a beta-3 adrenergic agonist or an anticholinergic medication. For treatment of adult urinary incontinence associated with a neurological condition, refer to FDA-Approved Indications below.

   Dosing. Approve up to a maximum dose of 100 units, administered not more frequently than once every 12 weeks.

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7. **Spasticity, Limb.** Approve for 1 year if the patient is ≥ 2 years of age.

   Dosing. Approve ONE of the following regimens (A or B):
   A) Lower limb spasticity: Approve one of the following regimens (i or ii):
      i. Patient is ≥ 18 years of age: Approve up to a maximum dose of 400 units, administered not more frequently than once every 12 weeks.
      ii. Patient is < 18 years of age: Approve up to a maximum dose of 8 units/kg (not to exceed 300 units), administered not more frequently than once every 12 weeks.
   B) Upper limb spasticity: Approve one of the following regimens (i or ii):
      i. Patient is ≥ 18 years of age: Approve up to a maximum dose of 400 units, administered not more frequently than once every 12 weeks.
      ii. Patient is < 18 years of age: Approve up to a maximum dose of 6 units/kg (not to exceed 200 units), administered not more frequently than once every 12 weeks.

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8. **Strabismus**. Approve for 1 year if the patient is ≥ 12 years of age.

   Dosing. Approve up to a maximum dose of 25 units in any one muscle, administered not more frequently than once every 3 months.

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9. **Urinary Incontinence Associated with a Neurological Condition (Adult).** Approve for 1 year if the patient meets BOTH of the following (A and B):
   Note: Examples of neurological conditions associated with urinary incontinence include spinal cord injury, multiple sclerosis, or spina bifida.
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried at least one other pharmacologic therapy for the treatment of urinary incontinence.
   Note: Examples of other pharmacologic therapies for urinary incontinence include a beta-3 adrenergic agonist or an anticholinergic medication. For treatment of adult overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, see FDA-Approved Indications above.

Dosing. Approve up to a maximum dose of 200 units, administered not more frequently than once every 12 weeks.

Other Uses with Supportive Evidence

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10. Achalasia. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 100 units, administered not more frequently than once every 3 months.

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11. Anal Fissure. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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12. Chronic Facial Pain/Pain Associated with Temporomandibular Dysfunction. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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13. Chronic Low Back Pain. Approve for 1 year if the patient meets ALL of the following (A, B and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has tried at least TWO other pharmacologic therapies for the treatment of chronic low back pain; AND
  Note: Examples of pharmacologic therapies include nonsteroidal anti-inflammatory drugs (NSAIDs), antispasmodics, muscle relaxants, opioids, or antidepressants.
- **C)** Botox is being used as part of a multimodal therapeutic pain management program.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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14. Dystonia, other than Cervical. Approve for 1 year if the patient is ≥ 18 years of age.
Note: Examples of dystonias include focal dystonias, tardive dystonia, anismus, or laryngeal dystonia/spasmodic dysphonia. For cervical dystonia, refer to FDA-Approved Indications above.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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15. Essential Tremor. Approve for 1 year if the patient meets BOTH of the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has tried at least one other pharmacologic therapy for the treatment of tremors.

Note: Examples of pharmacologic therapies for essential tremor include primidone, propranolol, benzodiazepines, gabapentin, topiramate.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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16. Hemifacial Spasm. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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17. Hyperhidrosis, Gustatory. Approve for 1 year if the patient is ≥ 18 years of age.
Note: Gustatory hyperhidrosis is also referred to as Frey's Syndrome.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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18. Hyperhidrosis, Palmar/Plantar and Facial. Approve for 1 year if the patient meets BOTH of the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient has tried at least one topical agent for the treatment of hyperhidrosis (e.g., aluminum chloride).

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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19. Myofascial Pain. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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20. Ophthalmic Disorders, other than Blepharospasm or Strabismus. Approve for 1 year if the patient is ≥ 18 years of age.
Note: Examples of ophthalmic disorders include esotropia, exotropia, nystagmus, or facial nerve paresis. For blepharospasm or strabismus, refer to FDA-Approved Indications above.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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21. Plantar Fasciitis. Approve for 1 year if the patient meets BOTH of the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient has tried two other treatment modalities for the treatment of plantar fasciitis.

Note: Examples of other treatment modalities include padding and strapping of the foot, therapeutic orthotic insoles, oral anti-inflammatory drugs, corticosteroid injections, or stretching.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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22. Sialorrhea, Chronic. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 100 units (50 units per side), administered not more frequently than once every 16 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Botox is not recommended in the following situations:

1. **Cosmetic Uses**. Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical medical benefit.
   Note: Examples of cosmetic uses include facial rhytides, frown lines, glabellar wrinkling, horizontal neck rhytides, mid and lower face and neck rejuvenation, platsymal bands, or rejuvenation of the periorbital region.

2. **Gastroparesis.** The ACG issued clinical guidelines on the management of gastroparesis (2013).[38] ACG does not recommend the use of botulinum toxin injected into the pylorus as a treatment for gastroparesis. This is based on two double-blind, placebo-controlled studies which did show some improvement in gastric emptying, but no improvement in symptoms compared with placebo.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Hemifacial Spasm:** This Other Use with Supportive Evidence was reworded to as listed; previously, the indication was titled "Spasticity, other than Limb (i.e., spasticity or hypertonia due to cerebral palsy, stroke, brain injury, spinal cord injury, multiple sclerosis, hemifacial spasm)".	01/11/2023
Selected Revision	**Migraine Headache Prevention:** The following sentence was added to the current Note regarding the requirement for standard prophylactic (preventative) pharmacologic therapies**:** A patient who has already tried a calcitonin gene-related peptide (CGRP) inhibitor indicated for the prevention of chronic migraine, is not required to try two standard prophylactic pharmacologic therapies [verification of therapy required]. The Overview was updated to include a list of medications with established efficacy from the American Headache Society for the treatment of migraine prevention.	08/02/2023
Update	08/08/2023: The Overview was updated to include the following sentence: Additionally, the following treatments are possibly effective and can be considered for migraine prevention: calcium channel blocker (e.g., verapamil) and angiotensin converting enzyme inhibitors (e.g., lisinopril).	N/A
Early Annual Revision	**Blepharospasm**: Diagnosis was changed from "Blepharospasm associated with dystonia or Strabismus" to "Blepharospasm" with the following Note added: "This includes blepharospasm associated with dystonia, including benign essential blepharospasm and seventh (VII) nerve disorders." An age requirement of ≥ 12 years was added. Previously there was not an age requirement in place. **Cervical Dystonia**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. **Hyperhidrosis, Primary Axillary**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. **Migraine Headache Prevention**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. **Neurogenic Detrusor Overactivity (NDO), Pediatric:** New indication, age ≥ 5 years, criteria, and dosing added. Previously, diagnosis and dosing was captured under FDA Labeled Indications as "Urinary Incontinence Associated with a Neurological Condition". **Overactive Bladder with Symptoms of Urge Urinary Incontinence, Urgency, and Frequency (Adult)**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. "Adult" was added to diagnosis to distinguish from pediatric NDO indication. **Spasticity, Limb**: An age requirement of ≥ 2 years was added. Previously there was not an age requirement in place. **Strabismus**: New indication, requirement of age ≥ 12 years, criteria, and dosing added. Previously, diagnosis and dosing was captured under FDA Labeled Indications as "Blepharospasm associated with dystonia or Strabismus". **Urinary Incontinence Associated with a Neurological Condition (Adult)**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. "Adult" was added to diagnosis to distinguish from pediatric NDO indication. Dosing considerations for patients ≤ 18 years of age were removed. **Achalasia**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Anal Fissure**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Chronic Facial Pain/Pain Associated with Temporomandibular Dysfunction**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Chronic Low Back Pain**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed.	10/11/2023

	Dystonia other than cervical: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Essential Tremor**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Hemifacial Spasm**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Hyperhidrosis, Gustatory**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Hyperhidrosis, Palmar/Plantar and Facial**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Myofascial Pain**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Ophthalmic Disorders, other than Blepharospasm or Strabismus**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Plantar Fasciitis**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Sialorrhea, Chronic**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed.	
Selected Revision	**Migraine Headache Prevention:** The requirement that the patient has tried and had an inadequate efficacy or adverse event to at least two standard prophylactic pharmacologic therapies was removed from the criteria.	04/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Botulinum Toxin – Daxxify Utilization Management Medical Policy
- Daxxify® (daxibotulinumtoxinA-lanm injection – Revance)

REVIEW DATE: 08/30/2023

OVERVIEW

Daxxify (daxibotulinumtoxinA-lanm), is indicated for the following uses:[1]
- **Cervical dystonia** in adults.

The medication labeling, like all other botulinum toxin products, state the potency units of Daxxify are specific to the preparation and test method utilized and not interchangeable with other preparations of other botulinum toxin products [Botox® (onabotulinumtoxinA), Xeomin® (incobotulinumtoxinA), Dysport® (abobotulinumtoxinA), Myobloc® (rimabotulinumtoxinB)]; therefore, units of biological activity of Daxxify cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific test method.[1] Daxxify does not contain any human serum albumin in its formulation. The labeling also indicates a warning for potential serious adverse reactions after administration of Daxxify for unapproved uses.

Dosing Considerations

After reconstitution, the recommended dose of Daxxify for the treatment of cervical dystonia ranges from 125 units to 250 units given intramuscularly as a divided dose among affected muscles.[1] In patients previously treated with another botulinum toxin, their past dose, response to treatment, duration of effect, and adverse event history should be taken into consideration when determining the Daxxify dose. If dose modification is necessary, dose adjustments can be made in 50 to75 unit increments according to individual patient response. Daxxify should be administered no more frequently than once every 3 months for any indication.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Daxxify. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Requests for doses outside the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for 1 year in duration.

Medical benefit coverage is not recommended for cosmetic conditions.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Daxxify is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Cervical Dystonia**. Approve for 1 year if the patient is ≥ 18 years of age.

Note: Cervical dystonia is also known as spasmodic or cervical torticollis.

Dosing. Approve up to a maximum dose of 300 units, administered not more frequently than once every 3 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Daxxify is not recommended in the following situations:

1. **Cosmetic Uses**. Note: Examples of cosmetic uses include facial rhytides, frown lines, glabellar wrinkling, horizontal neck rhytides, mid and lower face and neck rejuvenation, platsymal bands, or rejuvenation of the periorbital region. Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical medical benefit.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Daxxify® injection [prescribing information]. Newark, CA: Revance; August 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/30/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Botulinum Toxin – Dysport Utilization Management Medical Policy
- Dysport® (abobotulinumtoxinA injection – Ipsen/Galderma)

REVIEW DATE: 10/11/2023

OVERVIEW

Dysport (abobotulinumtoxinA) is indicated for the following uses:[1]
- **Cervical dystonia** in adults.
- **Spasticity** in patients ≥ 2 years of age.

Other Uses with Supportive Evidence

Botulinum toxins have been studied in a variety of indications outside of FDA-approved uses. Literature is available to support use of Dysport in the following conditions:
- **Anal Fissure:** There is an extensive amount of data from open-label studies; randomized, placebo-controlled trials; and randomized, comparative trials supporting the efficacy of botulinum toxin A in the treatment of anal fissures.[2-4] Injection of botulinum toxin allows healing in approximately 60% to 80% of anal fissures.[5] There is no consensus on the dose, site of injection, or number of injections. Botulinum toxin A has been shown to be more effective than topical nitroglycerin but less effective than surgery in inducing and maintaining fissure healing.[6] The American College of Gastroenterology clinical guideline for the management of benign anorectal disorders (2021) suggests that botulinum toxin A injections may be attempted for patients in whom calcium channel blockers fail or as an alternative option to calcium channel blockers (conditional recommendation; quality of evidence low).[4]
- **Blepharospasm:** Dysport has demonstrated efficacy in clinical trials in patients with blepharospasm.[7,8] American Academy of Neurology (AAN) guidelines (2016, reaffirmed 2022) support the use of Dysport for blepharospasm with a Level C recommendation ("possibly effective").[9]
- **Hemifacial Spasm:** Per the AAN, botulinum toxin (formulation not specified) may be considered in hemifacial spasm (Level C).[13] Data with Botox and Dysport are cited in the recommendations regarding hemifacial spasm.
- **Sialorrhea, Chronic:** Botulinum toxin A has been studied in the treatment of sialorrhea associated with Parkinson's Disease, parkinsonian syndromes, cerebral palsy, head and neck carcinoma, neurodegenerative disease, stroke, and amyotrophic lateral sclerosis.[10-12] Data with Dysport come from two small controlled trials.[10,11]

Dosing Considerations

Toxin distribution varies between the commercially available botulinum toxin products.[1,14,15] The labels for the botulinum toxin products state that there is a lack of interchangeability between the products for various reasons, including differences in the units of biological activity. Studies have attempted to establish a conversion ratio between botulinum toxin products, with variable results.[18] In general, conversion ratios of 1:1 for Botox to Xeomin, 1:3 for Botox to Dysport, and 1:50 to 1:100 for Botox to Myobloc have been suggested.

Definitive dosing has not been established for off-label uses of botulinum toxins, including Dysport. Specific dosing considerations by indication are noted below. For other indications addressed in this policy,

specific dosing guidance is not available. In these cases, dosing is based on the Botox prescribing information, which states that in a 3-month interval, adults should not exceed a total dose of 400 units, and pediatric patients should not exceed a total dose of the lesser of 10 units/kg or 340 units in a 3-month interval.[14] Recommendations for maximum dosing and frequency for Dysport are based on a suggested relative conversion of 3:1 between Dysport and Botox units.[1] Additionally, the maximum dose supported for a patient < 18 years of age in Dysport labeling is 30 units/kg (not to exceed 1,000 units). Specific considerations by indication are noted below.

- **Blepharospasm:** A maximum dose of 120 units of Dysport, not more frequently than once every 12 weeks, has been suggested.[16,17]
- **Sialorrhea, Chronic:** Xeomin is indicated for this use.[15] Per Xeomin labeling, the maximum recommended dose for adults is 100 units (50 units per side) and for pediatric patients is 75 units (37.5 units per side), administered not more frequently than once every 16 weeks.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Dysport. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Requests for doses outside the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for 1 year in duration.

Medical benefit coverage is not recommended for cosmetic conditions.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Dysport is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. Cervical Dystonia. Approve for 1 year if the patient is ≥ 18 years of age.
Note: Cervical dystonia is also referred to as spasmodic or cervical torticollis.

Dosing. Approve up to a maximum dose of 1,000 units, administered not more frequently than once every 12 weeks.

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2. Spasticity, Limb. Approve for 1 year if the patient is ≥ 2 years of age.

Dosing. Approve one of the following regimens (A or B):

A) Lower limb spasticity (or combined upper and lower limb spasticity): Approve one of the following regimens (i or ii):
  - **i.** Patient is ≥ 18 years of age: Approve up to a maximum dose of 1,500 units, administered not more frequently than once every 12 weeks.
  - **ii.** Patient is < 18 years of age: Approve up to a maximum dose of 30 units/kg (not to exceed 1,000 units), administered not more frequently than once every 12 weeks.

B) Upper limb spasticity: Approve one of the following regimens (i or ii):
  - **i.** Patient is ≥ 18 years of age: Approve up to a maximum dose of 1,000 units, administered not more frequently than once every 12 weeks.

ii. Patient is < 18 years of age: Approve up to a maximum dose of 16 units/kg (not to exceed 640 units), administered not more frequently than once every 12 weeks.

Other Uses with Supportive Evidence

3. Anal Fissure. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 1,200 units, administered not more frequently than once every 3 months.

4. Blepharospasm. Approve for 1 year if the patient is ≥ 18 years of age.
Note: This includes blepharospasm associated with dystonia, benign essential blepharospasm, seventh (VII) nerve disorders.

Dosing. Approve up to a maximum dose of 120 units, administered not more frequently than once every 12 weeks.

5. Hemifacial Spasm. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 1,200 units, administered not more frequently than once every 3 months.

6. Sialorrhea, Chronic. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 300 units (150 units per side), administered not more frequently than once every 16 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Dysport is not recommended in the following situations:

1. **Cosmetic Uses**. Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical medical benefit.
   Note: Examples of cosmetic uses include facial rhytides, frown lines, glabellar wrinkling, horizontal neck rhytides, mid and lower face and neck rejuvenation, platsymal bands, or rejuvenation of the periorbital region.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Dysport® injection [prescribing information]. Cambridge, MA and Fort Worth, TX: Ipsen/Galderma; July 2020.
2. Brisinda G, Bentivoglio AR, Maria G, et al. Treatment with botulinum neurotoxin of gastrointestinal smooth muscles and sphincters spasms. *Mov Disord*. 2004;19(Suppl 8):S146-S156.
3. Friedenberg F, Gollamudi S, Parkman HP. The use of botulinum toxin for the treatment of gastrointestinal motility disorders. *Dig Dis Sci*. 2004;49(2):165-175.
4. Wald A, Bharucha AE, Limketkai B, et al. ACG Clinical Guidelines: management of benign anorectald. *Am J Gastroenterol*. 2021;116(10):1987-2008.
5. Bansal C, Omlin KJ, Hayes CM, et al. Novel cutaneous uses for botulinum toxin type A. *J Cosmet Dermatol*. 2006;5(3):268-272.
6. Cheng CM, Chen JS, Patel RP. Unlabeled uses of botulinum toxins: A review, part 2. *Am J Health Syst Pharm*. 2006;63(3):225-232.
7. Truong D, Comella C, Fernandez HH, et al.; Dysport Benign Essential Blepharospasm Study Group. Efficacy and safety of purified botulinum toxin type A (Dysport) for the treatment of benign essential blepharospasm: a randomized, placebo-controlled, phase II trial. *Parkinsonism Relat Disord*. 2008;14(5):407-414.
8. Kollewe K, Mohammadi B, Köhler S, et al. Blepharospasm: long-term treatment with either Botox®, Xeomin® or Dysport®. *J Neural Transm*. 2015;122(3):427-431.
9. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache. Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2016;86:1818-1826.
10. Bhidayasiri R, Truong DD. Expanding use of botulinum toxin. *J Neurol Sci*. 2005;235(1-2):1-9.
11. Tan EK. Botulinum toxin treatment of sialorrhea: comparing different therapeutic preparations. *Eur J Neurol.* 2006;13 (Suppl 1):60-64.
12. Sheffield JK, Jakovic J. Botulinum toxin in the treatment of tremors, dystonias, sialorrhea and other symptoms associated with Parkinson's disease. *Expert Rev Neurotherapeutics.* 2007;7(6):637-647.
13. Simpson DM, Blitzer A, Brashear A, et al. Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2008;70:1699-1706.
14. Botox® injection [prescribing information]. Madison, NJ: Allergan; August 2022.
15. Xeomin® injection [prescribing information]. Raleigh, NC: Merz; August 2021.
16. Micromedex®. IBM Corporation. Available at: http://www.micromedexsolutions.com Accessed on October 9, 2023. Search terms: Dysport.
17. Clinical Pharmacology [database online]. Tampa, FL: Elsevier, Inc.; 2022. Available at: https://www.clinicalkey.com/pharmacology/. Accessed on October 9, 2023. Search terms: Dysport.
18. Scaglione F. Conversion ratio between Botox®, Dysport®, and Xeomin® in clinical practice. *Toxins (Basel)*. 2016;8(3):65.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Hemifacial Spasm:** This Other Use with Supportive Evidence was reworded to as listed; previously, the indication was titled "Spasticity, other than Limb (i.e., spasticity or hypertonia due to cerebral palsy, stroke, brain injury, spinal cord injury, multiple sclerosis, hemifacial spasm)". **Hyperhidrosis, Gustatory:** This Other Use with Supportive Evidence was removed from the policy. **Hyperhidrosis, Primary Axillary:** This Other Use with Supportive Evidence was removed from the policy.	01/11/2023
Early Annual Revision	**Cervical Dystonia**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. **Spasticity, Limb**: An age requirement of ≥ 2 years was added. Previously there was not an age requirement in place. **Anal Fissure**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Blepharospasm**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. The following note was added to the indication: "This includes blepharospasm associated with dystonia, benign essential blepharospasm, seventh (VII) nerve disorders." **Hemifacial Spasm**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Sialorrhea, Chronic**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed.	10/11/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Botulinum Toxins – Myobloc Utilization Management Medical Policy
- Myobloc® (rimabotulinumtoxinB injection – Solstice Neurosciences)

REVIEW DATE: 01/24/2024

OVERVIEW

Myobloc (rimabotulinumtoxinB) is indicated for the following uses:[1]
- **Cervical dystonia** in adults.
- **Sialorrhea, chronic** in adults.

Other Uses with Supportive Evidence

Spasticity, Upper Limb: In 2016 American Academy of Neurology guidelines (reaffirmed 2022), Myobloc is supported for use in upper limb spasticity (Level B; probably effective).[2] Of note, evidence is insufficient for Myobloc in the setting of lower limb spasticity (Level U).

Dosing Considerations

Definitive dosing has not been established for off-label uses of botulinum toxins, including Myobloc. Recommendations for maximum dosing and frequency for Myobloc are based on a suggested relative conversion of 50:1 between Myobloc and Botox units.[3] For **Spasticity, Upper Limb**, dosing is based on the Botox prescribing information, which states that in a 3-month interval, adults should not exceed a total dose of 400 units.[4]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Myobloc. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Requests for doses outside the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the dosing interval is provided in months, 1 month is equal to 30 days.

Medical benefit coverage is not recommended for cosmetic conditions.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Myobloc is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Cervical Dystonia. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 5,000 units, administered not more frequently than once every 12 weeks.

2. Sialorrhea, Chronic. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 3,500 units (1,750 units per side), administered not more frequently than once every 12 weeks.

Other Uses with Supportive Evidence

3. Spasticity, Upper Limb. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 20,000 units, administered not more frequently than once every 3 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Myobloc is not recommended in the following situations:

1. **Cosmetic Uses.** Note: Examples of cosmetic uses include facial rhytides, frown lines, glabellar wrinkling, horizontal neck rhytides, mid and lower face and neck rejuvenation, platysmal bands, or rejuvenation of the periorbital region. Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical medical benefit.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Myobloc® injection [prescribing information]. San Francisco, CA: Solstice Neurosciences; December 2023.
2. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache. Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2016;86:1818-1826.
3. Walker TJ, Dayan SH. Comparison and overview of currently available neurotoxins. *Clin Aesthet Dermatol*. 2014;7(21):31-39.
4. Botox® injection [prescribing information]. Madison, NJ: Allergan; August 2022.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Cervical Dystonia:** An age requirement of ≥ 18 years was added to criteria. Previously there was not an age requirement in place. **Sialorrhea, Chronic:** An age requirement of ≥ 18 years was added to criteria. Previously there was not an age requirement in place. **Hyperhidrosis, Palmar or Primary Axillary:** This Other Use with Supportive Evidence was removed from the policy. **Spasticity, Upper Limb:** This Other Use with Supportive Evidence was reworded as listed; previously the indication was listed as "Spasticity (i.e., spasticity due to cerebral palsy, stroke, brain injury, spinal cord injury, multiple sclerosis, hemifacial spasm)". Additionally, an age requirement of ≥ 18 years was added to criteria. Previously there was not an age requirement in place. With this change, pediatric dosing was removed from the dosing section.	01/11/2023
Annual Revision	No criteria changes.	01/24/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Botulinum Toxin – Xeomin Utilization Management Medical Policy
- Xeomin® (incobotulinumtoxinA injection – Merz)

REVIEW DATE: 10/11/2023

OVERVIEW

Xeomin (incobotulinumtoxinA) is indicated for the following uses:[1]
- **Blepharospasm** in adults.
- **Cervical dystonia** in adults.
- **Sialorrhea**, chronic, in patients ≥ 2 years of age.
- **Upper limb spasticity**:
  - In adults.
  - In pediatric patients ≥ 2 years of age, excluding spasticity caused by cerebral palsy.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Xeomin. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

Medical benefit coverage is not recommended for cosmetic conditions.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xeomin is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Blepharospasm. Approve for 1 year if the patient is ≥ 18 years of age.
Note: This includes blepharospasm associated with dystonia, benign essential blepharospasm, seventh (VII) nerve disorders.

Dosing. Approve up to a maximum dose of 100 units (50 units per eye), administered not more frequently than once every 12 weeks.

2. Cervical Dystonia. Approve for 1 year if the patient is ≥ 18 years of age.
Note: Cervical dystonia is also known as spasmodic or cervical torticollis.

Dosing. Approve up to a maximum dose of 120 units, administered not more frequently than once every 12 weeks.

3. Sialorrhea, Chronic. Approve for 1 year if the patient is ≥ 2 years of age.

Dosing. Approve one of the following regimens (A or B):
A) Patient is ≥ 18 years of age: Approve up to a maximum dose of 100 units (50 units per side), administered not more frequently than once every 16 weeks.
B) Patient is < 18 years of age: Approve up to a maximum dose of 75 units (37.5 units per side), administered not more frequently than once every 16 weeks.

4. Spasticity, Upper Limb. Approve for 1 year if the patient is ≥ 2 years of age.

Dosing. Approve one of the following regimens (A or B):
A) Patient is ≥ 18 years of age: Approve up to a maximum dose of 400 units, administered not more frequently than once every 12 weeks.
B) Patient is < 18 years of age: Approve up to a maximum dose of 16 units/kg (not to exceed 400 units), administered not more frequently than once every 12 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xeomin is not recommended in the following situations:

1. **Cosmetic Uses**. Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical medical benefit.
   Note: Examples of cosmetic uses include facial rhytides, frown lines, glabellar wrinkling, horizontal neck rhytides, mid and lower face and neck rejuvenation, platsymal bands, or rejuvenation of the periorbital region.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Xeomin® injection [prescribing information]. Raleigh, NC and Franksville, WI: Merz; August 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Hyperhidrosis, Primary Axillary, Palmar/Plantar, and Facial:** This Other Use with Supportive Evidence was removed from the policy. **Spasticity, other than Upper Limb:** This Other Use with Supportive Evidence was removed from the policy.	01/11/2023
Early Annual Revision	**Blepharospasm:** An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. The following note was added to the indication: "This includes blepharospasm associated with dystonia, benign essential blepharospasm, seventh (VII) nerve disorders." **Cervical Dystonia:** An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. **Sialorrhea, Chronic:** An age requirement of ≥ 2 years was added. Previously there was not an age requirement in place. **Spasticity, Upper Limb**: An age requirement of ≥ 2 years was added. Previously there was not an age requirement in place.	10/11/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Chemoprotective Agent – Pedmark Utilization Management Medical Policy
- Pedmark® (sodium thiosulfate intravenous infusion – Fennec)

REVIEW DATE: 10/04/2023

OVERVIEW

Pedmark, an inorganic salt, is indicated to **reduce the risk of ototoxicity associated with cisplatin** in patients ≥ 1 month to 18 years of age with localized, non-metastatic solid tumors.[1]

Limitation of use: The safety and efficacy of Pedmark have not been established when administered following cisplatin infusions longer than 6 hours.[1] Pedmark may not reduce the risk of ototoxicity when administered following longer cisplatin infusions, because irreversible ototoxicity may have already occurred.

Dosing Information

The recommended dose of Pedmark is based on body surface area according to actual body weight and is administered as an intravenous infusion over 15 minutes.[1] The dose should be administered 6 hours after administration of cisplatin and if cisplatin is administered on multiple days, the dose should be given at least 10 hours before the subsequent dose of cisplatin. Do not administer Pedmark if the next dose of cisplatin is scheduled to begin in less than 10 hours. Pedmark should not be started if the serum sodium level is > 145 mmol/L. The recommended dosing of Pedmark is summarized in Table 1.

Table 1. Recommended Dosing of Pedmark.[1]

Actual Body Weight	Pedmark Dose
Less than 5 kg	10 g/m^2
5 to 10 kg	15 g/m^2
Greater than 10 kg	20 g/m^2

Premedicate with an antiemetic before each dose of Pedmark.[1] For patients who develop a hypersensitivity reaction to Pedmark, administer an antihistamine and glucocorticoids before each subsequent dose of Pedmark.

Guidelines

Pedmark has not been addressed in National Comprehensive Cancer Network clinical practice guidelines.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Pedmark. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Pedmark as well as the monitoring required for adverse events and long-term efficacy, approval requires Pedmark to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Pedmark is recommended in those who meet the following criteria:

FDA-Approved Indication

1. Ototoxicity Risk Reduction. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, D, E, and F):

A) Patient is ≥ 1 month and < 18 years of age; AND

B) Patient is receiving cisplatin chemotherapy; AND

C) Patient has a solid tumor; AND

Note: Examples of solid tumors include medulloblastoma, osteosarcoma, germ cell tumor, neuroblastoma, hepatoblastoma, anaplastic astrocytoma.

D) Patient has localized, non-metastatic disease; AND

E) Patient has a baseline serum sodium level ≤ 145 mmol/L; AND

F) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 20 g/m^2 administered by intravenous infusion, given 6 hours after each dose of cisplatin.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Pedmark is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Pedmark intravenous infusion [prescribing information]. Hoboken, NJ: Fennec Pharmaceuticals; September 2022.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/05/2022
Annual Revision	No criteria changes.	10/04/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Colony Stimulating Factors – Filgrastim Products Utilization Management Medical Policy
- Neupogen® (filgrastim intravenous or subcutaneous injection – Amgen)
- Nivestym™ (filgrastim intravenous or subcutaneous injection – Hospira/Pfizer)
- Releuko® (filgrastim-ayow intravenous or subcutaneous injection – Amneal)
- Zarxio® (filgrastim-sndz intravenous or subcutaneous injection – Sandoz)

REVIEW DATE: 09/20/2023

OVERVIEW

Filgrastim, a leukocyte growth factor, is indicated for the following uses:[1-4]

- **Decrease the incidence of infection as manifested by febrile neutropenia**, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.
- **Mobilization of hematopoietic progenitor cells,** into the peripheral blood for collection by leukapheresis.
- **Reduce the time to neutrophil recovery and the duration of fever,** following induction or consolidation chemotherapy treatment of adults with acute myeloid leukemia (AML).
- **Reduce the duration of neutropenia and neutropenia-related clinical sequelae (e.g., febrile neutropenia),** in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.
- **Reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers),** in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

Nivestym, Releuko, and Zarxio are biosimilars to Neupogen.[2-4] Releuko indication labeling does not include mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.[4] Neupogen is additionally indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) addresses the use of filgrastim products in several guidelines.

- **Acute Lymphoblastic Leukemia (ALL):** Guidelines (version 2.2023 – July 28, 2023) recommend granulocyte colony stimulating factors (CSFs) as supportive care for myelosuppressive blocks of therapy or as directed by treatment protocol.[5]
- **Hematopoietic Cell Transplantation:** Guidelines (version 1.2023 – March 31, 2023) recommend filgrastim for hematopoietic cell mobilization for allogeneic or autologous donors as a single agent or in combination with other treatments.[6]
- **Hematopoietic Growth Factors:** Guidelines (version 2.2023 – March 6, 2023) recommend filgrastim, along with other CSFs, for prophylactic use if the patient is receiving anti-cancer medications that are associated with a high (> 20%) incidence of severe neutropenia with fever.[7] Consider CSF therapy for patients with an intermediate (10% to 20%) probability of developing febrile neutropenia based on risk factors. The NCCN guidelines also recommend therapy with CSFs in other scenarios in those given myelosuppressive chemotherapy. Filgrastim products are also recommended for mobilization and following hematopoietic cell transplant.

- **Management of Immunotherapy-Related Toxicities:** Guidelines (version 2.2023 – May 9, 2023) recommend granulocyte CSFs as supportive care for neutropenic patients with Grade 1 cytokine release syndrome resulting from chimeric antigen receptor T-cell therapy.[8]
- **Myelodysplastic Syndromes (MDS):** Guidelines (version 1.2023 – September 12, 2022) consider filgrastim for use in certain patients (e.g., neutropenic patients with recurrent or resistant infections, combination use with epoetin alfa or Aranesp® [darbepoetin alfa injection] in patients with anemia).[9]

The American Society of Clinical Oncology clinical practice guidelines for the use of white blood cell growth factors (2015) recommend CSFs to reduce the risk of febrile neutropenia in patients receiving cancer chemotherapy.[10] CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected. The guidelines state CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum.

Other Uses with Supportive Evidence

Neutropenia occurs in patients with human immunodeficiency virus (HIV) and may be caused by medications or due to the disease process. Studies have demonstrated positive outcomes with the use of filgrastim for the treatment of neutropenia in this patient population.[11-14]

Filgrastim has been used for agranulocytosis caused by non-cytotoxic medications, primarily described in case series, case reports and literature reviews.[15-21]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of filgrastim products. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with filgrastim as well as the monitoring required for adverse events and long-term efficacy, approval for some conditions requires filgrastim to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

*Indications and/or approval conditions noted with **[eviCore]** are managed by eviCore healthcare for those clients who use eviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to eviCore at www.eviCore.com.*

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of filgrastim products is recommended in those who meet one of the following:

FDA-Approved Indications

1. **Acute Myeloid Leukemia (AML) in a Patient Receiving Chemotherapy.** ***[eviCore]*** Approve for 6 months if prescribed by or in consultation with an oncologist or hematologist.

Dosing. Approve up to 10 mcg/kg per day by intravenous or subcutaneous injection.

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2. **Bone Marrow Transplant in a Patient with Cancer Who Received Chemotherapy.** Approve for 1 month if prescribed by or in consultation with a hematologist, an oncologist, or a physician who specializes in transplantation.

   Dosing. Approve up to 30 mcg/kg per day by intravenous or subcutaneous injection.

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3. **Cancer in a Patient Receiving Myelosuppressive Chemotherapy.** ***[eviCore]*** Approve for 6 months if the patient meets the following (A and B):
   - **A)** Patient meets ONE of the following (i, ii, iii, or iv):
     - **i.** Patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk is at least 20% based on the chemotherapy regimen); OR
     - **ii.** Patient meets both of the following (a and b):
       - **a)** Patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia, but the risk is less than 20% based on the chemotherapy regimen; AND
       - **b)** Patient has at least one risk factor for febrile neutropenia according to the prescriber; OR
         Note: Examples of risk factors include age ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus (HIV) infection.
     - **iii.** Patient meets both of the following (a and b):
       - **a)** Patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor; AND
         Note: Examples of colony stimulating factors include filgrastim products, pegfilgrastim products, and sargramostim products (e.g., Leukine).
       - **b)** A reduced dose or frequency of chemotherapy may compromise treatment outcome; OR
     - **iv.** Patient who has received chemotherapy has febrile neutropenia and has at least one risk factor for poor clinical outcomes or for developing infection-associated complications according to the prescriber; AND
       Note: Examples of risk factors include sepsis syndrome; age > 65 years; severe neutropenia (absolute neutrophil count [ANC] < 100 cells/mm^3); neutropenia expected to be > 10 days in duration; invasive fungal infection; or other clinically documented infections.
   - **B)** The medication is prescribed by or in consultation with an oncologist or hematologist.

   Dosing. Approve up to 10 mcg/kg per day by intravenous or subcutaneous injection for up to 14 days per month.

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4. **Peripheral Blood Progenitor Cell Collection and Therapy.** ***[eviCore]*** Approve for 1 month if prescribed by or in consultation with an oncologist, a hematologist, or a physician who specializes in transplantation.

   Dosing. Approve up to 32 mcg/kg per day by intravenous or subcutaneous injection.

5. **Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome).** *[eviCore]* Approve for 1 month if prescribed by or in consultation with a physician who has expertise in treating acute radiation syndrome.
   Dosing. Approve up to 10 mcg/kg per day as a subcutaneous injection.

6. **Severe Chronic Neutropenia (e.g., Congenital Neutropenia, Cyclic Neutropenia, Idiopathic Neutropenia).** Approve for 6 months if prescribed by or in consultation with a hematologist.

   Dosing. Approve up to 12 mcg/kg per day by subcutaneous injection.

Other Uses with Supportive Evidence

7. **Acute Lymphoblastic Leukemia (ALL).** *[eviCore]* Approve for 1 month if prescribed by or in consultation with an oncologist or a hematologist.

   Dosing. Approve up to 10 mcg/kg per day as a subcutaneous injection.

8. **Cytokine Release Syndrome Associated with Chimeric Antigen Receptor (CAR) T-Cell Therapy.** *[eviCore]* Approve for 1 month if prescribed for a patient who has neutropenia.
   Note: Examples of CAR T-cell therapy include Kymriah (tisagenlecleucel intravenous infusion) and Yescarta (axicabtagene ciloleucel intravenous infusion).

   Dosing. Approve up to 10 mcg/kg per day by intravenous or subcutaneous injection.

9. **Drug-Induced (Non-Chemotherapy) Agranulocytosis or Neutropenia.** Approve for 1 month.

   Dosing. Approve up to 10 mcg/kg per day as a subcutaneous injection.

10. **Myelodysplastic Syndromes (MDS).** *[eviCore]* Approve for 3 months if prescribed by or in consultation with an oncologist or hematologist.

    Dosing. Approve up to 5 mcg/kg per day as a subcutaneous or intravenous injection.

11. **Neutropenia Associated with Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome (AIDS).** Approve for 4 months if the agent is prescribed by or in consultation with a physician that specializes in infectious diseases, a hematologist, or a physician who specializes in the management of HIV/AIDS.

    Dosing. Approve up to 10 mcg/kg per day as a subcutaneous injection.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of filgrastim products is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Neupogen® subcutaneous or intravenous injection [prescribing information]. Thousand Oaks, CA: Amgen; April 2023.
2. Zarxio™ subcutaneous or intravenous injection [prescribing information]. Princeton, NJ: Sandoz; March 2021.
3. Nivestym™ subcutaneous or intravenous injection [prescribing information]. Lake Forest, IL and New York, NY: Hospira and Pfizer; March 2023.
4. Releuko® subcutaneous or intravenous injection [prescribing information]. Bridgewater, NJ: Amneal; June 2023.
5. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 2.2023 – July 28, 2023). © 2023 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on September 7, 2023.
6. The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines in Oncology (version 1.2023 – March 31, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 7, 2023.
7. The NCCN Hematopoietic Growth Factors Clinical Practice Guidelines in Oncology (version 2.2023 – March 6, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 7, 2023.
8. The NCCN Management of Immunotherapy-Related Toxicities Clinical Practice Guidelines in Oncology (version 2.2023 – May 9, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 7, 2023.
9. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 1.2023 – September 12, 2022). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 7, 2023.
10. Smith TJ, Bohlke K, Lyman GH, Carson KR, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2015;33(28):3199-3212.
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14. Mitsuyasu R. Prevention of bacterial infections in patients with advanced HIV infection. *AIDS*. 1999;13(Suppl 2):S19-S23.
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16. Andersohn F, Konzen C, Garbe E. Systematic review: Agranulocytosis induced by nonchemotherapy drugs. *Ann Intern Med*. 2007;146:657-665.
17. Beaushesne MF, Shalansky SJ. Nonchemotherapy drug-induced agranulocytosis: A review of 118 patients treated with colony-stimulating factors. *Pharmacother*. 1999;19(3):299-305.
18. Bhatt V, Saleem A. Review: Drug-induced neutropenia-pathophysiology, clinical features, and management. *Ann Clin Lab Sci*. 2004;34(2):131-136.
19. Curtis BR. Drug-induced immune neutropenia/agranulocytosis. *Immunohematology*. 2014;30(2):95-101.
20. Andres E, Mourot-Cottet R. Non-chemotherapy drug-induced neutropenia – an update. *Expert Opin Drug Saf*. 2017;16(11):1235-1242.
21. Andres E, Mourot-Cottet R, Maloisel F, et al. Idiosyncratic drug-induced neutropenia and agranulocytosis. *QJM*. 2017 May;110(5):299-305.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/31/2022
Update	03/21/2023: **Bone Marrow Transplant in a Patient with Cancer Who Received Chemotherapy** diagnosis was updated to remove eviCore routing.	-
Annual Revision	**Other Uses with Supportive Evidence**: **Radiation-Induced Neutropenia** was removed from the policy.	09/20/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Colony Stimulating Factors – Granix Utilization Management Medical Policy
- Granix® (tbo-filgrastim subcutaneous injection – Teva)

REVIEW DATE: 09/20/2023

OVERVIEW

Granix, a leukocyte growth factor, is indicated to reduce the duration of severe neutropenia in adults and pediatric patients ≥ 1 month of age with non-myeloid malignancies receiving myelosuppressive anti-cancer medications associated with a clinically significant incidence of febrile neutropenia.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) addresses the use of Granix in guidelines.

- **Hematopoietic Cell Transplantation:** Guidelines (version 1.2023 – March 31, 2023) recommend filgrastim for hematopoietic cell mobilization for allogeneic or autologous donors as a single agent or in combination with other treatments.[4] NCCN states Granix is an appropriate substitute for filgrastim.
- **Hematopoietic Growth Factors:** Guidelines (version 2.2023 – March 6, 2023) recommend Granix, along with other granulocyte colony stimulating factors (CSFs), for prophylactic use if the patient is receiving anti-cancer medications that are associated with a high (> 20%) incidence of severe neutropenia with fever.[2] Consider CSF therapy for patients with an intermediate (10% to 20%) probability of developing febrile neutropenia based on risk factors. The NCCN guidelines also recommend therapy with CSFs in other scenarios in those given myelosuppressive chemotherapy. Granix is also recommended for mobilization and following hematopoietic cell transplant.
- **Myelodysplastic Syndromes (MDS):** Guidelines (version 1.2023 – September 12, 2022) recommend Granix for use in certain patients with MDS (e.g., neutropenic patients with recurrent or resistant infections, combination use with epoetin alfa or Aranesp® [darbepoetin alfa injection] in patients with anemia).[3]

The American Society of Clinical Oncology clinical practice guidelines for the use of white blood cell growth factors (2015) recommends CSFs to reduce the risk of febrile neutropenia in patients receiving cancer chemotherapy.[5] CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected. The guidelines state CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Granix. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Granix as well as the monitoring required for adverse events and

long-term efficacy, approval requires Granix to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Granix is recommended in those who meet one of the following:

FDA-Approved Indication

1. **Cancer in a Patient Receiving Myelosuppressive Chemotherapy.** Approve for 6 months if the patient meets the following (A and B):
   - **A)** Patient meets ONE of the following (i, ii, iii, or iv):
     - **i.** Patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk is at least 20% based on the chemotherapy regimen); OR
     - **ii.** Patient meets both of the following (a and b):
       - **a)** Patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia, but the risk is less than 20% based on the chemotherapy regimen; AND
       - **b)** Patient has at least one risk factor for febrile neutropenia according to the prescriber; OR
         Note: Examples of risk factors include age ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus (HIV) infection.
     - **iii.** Patient meets both of the following (a and b):
       - **a)** Patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor; AND
         Note: Examples of colony stimulating factors include filgrastim products, pegfilgrastim products, and sargramostim products (e.g., Leukine).
       - **b)** A reduced dose or frequency of chemotherapy may compromise treatment outcome; OR
     - **iv.** Patient who has received chemotherapy has febrile neutropenia and has at least one risk factor for poor clinical outcomes or for developing infection-associated complications according to the prescriber; AND
       Note: Examples of risk factors include sepsis syndrome; age > 65 years; severe neutropenia (absolute neutrophil count [ANC] < 100 cells/mm^3); neutropenia expected to be > 10 days in duration; invasive fungal infection; other clinically documented infections; or prior episode of febrile neutropenia.
   - **B)** The medication is prescribed by or in consultation with an oncologist or hematologist.

   Dosing. Approve up to 5 mcg/kg per day by subcutaneous injection given for up to 14 days per month.

Other Uses with Supportive Evidence

2. **Myelodysplastic Syndromes (MDS).** Approve for 3 months if prescribed by or in consultation with an oncologist or hematologist.

Dosing. Approve up to 5 mcg/kg per day by subcutaneous injection.

3. **Peripheral Blood Progenitor Cell Collection and Therapy.** Approve for 1 month if prescribed by or in consultation with an oncologist, a hematologist, or a physician who specializes in transplantation.

   Dosing. Approve up to 32 mcg/kg per day by subcutaneous injection.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Granix is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Granix® subcutaneous injection [prescribing information]. North Wales, PA: Teva; April 2020.
2. The NCCN Hematopoietic Growth Factors Clinical Practice Guidelines in Oncology (version 2.2023 – March 6, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 7, 2023.
3. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 1.2023 – September 12, 2022). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 7, 2023.
4. The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines in Oncology (version 1.2023 – March 31, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 7, 2023.
5. Smith TJ, Bohlke K, Lyman GH, Carson KR, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2015; 33(28):3199-3212.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/31/2022
Annual Revision	No criteria changes	09/20/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Colony Stimulating Factors – Leukine Utilization Management Medical Policy
- Leukine® (sargramostim intravenous or subcutaneous injection – Partner Therapeutics)

REVIEW DATE: 09/20/2023; selected revision 01/10/2024

OVERVIEW

Leukine, a recombinant human granulocyte-macrophage colony stimulating factor (GM-CSF), is indicated for the following uses:[1]

- **Acute exposure to myelosuppressive doses of radiation,** to increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome).
- **Acute myeloid leukemia** (AML) **following induction chemotherapy**, to shorten the time to neutrophil recovery and to reduce the incidence of severe, life-threatening, or fatal infections in patients ≥ 55 years of age.
- **Allogeneic bone marrow transplantation,** for acceleration of myeloid reconstitution in patients ≥ 2 years of age undergoing allogeneic bone marrow transplantation from human leukocyte antigen (HLA)-matched related donors.
- **Allogeneic or autologous bone marrow transplantation: treatment of delayed neutrophil recovery or graft failure,** treatment of patients ≥ 2 years of age who have undergone allogeneic or autologous bone marrow transplantation in whom neutrophil recovery is delayed or failed.
- **Autologous peripheral blood progenitor cell mobilization and collection,** in adult patients with cancer undergoing autologous hematopoietic stem cell transplantation for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis.
- **Autologous peripheral blood progenitor cell** (PBPC) **and bone marrow transplantation,** for acceleration of myeloid reconstitution after autologous PBPC or bone marrow transplantation in patients ≥ 2 years of age with non-Hodgkin's lymphoma, acute lymphoblastic leukemia, and Hodgkin's lymphoma.

Other Uses with Supportive Evidence

Unituxin® (dinutuximab intravenous infusion) is indicated for use in combination with GM-CSF, interleukin-2, and 13-cis-retinoic acid for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to first-line, multiagent, multimodality therapy.[2] Danyelza® (naxitamab-gqgk intravenous infusion) is indicated for use in combination with GM-CSF, for the treatment of patients 1 year of age and older with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a partial response, minor response, or stable disease to prior therapy.[3]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Leukine. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Leukine as well as the monitoring required for adverse events and

long-term efficacy, approval requires Leukine to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Leukine is recommended in those who meet one of the following:

FDA-Approved Indications

1. **Acute Myeloid Leukemia.** Approve for 6 months if the medication is prescribed by or in consultation with an oncologist or a hematologist.

   Dosing. Approve up to 250 mcg/m^2 per day by intravenous or subcutaneous injection.

2. **Bone Marrow Transplant.** Approve for 1 month if the medication is prescribed by or in consultation with a hematologist, an oncologist, or a physician who specializes in transplantation.

   Dosing. Approve up to 250 mcg/m^2 per day by intravenous injection.

3. **Peripheral Blood Progenitor Cell Collection and Therapy.** Approve for up to 14 days if the medication is prescribed by or in consultation with an oncologist, a hematologist, or a physician that specializes in transplantation.

   Dosing. Approve one of the following (A or B):
   A) Approve up to 500 mcg/m^2 per day given by intravenous or subcutaneous injection; OR
   B) Approve up to 7.5 mcg/kg per day by subcutaneous injection.

4. **Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome).** Approve for 1 month if the medication is prescribed by or in consultation with a physician with expertise in treating acute radiation syndrome.

   Dosing. Approve up to 12 mcg/kg per day as a subcutaneous injection.

Other Uses with Supportive Evidence

5. **Neuroblastoma.** Approve for 6 months if the patient meets the following (A and B):
   A) Patient is receiving Leukine in a regimen that recommends administration in combination with a granulocyte-macrophage colony stimulating factor (GM-CSF); AND
   Note: Examples of medications that are administered in combination with a GM-CSF include Unituxin (dinutuximab intravenous infusion), Danyelza (naxitamab intravenous infusion).
   B) The medication is prescribed by or in consultation with an oncologist.

   Dosing. Approve up to 250 mcg/m^2 per day by intravenous or subcutaneous injection.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Leukine is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Leukine® intravenous or subcutaneous injection [prescribing information]. Lexington, MA: Partner Therapeutics; August 2023.
2. Unituxin™ intravenous infusion [prescribing information]. Silver Springs, MD: United Therapeutic; March 2022.
3. Danyelza® intravenous infusion [prescribing information]. New York, NY: Y-mAbs Therapeutics; November 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/31/2022
Annual Revision	No criteria changes.	09/20/2023
Selected Revision	**Neuroblastoma**: The age requirement for this diagnosis was removed. The requirement that the "Patient is receiving Leukine in a regimen with Unituxin" was updated to "Patient is receiving Leukine in a regimen that recommends administration in combination with a granulocyte-macrophage colony stimulating factor (GM-CSF)" with the addition of the following note "Note: Examples of medications that are administered in combination with a GM-CSF include Unituxin (dinutuximab intravenous infusion), Danyelza (naxitamab intravenous infusion)."	01/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Colony Stimulating Factors – Pegfilgrastim Products Utilization Management Medical Policy

- **Neulasta**® (pegfilgrastim subcutaneous injection – Amgen)
- Fulphila™ (pegfilgrastim-jmdb subcutaneous injection – Mylan)
- Fylnetra® (pegfilgrastim-pbbk subcutaneous injection – Kashiv)
- Nyvepria™ (pegfilgrastim-apgf subcutaneous injection – Pfizer)
- Stimufend® (pegfilgrastim-fpgk subcutaneous injection – Fresenius Kabi)
- Udenyca® (pegfilgrastim-cbqv subcutaneous injection – Coherus)
- Ziextenzo™ (pegfilgrastim-bmez subcutaneous injection – Sandoz)

REVIEW DATE: 09/20/2023

OVERVIEW

Pegfilgrastim, a leukocyte growth factor, is indicated to **decrease the incidence of infection as manifested by febrile neutropenia**, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.[1-5,11,12]

Fulphila, Fylnetra, Nyvepria, Stimufend, Udenyca, and Ziextenzo are biosimilars to Neulasta.[1-5,11,12] Neulasta is additionally indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) addresses the use of pegfilgrastim products in several guidelines.

- **Hematopoietic Cell Transplantation:** Guidelines (version 1.2023 – March 31, 2023) recommend pegfilgrastim for hematopoietic cell mobilization for allogeneic or autologous donors as a single agent or in combination with other treatments.[6]
- **Hematopoietic Growth Factors:** Guidelines (version 2.2023 – March 6, 2023) recommend pegfilgrastim, along with other colony stimulating factors (CSFs), for prophylactic use if the patient is receiving anti-cancer medications that are associated with a high (> 20%) incidence of severe neutropenia with fever.[7] Consider CSF therapy for patients with an intermediate (10% to 20%) probability of developing febrile neutropenia based on risk factors. The NCCN guidelines also recommend therapy with CSFs in other scenarios in those given myelosuppressive chemotherapy.

The American Society of Clinical Oncology clinical practice guidelines for the use of white blood cell growth factors (2015) recommends CSFs to reduce the risk of febrile neutropenia in patients receiving cancer chemotherapy.[8] CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected. The guidelines state CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of pegfilgrastim products. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the

established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with pegfilgrastim as well as the monitoring required for adverse events and long-term efficacy, approval requires pegfilgrastim to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of pegfilgrastim products is recommended in those who meet one of the following:

FDA-Approved Indications

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1. **Cancer in a Patient Receiving Myelosuppressive Chemotherapy**. Approve for 6 months if the patient meets the following (A and B):
   - **A)** Patient meets ONE of the following (i, ii, or iii):
     - **i.** Patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk is at least 20% based on the chemotherapy regimen); OR
     - **ii.** Patient meets both of the following (a and b):
       - **a)** Patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia, but the risk is less than 20% based on the chemotherapy regimen; AND
       - **b)** Patient has at least one risk factor for febrile neutropenia according to the prescriber; OR
         Note: Examples of risk factors include age ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus (HIV) infection.
     - **iii.** Patient meets both of the following (a and b):
       - **a)** Patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor; AND
         Note: Examples of colony-stimulating factors include filgrastim products, pegfilgrastim products, and sargramostim products (e.g., Leukine).
       - **b)** A reduced dose or frequency of chemotherapy may compromise treatment outcome; AND
   - **B)** The medication is prescribed by or in consultation with an oncologist or hematologist.

   Dosing. Approve up to 6 mg given by subcutaneous injection no more frequently than once every 2 weeks.

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2. **Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome).** Approve for 1 month if the agent is prescribed by or in consultation with a physician with expertise in treating acute radiation syndrome.

   Dosing. Approve two doses of up to 6 mg by subcutaneous injection given no more frequently than 1 week apart.

Other Uses with Supportive Evidence

3. **Peripheral Blood Progenitor Cell Transplantation (PBPC) in Patients with Cancer.** Approve one dose if prescribed by or in consultation with an oncologist, a hematologist, or a physician who specializes in transplantation.

   Dosing. Approve one dose as follows (A or B):
   A) In adults 6 mg by subcutaneous injection one time; OR
   B) In children up to 200 mcg/kg by subcutaneous injection.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of pegfilgrastim products is not recommended in the following situations:

1. **Myelodysplastic Syndrome (MDS).** Only limited data report use of pegfilgrastim for patients with MDS.[9] Guidelines from the NCCN for MDS (version 1.2023 – September 12, 2022) do not mention use of pegfilgrastim in this patient population.[10]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Neulasta® subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; March 2021.
2. Fulphila® subcutaneous injection [prescribing information]. Rockford, IL: Mylan; October 2021.
3. Udenyca® subcutaneous injection [prescribing information]. Redwood City, CA: Coherus BioSciences; March 2023.
4. Ziextenzo™ subcutaneous injection [prescribing information]. Princeton, NJ: Sandoz; March 2021.
5. Nyvepria™ subcutaneous injection [prescribing information]. New York, NY: Pfizer; June 2022.
6. The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines in Oncology (version 1.2023 – March 31, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 7, 2023.
7. The NCCN Hematopoietic Growth Factors Clinical Practice Guidelines in Oncology (version 2.2023 – March 6, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 7, 2023.
8. Smith TJ, Bohlke K, Lyman GH, Carson KR, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2015;33(28):3199-3212.
9. Jakob A, Hirsch FW, Engelhardt M. Successful treatment of a patient with myelodysplastic syndrome (RAEB) with darbepoetin alfa in combination with pegfilgrastim. *Ann Hematol*. 2005;84(10):694-695.
10. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 1.2023 – September 12, 2022). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 7, 2023.
11. Fylnetra® subcutaneous injection [prescribing information]. Piscataway, NJ: Kashiv; May 2022.
12. Stimufend® subcutaneous injection [prescribing information]. Lake Zurich, IL: Fresenius Kabi; September 2022.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/31/2022
Selected Revision	Fylnetra, a biosimilar to Neulasta, was added to the policy.	10/05/2022
Selected Revision	Stimufend, a biosimilar to Neulasta, was added to the policy.	01/04/2023
Annual Revision	No criteria changes.	09/20/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Colony Stimulating Factors – Rolvedon Utilization Management Medical Policy
- Rolvedon™ (eflapegrastim-xnst subcutaneous injection – Spectrum)

REVIEW DATE: 09/20/2023; selected revision 12/20/2023

OVERVIEW

Rolvedon, a leukocyte growth factor, is indicated to **decrease the incidence of infection, as manifested by febrile neutropenia**, in adults with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.[1]

Limitation of use: Rolvedon is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.[1]

Safety and effectiveness in pediatric patients have not been established.[1]

Guidelines

According to the National Comprehensive Cancer Network (NCCN) guidelines for **hematopoietic growth factors** (version 2.2024 – December 12, 2023), evaluation of risk for febrile neutropenia following chemotherapy in adults with solid tumors and non-myeloid malignancies should occur prior to the first chemotherapy cycle.[2] For a patient at high risk (> 20% risk), granulocyte colony-stimulating factor (G-CSF) is recommended (category 1). For a patient at intermediate risk (10% to 20% risk), consider G-CSF if the patient has at least one of the following risk factors: including prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver dysfunction; renal dysfunction; and age > 65 years receiving full chemotherapy dose intensity (category 2A). Evaluation prior to second and subsequent chemotherapy cycles should also be completed and patients who experienced febrile neutropenia or a dose-limiting neutropenic event without prior use of G-CSFs in which a reduction in dose or frequency is not appropriate, the use of G-CSFs should be considered (category 2A). Recommended G-CSFs include filgrastim (category 1), Granix® (tbo-filgrastim subcutaneous injection) [category 1], pegfilgrastim (category 1), Rolvedon (category 2A), and Ryzneuta® (efbemalenograstim alfa-vuxw subcutaneous injection) [category 2A]. It is noted that the long-acting G-CSFs, pegfilgrastim, Rolvedon, and Ryzneuta® (efbemalenograstim alfa-vuxw subcutaneous injection), have only been studied for prophylactic use, not for treatment of febrile neutropenia. For treatment of a patient with radiation-induced myelosuppression following a radiologic/nuclear incident, therapeutic use of filgrastim, pegfilgrastim, Granix® (tbo-filgrastim subcutaneous injection), Leukine® (sargramostim subcutaneous injection), Rolvedon, or Ryzneuta® (efbemalenograstim alfa-vuxw subcutaneous injection) may be used (category 2A). Of note, throughout the recommendations, it is acknowledged that an FDA-approved biosimilar is an appropriate substitute for filgrastim or pegfilgrastim.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Rolvedon. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is

authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rolvedon as well as the monitoring required for adverse events and long-term efficacy, approval requires Rolvedon to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rolvedon is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Cancer in a Patient Receiving Myelosuppressive Chemotherapy**. Approve for 6 months if the patient meets the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets ONE of the following (i, ii, or iii):
     - **i.** Patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk is at least 20% based on the chemotherapy regimen); OR
     - **ii.** Patient meets both of the following (a and b):
       - **a)** Patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia, but the risk is less than 20% based on the chemotherapy regimen; AND
       - **b)** Patient has at least one risk factor for febrile neutropenia according to the prescriber; OR
         Note: Examples of risk factors include age ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus (HIV) infection.
     - **iii.** Patient meets both of the following (a and b):
       - **a)** Patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor; AND
         Note: Examples of colony stimulating factors include filgrastim products, pegfilgrastim products, and Ryzneuta.
       - **b)** A reduced dose or frequency of chemotherapy may compromise treatment outcome; AND
   - **C)** The medication is prescribed by or in consultation with an oncologist or hematologist.

   Dosing. Approve 13.2 mg by subcutaneous injection no more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rolvedon is not recommended in the following situations:

1. **Peripheral Blood Progenitor Cell Collection and Therapy.** As a limitation of use in the Rolvedon prescribing information, it is noted that Rolvedon is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.[1]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Rolvedon™ subcutaneous injection [prescribing information]. Irvine, CA: Spectrum; June 2023.
2. The NCCN Hematopoietic Growth Factors Clinical Practice Guidelines in Oncology (version 2.2024 – December 12, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 12, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/12/2022
Update	**12/06/2022:** No criteria changes. The Overview section was updated to reflect National Comprehensive Cancer Network guidelines with the placement of Rolvedon.	--
Early Annual Revision	No criteria changes.	09/20/2023
Selected Revision	**Cancer in a Patient Receiving Myelosuppressive Chemotherapy**: The criterion for "Patient who has received chemotherapy has febrile neutropenia and has at least one risk factor for poor clinical outcomes or for developing infection-associated complications according to the prescriber" was removed. The note providing examples of colony-stimulating factors was updated to add Ryzneuta and remove sargramostim products (e.g. Leukine).	12/20/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Colony Stimulating Factors – Ryzneuta Utilization Management Medical Policy
- Ryzneuta® (efbemalenograstim alfa-vuxw subcutaneous injection – Evive)

REVIEW DATE: 12/20/2023

OVERVIEW

Ryzneuta, a leukocyte growth factor, is indicated to **decrease the incidence of infection, as manifested by febrile neutropenia**, in adults with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.[1]

Limitation of use: Ryzneuta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.[1]

Safety and effectiveness in pediatric patients have not been established.[1]

Guidelines

According to the National Comprehensive Cancer Network (NCCN) guidelines for **hematopoietic growth factors** (version 2.2024 – December 12, 2023), evaluation of risk for febrile neutropenia following chemotherapy in adults with solid tumors and non-myeloid malignancies should occur prior to the first chemotherapy cycle.[2] For a patient at high risk (> 20% risk), granulocyte colony-stimulating factor (G-CSF) is recommended (category 1). For a patient at intermediate risk (10% to 20% risk), consider G-CSF if the patient has at least one of the following risk factors: including prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver dysfunction; renal dysfunction; and age > 65 years receiving full chemotherapy dose intensity (category 2A). Evaluation prior to second and subsequent chemotherapy cycles should also be completed and patients who experienced febrile neutropenia or a dose-limiting neutropenic event without prior use of G-CSFs in which a reduction in dose or frequency is not appropriate, the use of G-CSFs should be considered (category 2A). Recommended G-CSFs include filgrastim (category 1), Granix® (tbo-filgrastim subcutaneous injection) [category 1], pegfilgrastim (category 1), Rolvedon™ (eflapegrastim-xnst subcutaneous injection) [category 2A], and Ryzneuta (category 2A). It is noted that the long-acting G-CSFs, pegfilgrastim, Rolvedon, and Ryzneuta, have only been studied for prophylactic use, not for treatment of febrile neutropenia. For treatment of a patient with radiation-induced myelosuppression following a radiologic/nuclear incident, therapeutic use of filgrastim, pegfilgrastim, Granix® (tbo-filgrastim subcutaneous injection), Leukine® (sargramostim subcutaneous injection), Rolvedon™ (eflapegrastim-xnst subcutaneous injection), or Ryzneuta may be used (category 2A). Of note, throughout the recommendations, it is acknowledged that an FDA-approved biosimilar is an appropriate substitute for filgrastim or pegfilgrastim.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Ryzneuta. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is

authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ryzneuta as well as the monitoring required for adverse events and long-term efficacy, approval requires Ryzneuta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ryzneuta is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Cancer in a Patient Receiving Myelosuppressive Chemotherapy**. Approve for 6 months if the patient meets the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets ONE of the following (i, ii, or iii):
     - **i.** Patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk is at least 20% based on the chemotherapy regimen); OR
     - **ii.** Patient meets both of the following (a and b):
       - **a)** Patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia, but the risk is less than 20% based on the chemotherapy regimen; AND
       - **b)** Patient has at least ONE risk factor for febrile neutropenia according to the prescriber; OR
         Note: Examples of risk factors include age ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus (HIV) infection.
     - **iii.** Patient meets both of the following (a and b):
       - **a)** Patient had a neutropenic complication from the previous chemotherapy cycle and did NOT receive prophylaxis with a colony stimulating factor; AND
         Note: Examples of colony stimulating factors include filgrastim products, pegfilgrastim products, and Rolvedon.
       - **b)** A reduced dose or frequency of chemotherapy may compromise treatment outcome; AND
   - **C)** The medication is prescribed by or in consultation with an oncologist or hematologist.

   Dosing. Approve 20 mg by subcutaneous injection no more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ryzneuta is not recommended in the following situations:

1. **Peripheral Blood Progenitor Cell Collection and Therapy.** As a limitation of use in the Ryzneuta prescribing information, it is noted that Ryzneuta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.[1]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Ryzneuta® subcutaneous injection [prescribing information]. Singapore: Evive; November 2023.
2. The NCCN Hematopoietic Growth Factors Clinical Practice Guidelines in Oncology (version 2.2024 – December 12, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 12, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/20/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT ADVANCED CLINICAL EVALUATION MEDICAL POLICY

POLICY: Complement Inhibitors – Soliris Utilization Management Medical Policy – Advanced Clinical Evaluation
- Soliris® (eculizumab intravenous infusion – Alexion)

REVIEW DATE: 09/20/2023; selected revision 01/17/2024, 03/27/2024

OVERVIEW

Soliris, a complement inhibitor, is indicated for the following uses:[1]

- **Atypical hemolytic uremic syndrome** (aHUS), to inhibit complement-mediated thrombotic microangiopathy.
  Limitation of Use. Soliris is not indicated for the treatment of patients with Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome.
- **Generalized myasthenia gravis** (gMG), in adults who are anti-acetylcholine receptor (AChR) antibody-positive.
- **Neuromyelitis optica spectrum disorder** (NMOSD), in adults who are anti-aquaporin-4 (AQP4) antibody positive.
- **Paroxysmal nocturnal hemoglobinuria** (PNH), to reduce hemolysis.

The Soliris prescribing information has a Boxed Warning about serious meningococcal infections.[1] Soliris is only available through a restricted access program, Soliris Risk Evaluation and Mitigation Strategy (REMS).

The safety and effectiveness of Soliris for the treatment of gMG, NMOSD, and PNH in pediatric patients have not been established.[1] The safety and effectiveness of Soliris in pediatric patients for aHUS is supported by evidence from four adequate and well-controlled clinical studies assessing the safety and effectiveness of Soliris for the treatment of aHUS.

Disease Overview

Hemolytic uremic syndrome (HUS) is defined as the triad of non-immune hemolytic anemia, thrombocytopenia, and acute renal failure, in which the underlying lesions are mediated by systemic thrombotic microangiopathy.[2] aHUS should be distinguished from a more common condition referred to as typical HUS.[3] aHUS is a sub-type of HUS in which thrombotic microangiopathy is the consequence of endothelial damage in the microvasculature of the kidneys and other organs due to a dysregulation of the activity of the complement system. The typical form is caused by infection with certain strains of *E. coli* bacteria that produce toxic substances called Shiga-like toxins; Soliris is not indicated for the treatment of Shiga toxin *E. coli*-related hemolytic uremic syndrome.[1-3]

Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs.[4] The hallmark of MG is muscle weakness that worsens after periods of activity and improves after periods of rest. Acquired MG results from the binding of autoantibodies to components of the neuromuscular junction, most commonly the AChR.[5] Soliris was studied in patients with gMG with anti-AChR antibodies with a Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV and a Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score ≥ 6.[1]

NMOSD is a rare, relapsing, autoimmune disorder of the brain and spinal cord with optic neuritis and/or myelitis as predominate characteristic symptoms.[6] NMOSD often causes significant, permanent damage to vision and/or spinal cord function resulting in blindness or impaired mobility.[7] Patients may experience pain, paralysis, loss of bowel and bladder control, loss of visual acuity, uncontrolled motor functions, and complications can cause death.

PNH is a rare, genetic disorder of hematopoietic stem cells.[8,9] The mutation in the X-linked gene phosphatidylinositol glycan class A (PIGA) results in a deficiency in the glycosylphosphatidylinositol (GPI) protein, which is responsible for anchoring other protein moieties to the surface of the erythrocytes. Loss of anchoring of these proteins causes cells to hemolyze and leads to complications such as hemolytic anemia, thrombosis, and peripheral blood cytopenias. PNH is a clinical diagnosis that should be confirmed with peripheral blood flow cytometry to detect the absence or severe deficiency of GPI-anchored proteins on at least two cell lineages.[8,10] Prior to the availability of complement inhibitors, only supportive measures, in terms of managing the cytopenias and controlling thrombotic risk were available. Supportive measures include platelet transfusion, immunosuppressive therapy for patients with bone marrow failure, use of erythropoietin for anemias, and aggressive anticoagulation.

Recommendations

There are no formal guidelines for treatment of aHUS.

A consensus statement for the diagnosis and treatment of PNH was published in 2021.[8] Treatment options for PNH are supportive care, allogeneic hematopoietic stem cell transplantation, and complement blockade by the anti-C5 monoclonal antibody (Soliris). Supportive care include use of oral iron to replace the large urinary losses; folate and vitamin B_{12} supplementation; red blood cell transfusion when these measures do not maintain adequate hemoglobin levels; use of antibiotics to treat bacterial infections as soon as possible since infections can exacerbate hemolytic crises in patients with PNH; use of corticosteroids to reduce the severity and duration of the hemolytic crises; use of Soliris as primary prophylaxis in patients with high PNH clone size (granulocyte close > 50%), high level of D dimer, pregnancy, perioperative condition and other associated thrombophilia risk factors; and use of immunosuppressives in patients with PNH and aplastic anemia and bone marrow deficiency.

An international consensus guidance for the management of MG was published in 2016.[5] The consensus guidance recommends pyridostigmine for the initial treatment in most patients with MG. The ability to discontinue pyridostigmine can indicate that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or immunosuppressant therapy should be used in all patients with MG who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal immunosuppressant agents used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Plasma exchange and intravenous immunoglobulin can be used as short-term treatments in certain patients. A 2020 update to this consensus guidance provides new recommendations for methotrexate, rituximab, and Soliris.[11] All recommendations should be considered extensions or additions to recommendations made in the initial international consensus guidance. Oral methotrexate may be considered as a steroid-sparing agent in patients with gMG who have not tolerated or responded to steroid-sparing agents. Rituximab should be considered as an early therapeutic option in patients with anti-muscle specific kinase antibody-positive MG who have an unsatisfactory response to initial immunotherapy. Soliris should be considered in the treatment of severe, refractory, anti-AChR antibody-positive MG.

The Neuromyelitis Optica Study Group (NEMOS) published revised recommendations for the treatment of NMOSD in 2024.[12] The standard of care for the treatment of NMOSD attacks (for both AQP4-IgG-positive

and double-negative cases) are high-dose glucocorticoids and/or apheresis therapy. Long term immunotherapy is recommended for patients with AQP4-IgG-positive NMOSD. NEMOS notes the first-choice therapies for the treatment of AQP4-IgG-positive NMOSD are Soliris, Ultomiris® (ravulizumab-cwyz intravenous infusion and subcutaneous injection) [awaiting FDA approval], Enspryng® (satralizumab-mwge subcutaneous injection), Uplizna® (inebilizumab-cdon intravenous infusion), and rituximab. The order of preference for these therapies is unclear and further comparative trials and real-world data are needed. The choice of treatment is dependent on several factors, including disease activity and severity, mode and onset of action, possibility to combine it with immunosuppressive drugs, effect on autoimmune and other comorbidities, gender (family planning issues), frequency and route of administration, side effect profile as well as patient and physician preference. In general, if a patient fails a first-choice treatment, another first-choice treatment should be tried; other options include use of a second-choice treatment (azathioprine, mycophenolate mofetil, low-dose oral glucocorticoids) or the addition of a second-choice treatment to the regimen.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Soliris. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is provided in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Soliris as well as the monitoring required for adverse events and long-term efficacy, approval requires Soliris to be prescribed by or in consultation with a physician who specializes in the condition being treated. All reviews will be forwarded to a Physician Medical Director for evaluation.

Documentation: Documentation is required for use of Soliris as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Complement Inhibitors – Soliris Advanced Clinical Evaluation Medical Policy*, and who is requesting reauthorization, the criteria utilized do NOT require re-submission of documentation for reauthorization, except for the criterion requiring documentation of a continued benefit from Soliris therapy.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Soliris is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Atypical Hemolytic Uremic Syndrome.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** Patient does not have Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome; AND
   - **B)** The medication is being prescribed by or in consultation with a nephrologist.

   Dosing. Approve if the dose meets ONE of the following (A or B):
   - **A)** For patients ≥ 18 years of age, the dose is administered intravenously and meets ONE of the following (i or ii):

i. The dose is ≤ 900 mg weekly for the first 4 weeks; OR
ii. The dose is ≤ 1,200 mg every 2 weeks thereafter.

B) For patients < 18 years of age, the dose is administered intravenously and meets ONE of the following (i, ii, iii, iv, or v):
i. ≥ 40 kg: 900 mg weekly x 4 doses, 1,200 mg at week 5; then 1,200 mg every 2 weeks; OR
ii. 30 kg to < 40 kg: 600 mg weekly x 2 doses, 900 mg at week 3; then 900 mg every 2 weeks; OR
iii. 20 kg to < 30 kg: 600 mg weekly x 2 doses, 600 mg at week 3; then 600 mg every 2 weeks; OR
iv. 10 kg to < 20 kg: 600 mg weekly x 1 dose, 300 mg at week 2; then 300 mg every 2 weeks; OR
v. 5 kg to < 10 kg: 300 mg weekly x 1 dose, 300 mg at week 2; then 300 mg every 3 weeks.

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2. Generalized Myasthenia Gravis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):
i. Patient is ≥ 18 years of age; AND
ii. Patient has confirmed anti-acetylcholine receptor antibody-positive generalized myasthenia gravis **[documentation required]**; AND
iii. Patient meets BOTH of the following (a and b):
a) Myasthenia Gravis Foundation of America classification of II to IV; AND
b) Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 6; AND
iv. Patient meets ONE of the following (a or b):
a) Patient previously received or is currently receiving pyridostigmine; OR
b) Patient has had inadequate efficacy, a contraindication, or significant intolerance to pyridostigmine; AND
v. Patient meets ONE of the following (a or b):
a) Patient previously received or is currently receiving two different immunosuppressant therapies for ≥ 1 year; OR
b) Patient had inadequate efficacy, a contraindication, or significant intolerance to two different immunosuppressant therapies; AND
Note: Examples of immunosuppressant therapies tried include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, and cyclophosphamide.
vi. Patient has evidence of unresolved symptoms of generalized myasthenia gravis; AND
Note: Evidence of unresolved symptoms of generalized myasthenia gravis includes difficulty swallowing, difficulty breathing, and a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility).
vii. The medication is being prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Soliris. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
i. Patient is ≥ 18 years of age; AND
ii. Patient is continuing to derive benefit from Soliris, according to the prescriber; AND
Note: Examples of derived benefit include reductions in exacerbations of myasthenia gravis, improvements in speech, swallowing, mobility, and respiratory function.
iii. The medication is being prescribed by or in consultation with a neurologist.

Dosing. Approve if the dose is administered intravenously and meets ONE of the following (A or B):
A) The dose is ≤ 900 mg weekly for the first 4 weeks; OR

B) The dose is ≤ 1,200 mg every 2 weeks thereafter.

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3. Neuromyelitis Optica Spectrum Disorder. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Diagnosis was confirmed by a positive blood serum test for anti-aquaporin-4 antibody **[documentation required]**; AND
- **iii.** The medication is being prescribed by or in consultation with a neurologist.

B) Patients is Currently Receiving Soliris. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Diagnosis was confirmed by positive blood serum test for anti-aquaporin-4 antibody; AND
- **iii.** According to the prescriber, patient has had clinical benefit from the use of Soliris; AND
  Note: Examples of clinical benefit include reduction in relapse rate, reduction in symptoms (e.g., pain, fatigue, motor function), and a slowing progression in symptoms.
- **iv.** The medication is being prescribed by or in consultation with a neurologist.

Dosing. Approve if the dose is administered intravenously and meets ONE of the following (A or B):

A) The dose is ≤ 900 mg weekly for the first 4 weeks; OR

B) The dose is ≤ 1,200 mg every 2 weeks thereafter.

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4. Paroxysmal Nocturnal Hemoglobinuria. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Diagnosis was confirmed by peripheral blood flow cytometry results showing the absence or deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins on at least two cell lineages **[documentation required]**; AND
- **iii.** The medication is being prescribed by or in consultation with a hematologist; OR

B) Patient is Currently Receiving Soliris. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient is continuing to derive benefit from Soliris, according to the prescriber; AND
  Note: Examples of derived benefit include stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis.
- **iii.** The medication is prescribed by or in consultation with a hematologist.

Dosing. Approve if the dose is administered intravenously and meets ONE of the following (A or B):

A) The dose is ≤ 600 mg weekly for the first 4 weeks; OR

B) The dose is ≤ 900 mg every 2 weeks thereafter.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Soliris is not recommended in the following situations:

1. Concomitant Use with Empaveli > 4 Weeks. Concomitant use of Soliris with Empaveli is not recommended. However, to reduce the risk of hemolysis from abrupt treatment discontinuation in a

patient switching from Soliris to Empaveli, patient should use both therapies for 4 weeks; after which, Soliris is discontinued and patient is continued on Empaveli monotherapy.

2. **Concomitant Use with a Rituximab Product, a Neonatal Fc Receptor Blocker, Enspryng (satralizumab-mwge subcutaneous injection), Fabhalta (iptacopan capsule), Ultomiris (ravulizumab-cwzy intravenous infusion or subcutaneous injection), Uplizna (inebilizumab-cdon intravenous infusion), or Zilbrysq (zilucoplan subcutaneous injection).** There is no evidence to support concomitant use of Soliris with a rituximab product, a neonatal Fc receptor blocker, Enspryng, Fabhalta, Ultomiris, Uplizna, or Zilbrysq,
   Note: Examples of Neonatal Fc receptor blockers are: Vyvgart (efgartigimod alfa-fcab intravenous infusion), Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection), and Rystiggo [rozanolixizumab-noli subcutaneous infusion).

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Conditions Not Recommended for Approval:** The conditions were combined and the title was changed to "**Concurrent Use with Another Complement Inhibitor, a Rituximab Product, Enspryng (satralizumab-mwge subcutaneous injection), or Vyvgart (efgartigimod alfa-fcab intravenous infusion)**". Vyvgart and Ultomiris subcutaneous were added to this condition.	08/31/2022
Selected Revision	**Generalized Myasthenia Gravis:** Revised the Myasthenia Gravis Activities of Daily Living (MG-ADL) score to ≥ 6 to align with the prescribing information; previously it was MG-ADL ≥ 5.	05/31/2023
Early Annual Revision	**Generalized Myasthenia Gravis:** Initial therapy, for the criterion regarding evidence of unresolved symptoms of generalized myasthenia gravis, the examples of evidence of unresolved symptoms of generalized myasthenia gravis were moved to a Note. **Conditions Not Recommended for Approval:** Criterion regarding concomitant use of Soliris with another complement inhibitor, a rituximab product, Enspryng, Ultomiris, Uplizna, or Vyvgart was revised to include other neonatal Fc receptor blockers (Vyvgart Hytrulo, Rystiggo). Examples of neonatal Fc receptor blockers (including Vyvgart) were added as a Note. In addition, Empaveli was removed from this statement and added as a separate criterion: Concomitant use with Empaveli > 4 weeks.	09/20/2023
Selected revision	**Conditions Not Recommended for Approval:** Criterion regarding concomitant use with other agents was revised to include Fabhalta and Zilbrysq.	01/17/2024
Selected Revision	**Neuromyelitis Optica Spectrum Disorder – Initial Therapy:** Removed criterion that requires prior use of two systemic therapies and criterion that patient has had a history of at least one relapse in the last 12 months or two relapses in the last 2 years. Soliris is listed as a first-line treatment option in the Neuromyelitis Optica Study Group (NEMOS) recommendations for the treatment of Neuromyelitis Optica Spectrum Disorder (2024).	03/27/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Complement Inhibitors – Soliris Utilization Management Medical Policy
- Soliris® (eculizumab intravenous infusion – Alexion)

REVIEW DATE: 09/20/2023; selected revision 01/17/2024, 03/20/2024

OVERVIEW

Soliris, a complement inhibitor, is indicated for the following uses:[1]

- **Atypical hemolytic uremic syndrome** (aHUS), to inhibit complement-mediated thrombotic microangiopathy.
  Limitation of Use. Soliris is not indicated for the treatment of patients with Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome.
- **Generalized myasthenia gravis** (gMG), in adults who are anti-acetylcholine receptor (AChR) antibody-positive.
- **Neuromyelitis optica spectrum disorder** (NMOSD), in adults who are anti-aquaporin-4 (AQP4) antibody positive.
- **Paroxysmal nocturnal hemoglobinuria** (PNH), to reduce hemolysis.

The Soliris prescribing information has a Boxed Warning about serious meningococcal infections.[1] Soliris is only available through a restricted access program, Soliris Risk Evaluation and Mitigation Strategy (REMS).

The safety and effectiveness of Soliris for the treatment of PNH, gMG, and NMOSD in pediatric patients have not been established.[1] The safety and effectiveness of Soliris in pediatric patients for aHUS is supported by evidence from four adequate and well-controlled clinical studies assessing the safety and effectiveness of Soliris for the treatment of aHUS.

Disease Overview

Hemolytic uremic syndrome (HUS) is defined as the triad of non-immune hemolytic anemia, thrombocytopenia, and acute renal failure, in which the underlying lesions are mediated by systemic thrombotic microangiopathy.[2] aHUS should be distinguished from a more common condition referred to as typical HUS.[3] aHUS is a sub-type of HUS in which thrombotic microangiopathy is the consequence of endothelial damage in the microvasculature of the kidneys and other organs due to a dysregulation of the activity of the complement system. The typical form is caused by infection with certain strains of *E. coli* bacteria that produce toxic substances called Shiga-like toxins; Soliris is not indicated for the treatment of Shiga toxin *E. coli*-related hemolytic uremic syndrome.[1-3]

Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs.[4] The hallmark of MG is muscle weakness that worsens after periods of activity and improves after periods of rest. Acquired MG results from the binding of autoantibodies to components of the neuromuscular junction, most commonly the AChR.[5] Soliris was studied in patients with gMG with anti-AChR antibodies with a Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV and a Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score ≥ 6.[1]

NMOSD is a rare, relapsing, autoimmune disorder of the brain and spinal cord with optic neuritis and/or myelitis as predominate characteristic symptoms.[6] NMOSD often causes significant, permanent damage to vision and/or spinal cord function resulting in blindness or impaired mobility.[7] Patients may experience pain, paralysis, loss of bowel and bladder control, loss of visual acuity, uncontrolled motor functions, and complications can cause death.

PNH is a rare, genetic disorder of hematopoietic stem cells.[8,9] The mutation in the X-linked gene phosphatidylinositol glycan class A (PIGA) results in a deficiency in the glycosylphosphatidylinositol (GPI) protein, which is responsible for anchoring other protein moieties to the surface of the erythrocytes. Loss of anchoring of these proteins causes cells to hemolyze and leads to complications such as hemolytic anemia, thrombosis, and peripheral blood cytopenias. PNH is a clinical diagnosis that should be confirmed with peripheral blood flow cytometry to detect the absence or severe deficiency of GPI-anchored proteins on at least two cell lineages.[8,10] Prior to the availability of complement inhibitors, only supportive measures, in terms of managing the cytopenias and controlling thrombotic risk were available. Supportive measures include platelet transfusion, immunosuppressive therapy for patients with bone marrow failure, use of erythropoietin for anemias, and aggressive anticoagulation.

Recommendations

There are no formal guidelines for treatment of aHUS.

A consensus statement for the diagnosis and treatment of PNH was published in 2021.[8] Treatment options for PNH are supportive care, allogeneic hematopoietic stem cell transplantation, and complement blockade by the anti-C5 monoclonal antibody (Soliris). Supportive care include use of oral iron to replace the large urinary losses; folate and vitamin B_{12} supplementation; red blood cell transfusion when these measures do not maintain adequate hemoglobin levels; use of antibiotics to treat bacterial infections as soon as possible since infections can exacerbate hemolytic crises in patients with PNH; use of corticosteroids to reduce the severity and duration of the hemolytic crises; use of Soliris as primary prophylaxis in patients with high PNH clone size (granulocyte close > 50%), high level of D dimer, pregnancy, perioperative condition, and other associated thrombophilia risk factors; and use of immunosuppressives in patients with PNH and aplastic anemia and bone marrow deficiency.

An international consensus guidance for the management of MG was published in 2016.[5] The consensus guidance recommends pyridostigmine for the initial treatment in most patients with MG. The ability to discontinue pyridostigmine can indicate that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or immunosuppressant therapy should be used in all patients with MG who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal immunosuppressant agents used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Plasma exchange and intravenous immunoglobulin can be used as short-term treatments in certain patients. A 2020 update to this consensus guidance provides new recommendations for methotrexate, rituximab, and Soliris.[11] All recommendations should be considered extensions or additions to recommendations made in the initial international consensus guidance. Oral methotrexate may be considered as a steroid-sparing agent in patients with gMG who have not tolerated or responded to steroid-sparing agents. Rituximab should be considered as an early therapeutic option in patients with anti-muscle specific kinase antibody-positive MG who have an unsatisfactory response to initial immunotherapy. Soliris should be considered in the treatment of severe, refractory, anti-AChR antibody-positive MG.

The Neuromyelitis Optica Study Group (NEMOS) published revised recommendations for the treatment of NMOSD in 2024.[12] The standard of care for the treatment of NMOSD attacks (for both AQP4-IgG-positive and double-negative cases) are high-dose glucocorticoids and/or apheresis therapy. Long term immunotherapy is recommended for patients with AQP4-IgG-positive NMOSD. NEMOS notes the first-choice therapies for the treatment of AQP4-IgG-positive NMOSD are Soliris, Ultomiris® (ravulizumab-cwyz intravenous infusion and subcutaneous injection) [awaiting FDA approval], Enspryng® (satralizumab-mwge subcutaneous injection), Uplizna® (inebilizumab-cdon intravenous infusion), and rituximab. The order of preference for these therapies is unclear and further comparative trials and real-world data are needed. The choice of treatment is dependent on several factors, including disease activity and severity, mode and onset of action, possibility to combine it with immunosuppressive drugs, effect on autoimmune and other comorbidities, gender (family planning issues), frequency and route of administration, side effect profile, as well as patient and physician preference. In general, if a patient fails a first-choice treatment, another first-choice treatment should be tried; other options include use of a second-choice treatment (azathioprine, mycophenolate mofetil, low-dose oral glucocorticoids) or the addition of a second-choice treatment to the regimen.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Soliris. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the dosing interval is provided in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Soliris as well as the monitoring required for adverse events and long-term efficacy, approval requires Soliris to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Soliris is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. Atypical Hemolytic Uremic Syndrome. Approve for 1 year if the patient meets BOTH of the following (A and B):
- **A)** Patient does not have Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome; AND
- **B)** The medication is being prescribed by or in consultation with a nephrologist.

Dosing. Approve if the dose meets ONE of the following (A or B):
- **A)** For patients ≥ 18 years of age, the dose is administered intravenously and meets ONE of the following (i or ii):
  - **i.** The dose is ≤ 900 mg weekly for the first 4 weeks; OR
  - **ii.** The dose is ≤ 1,200 mg every 2 weeks thereafter.
- **B)** For patients < 18 years of age, the dose is administered intravenously and meets ONE of the following (i, ii, iii, iv, or v):
  - **i.** ≥ 40 kg: 900 mg weekly x 4 doses, 1,200 mg at week 5; then 1,200 mg every 2 weeks; OR

ii. 30 kg to < 40 kg: 600 mg weekly x 2 doses, 900 mg at week 3; then 900 mg every 2 weeks; OR
iii. 20 kg to < 30 kg: 600 mg weekly x 2 doses, 600 mg at week 3; then 600 mg every 2 weeks; OR
iv. 10 kg to < 20 kg: 600 mg weekly x 1 dose, 300 mg at week 2; then 300 mg every 2 weeks; OR
v. 5 kg to < 10 kg: 300 mg weekly x 1 dose, 300 mg at week 2; then 300 mg every 3 weeks.

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2. Generalized Myasthenia Gravis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):
i. Patient is ≥ 18 years of age; AND
ii. Patient has confirmed anti-acetylcholine receptor antibody-positive generalized myasthenia gravis; AND
iii. Patient meets BOTH of the following (a and b):
a) Myasthenia Gravis Foundation of America classification of II to IV; AND
b) Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 6; AND
iv. Patient meets ONE of the following (a or b):
a) Patient previously received or is currently receiving pyridostigmine; OR
b) Patient has had inadequate efficacy, a contraindication, or significant intolerance to pyridostigmine; AND
v. Patient meets ONE of the following (a or b):
a) Patient previously received or is currently receiving two different immunosuppressant therapies for ≥ 1 year; OR
b) Patient had inadequate efficacy, a contraindication, or significant intolerance to two different immunosuppressant therapies; AND
Note: Examples of immunosuppressant therapies tried include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, and cyclophosphamide.
vi. Patient has evidence of unresolved symptoms of generalized myasthenia gravis; AND
Note: Evidence of unresolved symptoms of generalized myasthenia gravis includes difficulty swallowing, difficulty breathing, and a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility).
vii. The medication is being prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Soliris. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
i. Patient is ≥ 18 years of age; AND
ii. Patient is continuing to derive benefit from Soliris, according to the prescriber.
Note: Examples of derived benefit include reductions in exacerbations of myasthenia gravis, improvements in speech, swallowing, mobility, and respiratory function.
iii. The medication is being prescribed by or in consultation with a neurologist.

Dosing. Approve if the dose is administered intravenously and meets ONE of the following (A or B):
A) The dose is ≤ 900 mg weekly for the first 4 weeks; OR
B) The dose is ≤ 1,200 mg every 2 weeks thereafter.

3. **Neuromyelitis Optica Spectrum Disorder**. Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Diagnosis was confirmed by a positive blood serum test for anti-aquaporin-4 antibody; AND
     - **iii.** The medication is being prescribed by or in consultation with a neurologist.
   - **B)** Patients is Currently Receiving Soliris. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Diagnosis was confirmed by positive blood serum test for anti-aquaporin-4 antibody; AND
     - **iii.** According to the prescriber, patient has had clinical benefit from the use of Soliris; AND
       Note: Examples of clinical benefit include reduction in relapse rate, reduction in symptoms (e.g., pain, fatigue, motor function), and a slowing progression in symptoms.
     - **iv.** The medication is being prescribed by or in consultation with a neurologist.

   Dosing. Approve if the dose is administered intravenously and meets ONE of the following (A or B):
   - **A)** The dose is ≤ 900 mg weekly for the first 4 weeks; OR
   - **B)** The dose is ≤ 1,200 mg every 2 weeks thereafter.

4. **Paroxysmal Nocturnal Hemoglobinuria.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Diagnosis was confirmed by peripheral blood flow cytometry results showing the absence or deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins on at least two cell lineages; AND
     - **iii.** The medication is being prescribed by or in consultation with a hematologist; OR
   - **B)** Patient is Currently Receiving Soliris. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient is continuing to derive benefit from Soliris, according to the prescriber; AND
       Note: Examples of derived benefit include stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis.
     - **iii.** The medication is prescribed by or in consultation with a hematologist.

   Dosing. Approve if the dose is administered intravenously and meets ONE of the following (A or B):
   - **A)** The dose is ≤ 600 mg weekly for the first 4 weeks; OR
   - **B)** The dose is ≤ 900 mg every 2 weeks thereafter.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Soliris is not recommended in the following situations:

1. **Concomitant Use with Empaveli > 4 Weeks.** Concomitant use of Soliris with Empaveli is not recommended. However, to reduce the risk of hemolysis from abrupt treatment discontinuation in a patient switching from Soliris to Empaveli, patient should use both therapies for 4 weeks; after which, Soliris is discontinued and patient is continued on Empaveli monotherapy.

2. **Concomitant Use with a Rituximab Product, a Neonatal Fc Receptor Blocker, Enspryng (satralizumab-mwge subcutaneous injection), Fabhalta (iptacopan capsule), Ultomiris (ravulizumab-cwzy intravenous infusion or subcutaneous injection), or Uplizna (inebilizumab-cdon intravenous infusion), or Zilbrysq (zilucoplan subcutaneous injection)**. There is no evidence to support concomitant use of Soliris with a rituximab product, a neonatal Fc receptor blocker, Enspryng, Fabhalta, Ultomiris, Uplizna, or Zilbrysq.
   Note: Examples of Neonatal Fc receptor blockers are: Vyvgart (efgartigimod alfa-fcab intravenous infusion), Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection), and Rystiggo (rozanolixizumab-noli subcutaneous infusion).

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Soliris® intravenous infusion [prescribing information]. Boston, MA: Alexion; November 2020.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Generalized Myasthenia Gravis:** Revised the Myasthenia Gravis Activities of Daily Living (MG-ADL) score to ≥ 6 to align with the prescribing information; previously it was MG-ADL ≥ 5.	05/24/2023
Early Annual Revision	**Generalized Myasthenia Gravis:** Initial therapy, for the criterion regarding evidence of unresolved symptoms of generalized myasthenia gravis, the examples of evidence of unresolved symptoms of generalized myasthenia gravis were moved to a Note. **Conditions Not Recommended for Approval:** Criterion regarding concomitant use of Soliris with a rituximab product, Enspryng, Ultomiris, or Uplizna was revised to include neonatal Fc receptor blockers. Examples of neonatal Fc receptor blockers were added as a Note.	09/20/2023
Selected Revision	**Conditions Not Recommended for Approval:** Criterion regarding concomitant use with other agents was revised to include Fabhalta and Zilbrysq.	01/17/2024
Selected Revision	**Neuromyelitis Optica Spectrum Disorder – Initial Therapy:** Removed criterion that required prior use of two systemic therapies and criterion that patient has had a history of at least one relapse in the last 12 months or two relapses in the last 2 years. Soliris is listed as a first-line treatment option in the Neuromyelitis Optica Study Group (NEMOS) recommendations for the treatment of Neuromyelitis Optica Spectrum Disorder (2024).	03/20/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT ADVANCED CLINICAL EVALUATION MEDICAL POLICY

POLICY: Complement Inhibitors – Ultomiris Intravenous Utilization Management Medical Policy – Advanced Clinical Evaluation
- Ultomiris® (ravulizumab-cwvz intravenous infusion – Alexion)

REVIEW DATE: 09/20/2023; selected revision 04/10/2024

OVERVIEW

Ultomiris intravenous, a complement inhibitor, is indicated for the following uses:[1]

- **Atypical hemolytic uremic syndrome** (aHUS), to inhibit complement-mediated thrombotic microangiopathy in patients ≥ one month of age.
  Limitation of use: Ultomiris IV is not indicated for the treatment of patients with Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome.
- **Generalized myasthenia gravis** (gMG), in adults who are anti-acetylcholine receptor (AChR) antibody-positive.
- **Neuromyelitis Optica Spectrum Disorder (NMOSD)**, in adults who are anti-aquaporin-4 (AQP4) antibody-positive.
- **Paroxysmal nocturnal hemoglobinuria** (PNH), in patients ≥ one month of age.

Ultomiris is also available in a subcutaneous formulation that is indicated for maintenance therapy of aHUS and PNH in adults.[1]

Ultomiris has a Boxed Warning about serious meningococcal infections.[1] Ultomiris is only available through a restricted access program, Ultomiris Risk Evaluation and Mitigation Strategy (REMS).

Disease Overview

Hemolytic uremic syndrome (HUS) is defined as the triad of non-immune hemolytic anemia, thrombocytopenia, and acute renal failure, in which the underlying lesions are mediated by systemic thrombotic microangiopathy.[2] aHUS should be distinguished from a more common condition referred to as typical HUS.[3] aHUS is a sub-type of HUS in which thrombotic microangiopathy is the consequence of endothelial damage in the microvasculature of the kidneys and other organs due to a dysregulation of the activity of the complement system. The typical form is caused by infection with certain strains of *E. coli* bacteria that produce toxic substances called Shiga-like toxins; Ultomiris IV is not indicated for the treatment of Shiga toxin *E. coli*-related hemolytic uremic syndrome.[1,3]

Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs.[4] The hallmark of MG is muscle weakness that worsens after periods of activity and improves after periods of rest. Acquired MG results from the binding of autoantibodies to components of the neuromuscular junction, most commonly the AChR.[5] Ultomiris IV was studied in patients with gMG with anti-AChR antibodies with a Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV, and a Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score ≥ 6.[1]

NMOSD is a rare, relapsing, autoimmune disorder of the brain and spinal cord with optic neuritis and/or myelitis as predominate characteristic symptoms.[6] NMOSD often causes significant, permanent damage

to vision and/or spinal cord function resulting in blindness or impaired mobility.[7] Patients may experience pain, paralysis, loss of bowel and bladder control, loss of visual acuity, uncontrolled motor functions, and complications can cause death.

PNH is a rare, genetic disorder of hematopoietic stem cells.[8,9] The mutation in the X-linked gene phosphatidylinositol glycan class A (PIGA) results in a deficiency in the glycosylphosphatidylinositol (GPI) protein, which is responsible for anchoring other protein moieties to the surface of the erythrocytes. Loss of anchoring of these proteins causes cells to hemolyze and leads to complications such as hemolytic anemia, thrombosis, and peripheral blood cytopenias. PNH is a clinical diagnosis that should be confirmed with peripheral blood flow cytometry to detect the absence or severe deficiency of GPI-anchored proteins on at least two lineages.[8,10] Prior to the availability of complement inhibitors, only supportive measures in terms of managing the cytopenias and controlling thrombotic risk were available. Supportive measures include platelet transfusion, immunosuppressive therapy for patients with bone marrow failure, use of erythropoietin for anemias, and aggressive anticoagulation.

Recommendations

There are no formal guidelines for treatment of aHUS.

An international consensus guidance for the management of MG was published in 2016.[5] The consensus guidance recommends pyridostigmine for the initial treatment in most patients with MG. The ability to discontinue pyridostigmine can indicate that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or immunosuppressant therapy should be used in all patients with MG who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal immunosuppressant agents used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Plasma exchange and intravenous immunoglobulin can be used as short-term treatments in certain patients. A 2020 update to these guidelines provides new recommendations for methotrexate, rituximab, and Soliris® (eculizumab intravenous infusion).[11] All recommendations should be considered extensions or additions to recommendations made in the initial international consensus guidance. Oral methotrexate may be considered as a steroid-sparing agent in patients with gMG who have not tolerated or responded to steroid-sparing agents. Rituximab should be considered as an early therapeutic option in patients with anti-muscle specific kinase antibody-positive MG who have an unsatisfactory response to initial immunotherapy. Soliris should be considered in the treatment of severe, refractory, anti-AChR antibody-positive gMG.

The Neuromyelitis Optica Study Group (NEMOS) published revised recommendations for the treatment of NMOSD in 2024.[12] The standard of care for the treatment of NMOSD attacks (for both AQP4-IgG-positive and double-negative cases) are high-dose glucocorticoids and/or apheresis therapy. Long term immunotherapy is recommended for patients with AQP4-IgG-positive NMOSD. NEMOS notes the first-choice therapies for the treatment of AQP4-IgG-positive NMOSD are Soliris, Ultomiris®, Enspryng® (satralizumab-mwge subcutaneous injection), Uplizna® (inebilizumab-cdon intravenous infusion), and rituximab. The order of preference for these therapies is unclear and further comparative trials and real-world data are needed. The choice of treatment is dependent on several factors, including disease activity and severity, mode and onset of action, possibility to combine it with immunosuppressive drugs, effect on autoimmune and other comorbidities, gender (family planning issues), frequency and route of administration, side effect profile, as well as patient and physician preference. In general, if a patient fails a first-choice treatment, another first-choice treatment should be tried; other options include use of a second-choice treatment (azathioprine, mycophenolate mofetil, low-dose oral glucocorticoids) or the addition of a second-choice treatment to the regimen.

A consensus statement for the diagnosis and treatment of PNH was published in 2021.[8] Treatment options for PNH are supportive care, allogeneic hematopoietic stem cell transplantation, and complement blockade by the anti-C5 monoclonal antibody (Soliris). Supportive care include use of oral iron to replace the large urinary losses; folate and vitamin B_{12} supplementation; red blood cell transfusion when these measures do not maintain adequate hemoglobin levels; use of antibiotics to treat bacterial infections as soon as possible since infections can exacerbate hemolytic crises in patients with PNH; use of corticosteroids to reduce the severity and duration of the hemolytic crises; use of Soliris as primary prophylaxis in patients with high PNH clone size (granulocyte close > 50%), high level of D dimer, pregnancy, perioperative condition, and other associated thrombophilia risk factors; and use of immunosuppressives in patients with PNH and aplastic anemia and bone marrow deficiency.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Ultomiris intravenous. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is provided in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ultomiris intravenous as well as the monitoring required for adverse events and long-term efficacy, approval requires Ultomiris intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated. All reviews will be forwarded to a Physician Medical Director for evaluation.

Documentation: Documentation is required for use of Ultomiris intravenous as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Complement Inhibitors – Ultomiris Intravenous Advanced Clinical Evaluation Medical Policy*, and who is requesting reauthorization, the criteria utilized do NOT require re-submission of documentation for reauthorization, except for the criterion requiring documentation of a continued benefit from Ultomiris therapy.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ultomiris intravenous is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Atypical Hemolytic Uremic Syndrome.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** Patient does not have Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome; AND
   - **B)** The medication is prescribed by or in consultation with a nephrologist.

   Dosing. Approve ONE of the following weight-based regimens (A or B):
   - **A)** ≥ 5 kg to < 20 kg: ≤ 600 mg administered by intravenous infusion for one dose, followed by ≤ 600 mg administered by intravenous infusion once every 4 weeks; OR

B) ≥ 20 kg: ≤ 3,000 mg administered by intravenous infusion for one dose, followed by ≤ 3,600 mg administered by intravenous infusion once every 8 weeks.

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2. Generalized Myasthenia Gravis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):

i. Patient is ≥ 18 years of age; AND

ii. Patient has confirmed anti-acetylcholine receptor antibody-positive generalized myasthenia gravis **[documentation required]**; AND

iii. Patient meets both of the following (a and b):

a) Myasthenia Gravis Foundation of America classification of II to IV; AND

b) Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 6; AND

iv. Patient meets one of the following (a or b):

a) Patient previously received or is currently receiving pyridostigmine; OR

b) Patient has had inadequate efficacy, a contraindication, or significant intolerance to pyridostigmine; AND

v. Patient meets one of the following (a or b):

a) Patient previously received or is currently receiving two different immunosuppressant therapies for ≥ 1 year; OR

b) Patient had inadequate efficacy, a contraindication, or significant intolerance to two different immunosuppressant therapies; AND

Note: Examples of immunosuppressant therapies include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, and cyclophosphamide.

vi. Patient has evidence of unresolved symptoms of generalized myasthenia gravis; AND

Note: Evidence of unresolved symptoms of generalized myasthenia gravis includes difficulty swallowing, difficulty breathing, or a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility).

vii. The medication is being prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Ultomiris intravenous. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient is continuing to derive benefit from Ultomiris intravenous, according to the prescriber; AND

Note: Examples of derived benefit include reductions in exacerbations of myasthenia gravis; improvements in speech, swallowing, mobility, and respiratory function.

iii. The medication is being prescribed by or in consultation with a neurologist.

Dosing. Approve the following dose if the patient is ≥ 40 kg: ≤ 3,000 mg administered by intravenous infusion for one dose, followed by ≤ 3,600 mg administered by intravenous infusion once every 8 weeks.

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3. Neuromyelitis Optica Spectrum Disorder. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Diagnosis was confirmed by a positive blood serum test for anti-aquaporin-4 antibody; AND

iii. The medication is being prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Ultormiris Intravenous. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Diagnosis was confirmed by a positive blood serum test for anti-aquaporin-4 antibody; AND

iii. According to the prescriber, patient has had clinical benefit from the use of Ultomiris Intravenous; AND

Note: Examples of clinical benefit include reduction in relapse rate, reduction in symptoms (e.g., pain, fatigue, motor function), and a slowing progression in symptoms.

iv. The medication is being prescribed by or in consultation with a neurologist.

Dosing. Approve the following dose if the patient is ≥ 40 kg: ≤ 3,000 mg administered by intravenous infusion for one dose, followed by ≤ 3,600 mg administered by intravenous infusion once every 8 weeks.

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4. Paroxysmal Nocturnal Hemoglobinuria. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Diagnosis was confirmed by peripheral blood flow cytometry results showing the absence or deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins on at least two cell lineages **[documentation required]**; AND

ii. The medication is prescribed by or in consultation with a hematologist.

B) Patient is Currently Receiving Ultomiris (intravenous or subcutaneous). Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient is continuing to derive benefit from Ultomiris (intravenous or subcutaneous), according to the prescriber.

Note: Examples of benefit from Ultomiris (intravenous or subcutaneous) include stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis.

ii. The medication is prescribed by or in consultation with a hematologist.

Dosing. Approve ONE of the following weight-based regimens (A or B):

A) ≥ 5 kg to < 20 kg: ≤ 600 mg administered by intravenous infusion for one dose, followed by ≤ 600 mg administered by intravenous infusion once every 4 weeks; OR

B) ≥ 20 kg: ≤ 3,000 mg administered by intravenous infusion for one dose, followed by ≤ 3,600 mg administered by intravenous infusion once every 8 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ultomiris intravenous is not recommended in the following situations:

1. Concomitant Use with Another Complement Inhibitor, a Rituximab Product, a Neonatal Fc Receptor Blocker, Enspryng (satralizumab-mwge subcutaneous injection), or Uplizna (inebilizumab-cdon intravenous infusion). There is no evidence to support concomitant use of Ultomiris intravenous with another complement inhibitor, a rituximab product, a neonatal Fc receptor blocker, Enspryng, or Uplizna.

Note: Examples of complement inhibitors are Empaveli (pegcetacoplan subcutaneous injection, Fabhalta (iptacopan capsule), Soliris (eculizumab intravenous infusion), and Zilbrysq (zilucoplan subcutaneous injection).
Note: Examples of neonatal Fc receptor blockers are Rystiggo (rozanolixizumab-noli subcutaneous infusion), Vyvgart (efgartigimod alfa-fcab intravenous infusion], and Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection).

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	For the title and where applicable in the document, "intravenous" was added. **Generalized Myasthenia Gravis:** "intravenous" was added to Ultomiris to clarify product allowed for a patient who is currently receiving therapy. **[documentation required]** was added to the requirement for confirmed anti-acetylcholine receptor antibody positive generalized myasthenia gravis. **Paroxysmal Nocturnal Hemoglobinuria:** "intravenous or subcutaneous" was added to Ultomiris to clarify product allowed for a patient who is currently receiving therapy. **Concurrent Use with Another Complement Inhibitor or Vyvgart (efgartigimod alfa-fcab intravenous infusion):** The title was changed to this instead of stating specific complement inhibitors. Vyvgart was also added as a product to this condition.	08/31/2022
Selected Revision	**Generalized Myasthenia Gravis:** Revised the Myasthenia Gravis Activities of Daily Living (MG-ADL) score to ≥ 6 to align with the prescribing information; previously it was MG-ADL ≥ 5.	05/31/2023
Annual Revision	**Generalized Myasthenia Gravis:** Initial therapy, for the criterion regarding evidence of unresolved symptoms of generalized myasthenia gravis, the examples of evidence of unresolved symptoms of generalized myasthenia gravis were moved to a Note. **Conditions Not Recommended for Approval:** Criterion regarding concomitant use of Ultomiris IV with another complement inhibitor or Vyvgart was revised to add rituximab and other neonatal Fc receptor blockers (Vyvgart Hytrulo, Rystiggo). Examples of complement inhibitors and neonatal Fc receptor blockers were moved to a Note.	09/20/2023
Update	**01/17/2024:** No criteria changes. **Conditions Not Recommended for Approval:** Note regarding examples of complement inhibitors was updated to include Fabhalta and Zilbrysq.	--
Selected Revision	**Neuromyelitis Optica Spectrum Disorder:** This condition and criteria for approval were added to the policy. **Conditions Not Recommended for Approval,** Enspryng (satralizumab-mwge subcutaneous injection) and Uplisna (inebilizumab-cdon intravenous infusion) were added to the criterion "Concomitant Use with a Rituximab Product, Enspryng (satralizumab-mwge subcutaneous injection), or Soliris (eculizumab intravenous infusion)"; new criterion reads: "Concomitant Use with Another Complement Inhibitor, a Rituximab Product, or a Neonatal Fc Receptor Blocker, Enspryng (satralizumab-mwge subcutaneous injection), or Uplizna (inebilizumab-cdon intravenous infusion)".	04/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Complement Inhibitors – Ultomiris Intravenous Utilization Management Medical Policy
- Ultomiris® (ravulizumab-cwvz intravenous infusion – Alexion)

REVIEW DATE: 09/20/2023; selected revision 04/10/2024

OVERVIEW

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- **Generalized myasthenia gravis** (gMG), in adults who are anti-acetylcholine receptor (AChR) antibody-positive.
- **Neuromyelitis Optica Spectrum Disorder (NMOSD)**, in adults who are anti-aquaporin-4 (AQP4) antibody-positive.
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An international consensus guidance for the management of MG was published in 2016.[5] The consensus guidance recommends pyridostigmine for the initial treatment in most patients with MG. The ability to discontinue pyridostigmine can indicate that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or immunosuppressant therapy should be used in all patients with MG who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal immunosuppressant agents used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Plasma exchange and intravenous immunoglobulin can be used as short-term treatments in certain patients. A 2020 update to these guidelines provides new recommendations for methotrexate, rituximab, and Soliris® (eculizumab intravenous infusion).[11] All recommendations should be considered extensions or additions to recommendations made in the initial international consensus guidance. Oral methotrexate may be considered as a steroid-sparing agent in patients with gMG who have not tolerated or responded to steroid-sparing agents. Rituximab should be considered as an early therapeutic option in patients with anti-muscle specific kinase antibody-positive MG who have an unsatisfactory response to initial immunotherapy. Soliris should be considered in the treatment of severe, refractory, anti-AChR antibody-positive gMG.

The Neuromyelitis Optica Study Group (NEMOS) published revised recommendations for the treatment of NMOSD in 2024.[12] The standard of care for the treatment of NMOSD attacks (for both AQP4-IgG-positive and double-negative cases) are high-dose glucocorticoids and/or apheresis therapy. Long term immunotherapy is recommended for patients with AQP4-IgG-positive NMOSD. NEMOS notes the first-choice therapies for the treatment of AQP4-IgG-positive NMOSD are Soliris, Ultomiris. Enspryng® (satralizumab-mwge subcutaneous injection), Uplizna® (inebilizumab-cdon intravenous infusion), and rituximab. The order of preference for these therapies is unclear and further comparative trials and real-world data are needed. The choice of treatment is dependent on several factors, including disease activity and severity, mode and onset of action, possibility to combine it with immunosuppressive drugs, effect on autoimmune and other comorbidities, gender (family planning issues), frequency and route of administration, side effect profile, as well as patient and physician preference. In general, if a patient fails a first-choice treatment, another first-choice treatment should be tried; other options include use of a second-choice treatment (azathioprine, mycophenolate mofetil, low-dose oral glucocorticoids) or the addition of a second-choice treatment to the regimen.

A consensus statement for the diagnosis and treatment of PNH was published in 2021.[8] Treatment options for PNH are supportive care, allogeneic hematopoietic stem cell transplantation, and complement blockade by the anti-C5 monoclonal antibody (Soliris). Supportive care include use of oral iron to replace the large urinary losses; folate and vitamin B_{12} supplementation; red blood cell transfusion when these measures do not maintain adequate hemoglobin levels; use of antibiotics to treat bacterial infections as soon as possible since infections can exacerbate hemolytic crises in patients with PNH; use of corticosteroids to reduce the severity and duration of the hemolytic crises; use of Soliris as primary prophylaxis in patients with high PNH clone size (granulocyte close > 50%), high level of D dimer, pregnancy, perioperative condition, and other associated thrombophilia risk factors; and use of immunosuppressives in patients with PNH and aplastic anemia and bone marrow deficiency.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Ultomiris intravenous. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ultomiris intravenous as well as the monitoring required for adverse events and long-term efficacy, approval requires Ultomiris intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ultomiris intravenous is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. Atypical Hemolytic Uremic Syndrome. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient does not have Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome; AND

B) The medication is prescribed by or in consultation with a nephrologist.

Dosing. Approve ONE of the following weight-based regimens (A or B):

A) ≥ 5 kg to < 20 kg: ≤ 600 mg administered by intravenous infusion for one dose, followed by ≤ 600 mg administered by intravenous infusion once every 4 weeks; OR

B) ≥ 20 kg: ≤ 3,000 mg administered by intravenous infusion for one dose, followed by ≤ 3,600 mg administered by intravenous infusion once every 8 weeks.

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2. Generalized Myasthenia Gravis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):

i. Patient is ≥ 18 years of age; AND

ii. Patient has confirmed anti-acetylcholine receptor antibody-positive generalized myasthenia gravis; AND
iii. Patient meets BOTH of the following (a and b):
a) Myasthenia Gravis Foundation of America classification of II to IV; AND
b) Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 6; AND
iv. Patient meets ONE of the following (a or b):
a) Patient previously received or is currently receiving pyridostigmine; OR
b) Patient has had inadequate efficacy, a contraindication, or significant intolerance to pyridostigmine; AND
v. Patient meets ONE of the following (a or b):
a) Patient previously received or is currently receiving two different immunosuppressant therapies for ≥ 1 year; OR
b) Patient had inadequate efficacy, a contraindication, or significant intolerance to two different immunosuppressant therapies; AND
Note: Examples of immunosuppressant therapies include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, and cyclophosphamide.
vi. Patient has evidence of unresolved symptoms of generalized myasthenia gravis; AND
Note: Evidence of unresolved symptoms of generalized myasthenia gravis includes difficulty swallowing, difficulty breathing, or a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility).
vii. The medication is being prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Ultomiris intravenous. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
i. Patient is ≥ 18 years of age; AND
ii. Patient is continuing to derive benefit from Ultomiris intravenous, according to the prescriber; AND
Note: Examples of derived benefit include reductions in exacerbations of myasthenia gravis; improvements in speech, swallowing, mobility, and respiratory function.
iii. The medication is being prescribed by or in consultation with a neurologist.

Dosing. Approve the following dose if the patient is ≥ 40 kg: ≤ 3,000 mg administered by intravenous infusion for one dose, followed by ≤ 3,600 mg administered by intravenous infusion once every 8 weeks.

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3. Neuromyelitis Optica Spectrum Disorder. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
i. Patient is ≥ 18 years of age; AND
ii. Diagnosis was confirmed by a positive blood serum test for anti-aquaporin-4 antibody; AND
iii. The medication is being prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Ultormiris Intravenous. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, iii, and iv):
i. Patient is ≥ 18 years of age; AND
ii. Diagnosis was confirmed by a positive blood serum test for anti-aquaporin-4 antibody; AND
iii. According to the prescriber, patient has had clinical benefit from the use of Ultomiris Intravenous; AND
Note: Examples of clinical benefit include reduction in relapse rate, reduction in symptoms (e.g., pain, fatigue, motor function), and a slowing progression in symptoms.

iv. The medication is being prescribed by or in consultation with a neurologist.

Dosing. Approve the following dose if the patient is ≥ 40 kg: ≤ 3,000 mg administered by intravenous infusion for one dose, followed by ≤ 3,600 mg administered by intravenous infusion once every 8 weeks.

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4. Paroxysmal Nocturnal Hemoglobinuria. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
- **i.** Diagnosis was confirmed by peripheral blood flow cytometry results showing the absence or deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins on at least two cell lineages; AND
- **ii.** The medication is prescribed by or in consultation with a hematologist.

B) Patient is Currently Receiving Ultomiris (intravenous or subcutaneous). Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient is continuing to derive benefit from Ultomiris (intravenous or subcutaneous), according to the prescriber.
  Note: Examples of benefit from Ultomiris (intravenous or subcutaneous) include stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis.
- **ii.** The medication is prescribed by or in consultation with a hematologist.

Dosing. Approve ONE of the following weight-based regimens (A or B):

A) ≥ 5 kg to < 20 kg: ≤ 600 mg administered by intravenous infusion for one dose, followed by ≤ 600 mg administered by intravenous infusion once every 4 weeks; OR

B) ≥ 20 kg: ≤ 3,000 mg administered by intravenous infusion for one dose, followed by ≤ 3,600 mg administered by intravenous infusion once every 8 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ultomiris intravenous is not recommended in the following situations:

1. Concomitant Use with Another Complement Inhibitor, a Rituximab Product, a Neonatal Fc Receptor Blocker, Enspryng (satralizumab-mwge subcutaneous injection), or Uplizna (inebilizumab-cdon intravenous infusion). There is no evidence to support concomitant use of Ultomiris intravenous with another complement inhibitor, a rituximab product, a neonatal Fc receptor blocker, Enspryng, or Uplizna.
Note: Examples of complement inhibitors are Empaveli (pegcetacoplan subcutaneous injection), Fabhalta (iptcopan capsule), Soliris (eculizumab intravenous infusion), and Zilbrysq (zilucoplan subcutaneous injection).
Note: Examples of neonatal Fc receptor blockers are Vyvgart (efgartigimod alfa-fcab intravenous infusion), Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection), and Rystiggo (rozanolixizumab-noli subcutaneous infusion).

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/09/2022
Selected Revision	**Generalized Myasthenia Gravis:** Revised the Myasthenia Gravis Activities of Daily Living (MG-ADL) score to ≥ 6 to align with the prescribing information; previously it was MG-ADL ≥ 5.	05/24/2023
Early Annual Revision	**Generalized Myasthenia Gravis:** Initial therapy, for the criterion regarding evidence of unresolved symptoms of generalized myasthenia gravis, the examples of evidence of unresolved symptoms of generalized myasthenia gravis were moved to a Note. **Conditions Not Recommended for Approval:** Criterion regarding concomitant use of Ultomiris IV with another complement inhibitor or Vyvgart was revised to add rituximab and other neonatal Fc receptor blockers (Vyvgart Hytrulo, Rystiggo). Examples of complement inhibitors and neonatal Fc receptor blockers were moved to a Note.	09/20/2023
Update	**01/17/2024:** No criteria changes. **Conditions Not Recommended for Approval:** Note regarding examples of complement inhibitors was updated to include Fabhalta and Zilbrysq.	--
Selected Revision	**Neuromyelitis Optica Spectrum Disorder:** This condition and criteria for approval were added to the policy. **Conditions Not Recommended for Approval:** Enspryng (satralizumab-mwge subcutaneous injection) and Uplizna (inebilizumab-cdon intravenous infusion) were added to the criterion "Concomitant Use with a Rituximab Product, Enspryng (satralizumab-mwge subcutaneous injection), or Soliris (eculizumab intravenous infusion)"; new criterion reads: "Concomitant Use with Another Complement Inhibitor, a Rituximab Product, or a Neonatal Fc Receptor Blocker, Enspryng (satralizumab-mwge subcutaneous injection), or Uplizna (inebilizumab-cdon intravenous infusion)".	04/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Complement Inhibitors – Veopoz Utilization Management Medical Policy
- Veopoz™ (pozelimab-bbfg intravenous infusion and subcutaneous injection – Regeneron)

REVIEW DATE: 09/08/2023

OVERVIEW

Veopoz, a complement inhibitor, is indicated for the treatment of CD55-deficient protein-losing enteropathy, also known as CHAPLE disease, in adult and pediatric patients ≥ 1 year of age.[1]

Disease Overview

CHAPLE (which stands for Complement Hyperactivation, Angiopathic thrombosis, and Protein-Losing Enteropathy) disease is an ultra-rare inherited immune disease that causes the complement system to become overactive.[2-5] It is caused by biallelic loss-of-function mutations in the CD55 gene, which leads to loss of protein expression and can result in the complement system attacking the body's own cells. There are fewer than 100 patients diagnosed worldwide with CHAPLE disease; it is estimated to impact around 10 patients in the US. Symptoms can include abdominal pain, nausea, vomiting, diarrhea, loss of appetite, weight loss, impaired growth, and edema. Severe thrombotic vascular occlusions (blockage of blood vessels) can also occur among patients with CHAPLE disease, which can be life-threatening. The condition mainly impacts children, including infants, and is associated with morbidity and a higher risk of mortality.

Dosing Information

Veopoz is administered by a healthcare provider.[1] On Day 1, give a single 30 mg/kg loading dose by intravenous infusion. Day 8 and thereafter, the maintenance dose is 10 mg/kg as a subcutaneous injection once weekly. The maintenance dosage may be increased to 12 mg/kg once weekly if there is inadequate clinical response after at least three weekly doses (starting from Week 4). The maximum maintenance dosage is 800 mg once weekly. Doses exceeding 400 mg require two injections.

Safety

Veopoz has a Boxed Warning regarding serious meningococcal infections.[1] Life-threatening and fatal meningococcal infections have occurred in patients treated with complement inhibitors. Complete or update meningococcal vaccination at least 2 weeks before administering the first dose of Veopoz, unless the risks of delaying therapy outweigh the risks of developing meningococcal infection. Follow the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients receiving a complement inhibitor. Also, patients treated with Veopoz may be at increased risk of developing serious infections due to *Streptococcus pneumonia* and *Haemophilus influenza* type b; administer vaccinations for the prevention of these infections according to ACIP guidelines.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Veopoz. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is

authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Veopoz as well as the monitoring required for adverse events and long-term efficacy, approval requires Veopoz to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Veopoz as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory data, genetic tests, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirement for the genetic test criterion in the *Complement Inhibitors – Veopoz Utilization Management Medical Policy* through the Coverage Review Department and who is requesting reauthorization, do NOT require re-submission of documentation for reauthorization regarding the genetic test criterion.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Veopoz is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **CD55-Deficient Protein-Losing Enteropathy (CHAPLE Disease [Complement Hyperactivation, Angiopathic thrombosis, and Protein-Losing Enteropathy]).** Approve for the duration noted below if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets the following (i, ii, iii, iv, and v):
     - **i.** Patient is ≥ 1 year of age; AND
     - **ii.** Patient has had a genetic test confirming the diagnosis of CHAPLE disease with a biallelic CD55 loss-of-function mutation **[documentation required]**; AND
     - **iii.** Patient meets both of the following (a and b):
       - **a)** Patient has a serum albumin level ≤ 3.2 g/dL **[documentation required]**; AND
       - **b)** According to the prescribing physician, the patient has active disease and is experiencing one or more signs or symptoms within the last 6 months; AND
         Note: Examples of signs and symptoms include abdominal pain, diarrhea, vomiting, peripheral edema, or facial edema.
     - **iv.** Patient meets all of the following (a, b, and c):
       - **a)** Patient does not have a history of meningococcal infection; AND
       - **b)** Patient has received or is in compliance with updated meningococcal vaccinations according to the most current Advisory Committee on Immunization Practices recommendations; AND
       - **c)** Patient has received or is in compliance with updated vaccinations for the prevention of *Streptococcus pneumonia* and *Haemophilus influenza* type b infections according to the most current Advisory Committee on Immunization Practices guidelines; AND
     - **v.** Medication is prescribed by a physician with expertise in managing CHAPLE disease; OR
   - **B)** Patient Currently Receiving Veopoz. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 1 year of age; AND
     - **ii.** Patient has had a genetic test confirming the diagnosis of CHAPLE disease with a biallelic CD55 loss-of-function mutation **[documentation required]**; AND

iii. Medication is prescribed by a physician with expertise in managing CHAPLE disease; AND
iv. Patient had experienced a response to therapy **[documentation required]**.
Note: Examples of a response to therapy include increased serum albumin levels, maintenance of serum albumin levels within a normal range, a reduction in albumin transfusions, increases in or maintenance of protein and/or immunoglobulin levels, improvement in clinical outcomes after receipt of therapy (e.g., decreases in the frequency of problematic abdominal pain, bowel movement frequency, facial edema severity, and peripheral edema severity), reduced frequency in hospitalizations, increase in growth percentiles (e.g., body weight-for age and/or stature-for-age percentiles), and/or reduced use of corticosteroids.

Dosing. Approve a single 30 mg/kg loading dose by intravenous infusion on Day 1, followed by up to 12 mg/kg subcutaneously once weekly (up to a maximum of 800 mg).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Veopoz is not recommended in the following situations:

1. **Concomitant Use with Other Complement Inhibitors.** In the pivotal study, use of other complement inhibitors was prohibited.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Complement Inhibitors – Soliris Utilization Management Medical Policy
- Soliris® (eculizumab intravenous infusion – Alexion)

REVIEW DATE: 09/20/2023; selected revision 01/17/2024

OVERVIEW

Soliris, a complement inhibitor, is indicated for the following uses:[1]

- **Atypical hemolytic uremic syndrome** (aHUS), to inhibit complement-mediated thrombotic microangiopathy.
  Limitation of Use. Soliris is not indicated for the treatment of patients with Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome.
- **Generalized myasthenia gravis** (gMG), in adults who are anti-acetylcholine receptor (AChR) antibody-positive.
- **Neuromyelitis optica spectrum disorder** (NMOSD), in adults who are anti-aquaporin-4 (AQP4) antibody positive.
- **Paroxysmal nocturnal hemoglobinuria** (PNH), to reduce hemolysis.

The Soliris prescribing information has a Boxed Warning about serious meningococcal infections.[1] Soliris is only available through a restricted access program, Soliris Risk Evaluation and Mitigation Strategy (REMS).[1]

The safety and effectiveness of Soliris for the treatment of PNH, gMG, and NMOSD in pediatric patients have not been established.[1] The safety and effectiveness of Soliris in pediatric patients for aHUS is supported by evidence from four adequate and well-controlled clinical studies assessing the safety and effectiveness of Soliris for the treatment of aHUS.

Disease Overview

Hemolytic uremic syndrome (HUS) is defined as the triad of non-immune hemolytic anemia, thrombocytopenia, and acute renal failure, in which the underlying lesions are mediated by systemic thrombotic microangiopathy.[2] aHUS should be distinguished from a more common condition referred to as typical HUS.[3] aHUS is a sub-type of HUS in which thrombotic microangiopathy is the consequence of endothelial damage in the microvasculature of the kidneys and other organs due to a dysregulation of the activity of the complement system. The typical form is caused by infection with certain strains of *E. coli* bacteria that produce toxic substances called Shiga-like toxins; Soliris is not indicated for the treatment of Shiga toxin *E. coli*-related hemolytic uremic syndrome.[1-3]

Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs.[4] The hallmark of MG is muscle weakness that worsens after periods of activity and improves after periods of rest. Acquired MG results from the binding of autoantibodies to components of the neuromuscular junction, most commonly the AChR.[5] Soliris was studied in patients with gMG with anti-AChR antibodies with a Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV and a Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score ≥ 6.[1]

NMOSD is a rare, relapsing, autoimmune disorder of the brain and spinal cord with optic neuritis and/or myelitis as predominate characteristic symptoms.[6] NMOSD often causes significant, permanent damage to vision and/or spinal cord function resulting in blindness or impaired mobility.[7] Patients may experience pain, paralysis, loss of bowel and bladder control, loss of visual acuity, uncontrolled motor functions, and complications can cause death. Uplizna™ (inebilizumab-cdon intravenous infusion) and Enspryng™ (satralizumab-mwge subcutaneous injection) are two other FDA-approved medications for treatment of NMOSD in adults who are anti-AQP4 antibody-positive.[8,9] For acute attacks, typical treatment is high-dose intravenous corticosteroids.[10,11] Plasma exchange may be effective in patients who suffer acute severe attacks that do not respond to intravenous corticosteroids. For long-term control of the disease, a variety of immunosuppressive drugs are utilized as first-line therapy. While all are considered off-label uses, corticosteroids, azathioprine, mycophenolate mofetil, and rituximab are treatments prescribed as preventative therapy.

PNH is a rare, genetic disorder of hematopoietic stem cells.[12,13] The mutation in the X-linked gene phosphatidylinositol glycan class A (PIGA) results in a deficiency in the glycosylphosphatidylinositol (GPI) protein, which is responsible for anchoring other protein moieties to the surface of the erythrocytes. Loss of anchoring of these proteins causes cells to hemolyze and leads to complications such as hemolytic anemia, thrombosis, and peripheral blood cytopenias. PNH is a clinical diagnosis that should be confirmed with peripheral blood flow cytometry to detect the absence or severe deficiency of GPI-anchored proteins on at least two cell lineages.[12,14] Prior to the availability of complement inhibitors, only supportive measures, in terms of managing the cytopenias and controlling thrombotic risk were available. Supportive measures include platelet transfusion, immunosuppressive therapy for patients with bone marrow failure, use of erythropoietin for anemias, and aggressive anticoagulation.

Guidelines

An international consensus guidance for the management of MG was published in 2016.[5] The guidelines recommend pyridostigmine for the initial treatment in most patients with MG. The ability to discontinue pyridostigmine can indicate that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or immunosuppressant therapy should be used in all patients with MG who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal immunosuppressant agents used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Plasma exchange and intravenous immunoglobulin can be used as short-term treatments in certain patients. A 2020 update to these guidelines provides new recommendations for methotrexate, rituximab, and Soliris.[15] All recommendations should be considered extensions or additions to recommendations made in the initial international consensus guidance. Oral methotrexate may be considered as a steroid-sparing agent in patients with gMG who have not tolerated or responded to steroid-sparing agents. Rituximab should be considered as an early therapeutic option in patients with anti-muscle specific kinase antibody-positive MG who have an unsatisfactory response to initial immunotherapy. Soliris should be considered in the treatment of severe, refractory, anti-AChR antibody-positive MG.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Soliris. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the dosing interval is provided in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation

and diagnosis of patients treated with Soliris as well as the monitoring required for adverse events and long-term efficacy, approval requires Soliris to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Soliris is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. Atypical Hemolytic Uremic Syndrome. Approve for 1 year if the patient meets the following (A and B):

A) Patient does not have Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome; AND

B) The medication is being prescribed by or in consultation with a nephrologist.

Dosing. Approve if the dose meets ONE of the following (A or B):

A) For patients ≥ 18 years of age, the dose is administered intravenously and meets ONE of the following (i or ii):

- **i.** The dose is ≤ 900 mg weekly for the first 4 weeks; OR
- **ii.** The dose is ≤ 1,200 mg every 2 weeks thereafter.

B) For patients < 18 years of age, the dose is administered intravenously and meets ONE of the following (i, ii, iii, iv, or v):

- **i.** ≥ 40 kg: 900 mg weekly x 4 doses, 1,200 mg at week 5; then 1,200 mg every 2 weeks; OR
- **ii.** 30 kg to < 40 kg: 600 mg weekly x 2 doses, 900 mg at week 3; then 900 mg every 2 weeks; OR
- **iii.** 20 kg to < 30 kg: 600 mg weekly x 2 doses, 600 mg at week 3; then 600 mg every 2 weeks; OR
- **iv.** 10 kg to < 20 kg: 600 mg weekly x 1 dose, 300 mg at week 2; then 300 mg every 2 weeks; OR
- **v.** 5 kg to < 10 kg: 300 mg weekly x 1 dose, 300 mg at week 2; then 300 mg every 3 weeks.

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2. Generalized Myasthenia Gravis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, iv, v, vi, and vii):

- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has confirmed anti-acetylcholine receptor antibody-positive generalized myasthenia gravis; AND
- **iii.** Patient meets both of the following (a and b):
  - **a)** Myasthenia Gravis Foundation of America classification of II to IV; AND
  - **b)** Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 6; AND
- **iv.** Patient meets one of the following (a or b):
  - **a)** Patient previously received or is currently receiving pyridostigmine; OR
  - **b)** Patient has had inadequate efficacy, a contraindication, or significant intolerance to pyridostigmine; AND
- **v.** Patient meets one of the following (a or b):
  - **a)** Patient previously received or is currently receiving two different immunosuppressant therapies for ≥ 1 year; OR

b) Patient had inadequate efficacy, a contraindication, or significant intolerance to two different immunosuppressant therapies; AND
Note: Examples of immunosuppressant therapies tried include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, and cyclophosphamide.

vi. Patient has evidence of unresolved symptoms of generalized myasthenia gravis; AND
Note: Evidence of unresolved symptoms of generalized myasthenia gravis includes difficulty swallowing, difficulty breathing, and a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility).

vii. The medication is being prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Soliris. Approve for 1 year if the patient meets the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient is continuing to derive benefit from Soliris, according to the prescriber.
Note: Examples of derived benefit include reductions in exacerbations of myasthenia gravis, improvements in speech, swallowing, mobility, and respiratory function.

iii. The medication is being prescribed by or in consultation with a neurologist.

Dosing. Approve if the dose is administered intravenously and meets ONE of the following (A or B):

A) The dose is ≤ 900 mg weekly for the first 4 weeks; OR

B) The dose is ≤ 1,200 mg every 2 weeks thereafter.

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3. Neuromyelitis Optica Spectrum Disorder. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets the following (i, ii, iii, iv, and v):

i. Patient is ≥ 18 years of age; AND

ii. Diagnosis was confirmed by a positive blood serum test for anti-aquaporin-4 antibody; AND

iii. Patient is currently receiving or has previously tried two of the following systemic therapies (a, b, c, or d):

a) Azathioprine; OR

b) Corticosteroid; OR

c) Mycophenolate mofetil; OR

d) Rituximab; AND
Note: An exception to the requirement for a trial of a systemic therapy can be made if the patient has already tried Enspryng (satralizumab-mwge subcutaneous injection) or Uplizna (inebilizumab-cdon intravenous infusion) for neuromyelitis optica spectrum disorder (NMOSD). Patients who have already tried Enspryng or Uplizna for NMOSD are not required to try another systemic agent.

iv. Patient has a history of at least one relapse in the last 12 months or two relapses in the last 2 years; AND

v. The medication is being prescribed by or in consultation with a neurologist.

B) Patients is Currently Receiving Soliris. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Diagnosis was confirmed by positive blood serum test for anti-aquaporin-4 antibody; AND

iii. According to the prescriber, patient has had clinical benefit from the use of Soliris; AND
Note: Examples of clinical benefit include reduction in relapse rate, reduction in symptoms (e.g., pain, fatigue, motor function), and a slowing progression in symptoms.

iv. The medication is being prescribed by or in consultation with a neurologist.

Dosing. Approve if the dose is administered intravenously and meets ONE of the following (A or B):
A) The dose is ≤ 900 mg weekly for the first 4 weeks; OR
B) The dose is ≤ 1,200 mg every 2 weeks thereafter.

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4. **Paroxysmal Nocturnal Hemoglobinuria.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, and iii):
      i. Patient is ≥ 18 years of age; AND
      ii. Diagnosis was confirmed by peripheral blood flow cytometry results showing the absence or deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins on at least two cell lineages; AND
      iii. The medication is being prescribed by or in consultation with a hematologist; OR
   B) Patient is Currently Receiving Soliris. Approve for 1 year if the patient meets the following (i, ii, and iii):
      i. Patient is ≥ 18 years of age; AND
      ii. Patient is continuing to derive benefit from Soliris, according to the prescriber; AND
      Note: Examples of derived benefit include stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis.
      iii. The medication is prescribed by or in consultation with a hematologist.

   Dosing. Approve if the dose is administered intravenously and meets ONE of the following (A or B):
   A) The dose is ≤ 600 mg weekly for the first 4 weeks; OR
   B) The dose is ≤ 900 mg every 2 weeks thereafter.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Soliris is not recommended in the following situations:

1. **Concomitant Use with Empaveli > 4 Weeks.** Concomitant use of Soliris with Empaveli is not recommended. However, to reduce the risk of hemolysis from abrupt treatment discontinuation in a patient switching from Soliris to Empaveli, patient should use both therapies for 4 weeks; after which, Soliris is discontinued and patient is continued on Empaveli monotherapy.

2. **Concomitant Use with a Rituximab Product, a Neonatal Fc Receptor Blocker, Enspryng (satralizumab-mwge subcutaneous injection), Fabhalta (iptacopan capsule), Ultomiris (ravulizumab-cwzy intravenous infusion or subcutaneous injection), or Uplizna (inebilizumab-cdon intravenous infusion), or Zilbrysq (zilucoplan subcutaneous injection)**. There is no evidence to support concomitant use of Soliris with a rituximab product, a neonatal Fc receptor blocker, Enspryng, Fabhalta, Ultomiris, Uplizna, or Zilbrysq.
   Note: Examples of Neonatal Fc receptor blockers are: Vyvgart (efgartigimod alfa-fcab intravenous infusion), Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaenous injection), and Rystiggo (rozanolixizumab-noli subcutaneous infusion).

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Soliris® intravenous infusion [prescribing information]. Boston, MA: Alexion; November 2020.
2. Campistol JM, Arias M, Ariceta G, et al. An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document. *Nefrologia*. 2015;35:421–447.
3. Genetics Home Reference. Atypical hemolytic-uremic syndrome. National Institutes of Health (NIH). Available at: https://ghr.nlm.nih.gov/condition/atypical-hemolytic-uremic-syndrome#sourcesforpage. Accessed on September 18, 2023.
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5. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. *Neurology*. 2016;87:419–425.
6. National Organization for Rare Disorders. Neuromyelitis Optica Spectrum Disorder. Available at: https://rarediseases.org/rare-diseases/neuromyelitis-optica/. Last updated July 27, 2022. Accessed on September 18, 2023.
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8. Enspryng™ subcutaneous injection [prescribing information]. South San Francisco, CA: Genentech; March 2022.
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14. Roth A, Maciejewski J, Nishinura JI, et al. Screening and diagnostic clinical algorithm for paroxysmal nocturnal hemoglobinuria: Expert consensus. *Eur J Haematol*. 2018;101(1):3-11.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Generalized Myasthenia Gravis:** Revised the Myasthenia Gravis Activities of Daily Living (MG-ADL) score to ≥ 6 to align with the prescribing information; previously it was MG-ADL ≥ 5.	05/24/2023
Early Annual Revision	**Generalized Myasthenia Gravis:** Initial therapy, for the criterion regarding evidence of unresolved symptoms of generalized myasthenia gravis, the examples of evidence of unresolved symptoms of generalized myasthenia gravis were moved to a Note. **Conditions Not Recommended for Approval:** Criterion regarding concomitant use of Soliris with a rituximab product, Enspryng, Ultomiris, or Uplizna was revised to include neonatal Fc receptor blockers. Examples of neonatal Fc receptor blockers were added as a Note.	09/20/2023
Selected revision	**Conditions Not Recommended for Approval:** Criterion regarding concomitant use with other agents was revised to include Fabhalta and Zilbrysq.	01/17/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Coronavirus Disease – Veklury Utilization Management Medical Policy
- Veklury® (remdesivir intravenous infusion – Gilead)

REVIEW DATE: 12/13/2023, selected revision 03/13/2024

OVERVIEW

Veklury, a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleotide analog RNA polymerase inhibitor, is indicated for the treatment of **coronavirus disease 19 (COVID-19)** in patients from birth and weighing ≥ 1.5 kg, who are:
- Hospitalized, or
- Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.[1]

Dosing Information

The recommended dose of Veklury, for:[1,4]
- Adults, or patients who are < 18 years of age and weigh ≥ 40 kg, is a single 200 mg loading dose given by intravenous (IV) infusion on Day 1, followed by 100 mg once daily, starting on Day 2.
- Patients at least 28 days old and weighing ≥ 3 kg and < 40 kg, is a single 5.0 mg/kg loading dose given by IV infusion on Day 1, followed by 2.5 mg/kg once daily, starting on Day 2.
- Patients at least 28 days old and weighing ≥ 1.5 kg and < 3 kg, is a single 2.5 mg/kg loading dose given by IV infusion on Day 1, followed by 1.25 mg/kg once daily, starting on Day 2.
- Patients < 28 days old and weighing ≥ 1.5 kg, is a single 2.5 mg/kg loading dose given by IV infusion on Day 1, followed by 1.25 mg/kg once daily, starting on Day 2.

Guidelines

The Infectious Disease Society of America (IDSA) and the National Institutes of Health (NIH) have developed treatment guidelines for the management of COVID-19 and each address the use of Veklury.[2,3] Both the IDSA and NIH guidelines recommend Veklury for hospitalized patients with COVID-19 who require supplemental oxygen. For patients receiving supplemental oxygen, Veklury is recommended for 5 days of treatment. The IDSA and NIH recommend against the initiation of Veklury in patients receiving invasive mechanical ventilation or ECMO. In patients who require mechanical ventilation or ECMO after initiating Veklury, a full 10 day course of Veklury should be administered. The IDSA and NIH also recommend 3 days of Veklury for non-hospitalized patients with mild-to-moderate COVID-19 who are at high risk of progression.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Veklury. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. All reviews will be forwarded to the Medical Director for evaluation.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Veklury is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. **Coronavirus Disease 2019 (COVID-19), Treatment.** Approve for the duration noted if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient weight is ≥ 1.5 kilograms; AND
   - **B)** Patient has tested positive for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); AND
   - **C)** Patient meets ONE of the following (i or ii):
     - **i.** Approve for 10 days if the patient is being treated in a hospital; OR
     - **ii.** Approve for 3 days if the patient meets both of the following (a and b):
       - **a)** Patient is being treated in an outpatient setting; AND
       - **b)** Patient is at high risk of progression to severe COVID-19, according to the prescriber.

   Dosing. Approve ONE of the following dosing regimens (A, B, C, or D):
   - **A)** Adult, or patient who is < 18 years of age and weighs ≥ 40 kg and meets BOTH of the following (i and ii):
     - **i.** Loading dose: 200 mg intravenous dose given once on Day 1 of therapy; AND
     - **ii.** Maintenance dose: 100 mg intravenous dose given once daily beginning on Day 2; OR
   - **B)** Patient is ≥ 28 days of age and weighs ≥ 3 kg and < 40 kg and meets BOTH of the following (i and ii):
     - **i.** Loading dose: 5 mg/kg intravenous dose given on Day 1 of therapy; AND
     - **ii.** Maintenance dose: 2.5 mg/kg intravenous dose given once daily beginning on Day 2; OR
   - **C)** Patient is ≥ 28 days of age and weighs ≥ 1.5 kg and < 3 kg and meets BOTH of the following (i and ii):
     - **i.** Loading dose: 2.5 mg/kg intravenous dose given on Day 1 of therapy; AND
     - **ii.** Maintenance dose: 1.25 mg/kg intravenous dose given once daily beginning on Day 2; OR
   - **D)** Patient is < 28 days of age and weighs ≥ 1.5 kg and meets BOTH of the following (i and ii):
     - **i.** Loading dose: 2.5 mg/kg intravenous dose given on Day 1 of therapy; AND
     - **ii.** Maintenance dose: 1.25 mg/kg intravenous dose given once daily beginning on Day 2.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Veklury is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Veklury intravenous infusion [prescribing information]. Foster City, CA: Gilead; February 2024.
2. COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. November 02, 2023. Available at: https://www.covid19treatmentguidelines.nih.gov/. Accessed on December 11, 2023.
3. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Disease Society of America Guidelines on the treatment and management of patients with COVID-19. June 26, 2023. Available at: https://www.idsociety.org/COVID19guidelines. Accessed December 11, 2023.
4. Data on file. Veklury® (remdesivir) Dosing in adults weighing < 40 kg. Last update: March 23, 2023. Gilead; received March 4, 2024.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/07/2022
Annual Revision	No criteria changes.	12/13/2023
Selected Revision	**Coronavirus Disease 2019 (COVID-19), Treatment:** The requirement that the patient is ≥ 3 kg was revised to ≥ 1.5 kg. Dosing regimen requirement that patient weighs ≥ 40 kg was revised to "Adult, or patient who is < 18 years of age and weighs ≥ 40 kg"; and removed criterion for hospitalized patients and outpatient treatment. Dosing regimen requirement that the patient weighs ≥ 3 kg and < 40 kg was revised to "Patient is ≥ 28 days of age and weighs ≥ 3 kg and < 40 kg"; and removed criterion for hospitalized patients and outpatient treatment. Added dosing regimen for patient ≥ 28 days of age and weighs ≥ 1.5 kg and < 3 kg. Added dosing regimen for patient < 28 days of age and weighs ≥ 1.5 kg.	03/13/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Corticosteroids (Intraarticular) – Zilretta Utilization Management Medical Policy
- Zilretta® (triamcinolone acetonide extended-release intraarticular injection – Pacira)

REVIEW DATE: 05/08/2024

OVERVIEW

Zilretta, an **extended-release** synthetic corticosteroid, is indicated as an intraarticular injection for the management of **osteoarthritis pain of the knee**.[1]

Several other injectable corticosteroids (e.g., betamethasone sodium phosphate and betamethasone acetate, dexamethasone sodium phosphate, methylprednisolone acetate, and immediate-release triamcinolone acetonide) are indicated for intraarticular use for the management of osteoarthritic conditions.[2-5]

Dosing Information

Zilretta is administered as a single intraarticular injection that delivers 32 mg/5 mL.[1] Limitation of Use: The efficacy and safety of Zilretta for **repeat** administration have not been demonstrated.

Guidelines

Guidelines for the medical management of osteoarthritis of the hand, hip, and knee are available from the American College of Rheumatology (2019).[6] Multiple non-pharmacological modalities are recommended for knee osteoarthritis, including exercise, self-management programs, weight loss, Tai Chi, and use of assistive devices (i.e., bracing or a cane). Pharmacologic therapy for knee osteoarthritis consists of acetaminophen, oral and topical non-steroidal anti-inflammatory drugs, tramadol, intraarticular corticosteroid injections, duloxetine, and topical capsaicin. In the guidelines, no distinction is made between the available intraarticular corticosteroid products or between short-acting and long-acting products.

The American Academy of Orthopaedic Surgeons practice guideline for the management of osteoarthritis of the knee (2021) state intraarticular corticosteroids could provide short-term relief for patients with symptomatic osteoarthritis of the knee.[7] Additionally, extended-release intraarticular corticosteroids can be used over immediate-release to improve patient outcomes.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Zilretta. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for 30 days, which is an adequate duration for the patient to receive one dose per affected knee.

Documentation: Documentation is required for use of Zilretta as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zilretta is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Osteoarthritis Pain of the Knee.** Approve for one injection per treated knee if the patient meets ALL the following (A, B, and C):
   - **A)** Diagnosis of the knee to be treated is confirmed by radiologic evidence of knee osteoarthritis; AND
     Note: Examples of radiographic evidence include diagnosis based on x-ray, magnetic resonance imaging, computed tomography scan, and ultrasound.
   - **B)** Patient has tried at least ONE intraarticular corticosteroid injection in the knee to be treated **[documentation required]**.
     Note: Examples of intraarticular corticosteroid injections include immediate-release triamcinolone acetonide, betamethasone sodium phosphate and betamethasone acetate, dexamethasone sodium phosphate, and methylprednisolone acetate.
   - **C)** Patient is not receiving re-treatment of knee(s) previously treated with Zilretta.

   Dosing. Approve one injection (32 mg/5 mL) administered by intraarticular injection per treated knee.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zilretta is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Zilretta injection [prescribing information]. San Diego, CA: Pacira Pharmaceuticals; March 2022.
2. Betamethasone sodium phosphate and betamethasone acetate injection [prescribing information]. Shirley, NY: American Regent; June 2020.
3. Dexamethasone sodium phosphate injection [prescribing information]. Lehi, UT: Civica; November 2019.
4. Methylprednisolone acetate injection [prescribing information]. Bridgewater, NJ: Amneal; July 2021.
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6. Kolasinski SH, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res.* 2019;72(2):149-162.
7. American Academy of Orthopaedic Surgeons Management of Osteoarthritis of the Knee (Non-Arthroplasty) Evidence-Based Clinical Practice Guideline. Published August 30, 2021. Available at: https://www.aaos.org/oak3cpg. Accessed on May 3, 2024.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	05/03/2023
Annual Revision	No criteria changes.	05/08/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Crysvita Utilization Management Medical Policy
- Crysvita® (burosumab-twza subcutaneous injection – Ultragenyx/Kyowa)

REVIEW DATE: 07/12/2023

OVERVIEW

Crysvita, a fibroblast growth factor 23 (FGF23) blocking antibody, is indicated for[1]:
- **Tumor-induced osteomalacia**, for treatment of FGF-related hypophosphatemia associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in patients ≥ 2 years of age.
- **X-linked hypophosphatemia** in patients ≥ 6 months of age.

Disease Overview

Tumor-Induced Osteomalacia

Tumor-induced osteomalacia is an extremely rare condition caused by tumors that produce the phosphaturic hormone FGF23, which causes renal phosphate wasting, and ultimately leads to hypophosphatemia, rickets, and osteomalacia. Tumor-induced osteomalacia is generally caused by small, slow-growing, benign phosphaturic mesenchymal tumors; complete resection of the tumor results in cure. However, in some cases, locating the tumor is not possible or the tumor may be inoperable. Patients usually present in adulthood with symptoms of fatigue, muscle weakness, and bone pain, which can lead to impaired mobility.[8] They may also experience decreased bone mineral density and frequent fractures. Current treatment of patients with inoperable or unidentifiable tumors has been phosphate supplementation and active vitamin D (e.g., calcitriol).

X-Linked Hypophosphatemia

X-linked hypophosphatemia is a condition that is believed to result from an inactivating genetic mutation in phosphate regulating endopeptidase on the X chromosome (PHEX).[2-5] This mutation leads to increased levels of FGF23, which increases phosphate excretion and abnormal vitamin D metabolism, ultimately leading to hypophosphatemic rickets.[2-4,6] Signs and symptoms of X-linked hypophosphatemia differ in pediatric patients who are still growing vs. adults whose epiphyseal plates have fused. In adults, symptoms include calcification of tendons, ligaments, and joint capsules; joint pain; impaired mobility; spontaneous dental abscesses; stress fractures; and sensorineural hearing loss. The X-linked hypophosphatemia diagnosis can be established in patients with a low serum phosphate concentration, a reduced tubular resorption of phosphate corrected for glomerular filtration rate (TmP/GFR), an inappropriate calcitriol level for the severity of hypophosphatemia, and/or by identification on molecular genetic testing of a hemizygous PHEX pathogenic variant in a male patient or a heterozygous PHEX pathogenic variant in a female patient. Genetic testing can provide a negative or positive confirmation in 70 to 90% of patients with suspected X-linked hypophosphatemia who lack a family history.[5] If a genetic test is unavailable, an elevated FGF23 level can also support the diagnosis. However, FGF23 levels may be influenced by other factors, particularly phosphate and vitamin D therapy. FGF23 levels may be elevated in several other forms of hypophosphatemic rickets as well. Finally, the normal range of FGF23 varies according to the assay used.

Clinical Efficacy

Tumor-Induced Osteomalacia

Two studies evaluated the efficacy of Crysvita in patients with tumor-induced osteomalacia.[1,14,15] Eligible patients were adults with a confirmed diagnosis of FGF23-related hypophosphatemia produced by an underlying tumor that was not amenable to surgical excision or could not be located. In addition to low baseline serum phosphorus, patients were also required to have a low tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) and a high FGF23 level. The vast majority of patients had previously received phosphate and active vitamin D therapy. Crysvita was found to increase the mean serum phosphorus level from baseline through Week 24 (Month 6) when levels stabilized.

X-Linked Hypophosphatemia

The efficacy of Crysvita for the treatment of X-linked hypophosphatemia was evaluated in several clinical trials in pediatric and adult patients with X-linked hypophosphatemia.[1] Eligible patients had baseline serum phosphorus levels less than the lower limit of normal for age.[1,9-11] Across the studies, Crysvita was found to increase mean serum phosphorus levels significantly from baseline. Radiographic improvements and healing of fractures/pseudofractures were also observed. Sustained efficacy has been demonstrated out to Week 96.[12,16] One additional study compared Crysvita with conventional therapy in patients 1 to 12 years of age with X-linked hypophosphatemia.[13] Following 64 weeks of therapy, patients receiving Crysvita had demonstrated a significantly greater improvement in the Radiographic Global Impression of Change global score compared with the conventional therapy group. In patients 5 to 12 years of age, sustained efficacy has been observed for up to 160 weeks, while there are extension data up to 168 weeks in adults.[17-19]

GUIDELINES

An expert panel has published Clinical Practice Recommendations for the Diagnosis and Management of X-linked hypophosphatemia (2019).[5] It is recommended that a clinical diagnosis of X-linked hypophosphatemia be confirmed by genetic analysis of the PHEX gene if feasible. In regard to treatment, oral phosphate and active vitamin D (e.g., calcitriol) are recommended for symptomatic adults with X-linked hypophosphatemia. Crysvita therapy should be considered for the treatment of adults with X-linked hypophosphatemia with the following features: persistent bone/joint pain due to X-linked hypophosphatemia and/or osteomalacia that limits daily activities; pseudofractures or osteomalacia-related fractures; and insufficient response or refractory to oral phosphate and active vitamin D. If patients experience complications related to oral phosphate and active vitamin D, Crysvita is recommended as well.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Crysvita. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the durations noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Crysvita, as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Crysvita to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

*Indications and/or approval conditions noted with **[eviCore]** are managed by eviCore healthcare for those clients who use eviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to eviCore at www.eviCore.com.*

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Crysvita is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Tumor-Induced Osteomalacia.** ***[eviCore]*** Approve Crysvita for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):
     - **i.** Patient is ≥ 2 years of age; AND
     - **ii.** Patient has a mesenchymal tumor that cannot be curatively resected or identified/localized; AND
     - **iii.** Patient is currently exhibiting one or more signs or symptoms of tumor-induced osteomalacia, as determined by the prescriber; AND
       Note: Examples of signs and symptoms of tumor-induced osteomalacia include bone pain, impaired mobility, muscle weakness, and fatigue.
     - **iv.** Patient has had a baseline serum phosphorus level that was below the normal range for age; AND
       Note: "Baseline" is defined as prior to receiving any tumor-induced osteomalacia treatment, such as Crysvita, oral phosphate, or vitamin D therapy.
     - **v.** Patient has had a baseline tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) that was below the normal range for age and gender; AND
       Note: "Baseline" is defined as prior to receiving any tumor-induced osteomalacia treatment, such as Crysvita, oral phosphate, or vitamin D therapy.
     - **vi.** Patient meets ONE of the following (a or b):
       - **(1)** Patient has tried oral phosphate and calcitriol therapy; OR
       - **(2)** Per the prescriber the patient has a contraindication to oral phosphate therapy, calcitriol therapy, or both; AND
     - **vii.** The medication is prescribed by or in consultation with an endocrinologist or nephrologist.
   - **B)** Patient is Currently Receiving Crysvita. Approve for 1 year if the patient is continuing to derive benefit from Crysvita as determined by the prescriber.
     Note: Examples of a response to Crysvita therapy are increased phosphorus levels, decreased symptoms of bone pain and/or muscle weakness, and increased mobility.

   Dosing. Approve up to 180 mg given subcutaneously not more frequently than once every 2 weeks.

2. **X-Linked Hypophosphatemia.** Approve Crysvita for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient has had a baseline serum phosphorus level that was below the normal range for age; AND

Note: "Baseline" is defined as prior to receiving any X-linked hypophosphatemia treatment, such as Crysvita, oral phosphate, or vitamin D therapy.

ii. Patient meets ONE of the following (a or b):
- **a)** Patient has had a baseline tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) that was below the normal range for age and gender; OR
  Note: "Baseline" is defined as prior to receiving any X-linked hypophosphatemia treatment, such as Crysvita, oral phosphate, or vitamin D therapy.
- **b)** Patient has had a genetic test confirming the diagnosis of X-linked hypophosphatemia via identification of a PHEX mutation; AND

iii. If the patient is ≥ 18 years of age, the patient meets BOTH of the following (a and b):
- **a)** Patient is currently exhibiting one or more signs or symptoms of X-linked hypophosphatemia, as determined by the prescriber; AND
  Note: Examples of signs and symptoms of X-linked hypophosphatemia in patients ≥ 18 years of age include fractures/pseudofractures, bone and joint pain, muscle weakness, and impaired mobility.
- **b)** Patient meets ONE of the following (1 or 2):
  - **(1)** Patient has tried oral phosphate and calcitriol therapy; OR
  - **(2)** Per the prescriber the patient has a contraindication to oral phosphate therapy, calcitriol therapy, or both; AND

iv. The medication is prescribed by or in consultation with an endocrinologist or nephrologist.

B) Patient is Currently Receiving Crysvita. Approve for 1 year if the patient is continuing to derive benefit from Crysvita as determined by the prescriber.
Note: Examples of a response to Crysvita therapy are increased phosphorus levels, radiographic improvement in deformities, healing of fractures/pseudofractures, reduction in the incidence of new fractures/pseudofractures.

Dosing. Approve dosing that meets one of the following dosing regimens (A or B):

A) If the patient is ≥ 18 years of age, approve up to a maximum dose of 90 mg administered subcutaneously not more frequently than once every 4 weeks; OR

B) If the patient is < 18 years of age, approve up to a maximum dose of 90 mg administered subcutaneously not more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Crysvita is not recommended in the following situations:

1. **Chronic Kidney Disease, Severe Renal Impairment or End Stage Renal Disease**. Crysvita is contraindicated in patients with severe renal impairment or end stage renal disease.[1] These patients often have abnormal mineral metabolism which may be associated with FGF23. However, Crysvita has not been studied for the treatment of patients with chronic kidney disease who have elevations of FGF23 impacting phosphate regulation.[1,9]

2. **Epidermal Nevus Syndrome**. More data are necessary to establish the efficacy and safety of Crysvita in patients with epidermal nevus syndrome. Patients with epidermal nevus syndrome were eligible to enroll in one of the Phase II tumor-induced osteomalacia studies of Crysvita.[15] However, no patients with epidermal nevus syndrome enrolled.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	06/22/2022
Annual Revision	No criteria changes.	07/12/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Dermatology – Ycanth Utilization Management Medical Policy
- Ycanth™ (cantharidin 0.7% topical solution – Verrica)

REVIEW DATE: 02/28/2024

OVERVIEW
Ycanth, a cantharidin-based topical solution, is indicated for the treatment of molluscum contagiosum in patients 2 years of age and older.[1]

Disease Overview
Molluscum contagiosum is a viral skin infection of the Poxviridae family that can cause white, pink, or flesh colored bumps either alone, or in groups; it is spread by direct contact.[2,3] Common locations are the trunk, face, and extremities. Patients may experience pain, itching, and eczema, as well as secondary bacterial infections. Resolution usually occurs within 6 to 12 months; in selected cases it can take longer for the skin infection to completely disappear. The condition is found in children and adults; however, it is more common in younger patients. Immunocompetent patients can often clear the infection without treatment. However, patients with additional dermatologic conditions (e.g., atopic dermatitis), or in those who are immunocompromised, have more extensive infection that is harder to treat. Molluscum contagiosum is most common in warm, humid climates.

Clinical Efficacy
The efficacy of Ycanth for the treatment of molluscum contagiosum infections has been evaluated in two pivotal studies.[1,4] The studies included patients ≥ 2 years of age with a clinical diagnosis of molluscum contagiosum with treatable lesions. The primary efficacy endpoint was the proportion of the Ycanth treated patients achieving complete clearance of all molluscum contagiosum lesions compared to those who received the vehicle at Day 84 of trial.

Guidelines
Ycanth is not addressed in guidelines. The American Academy of Pediatrics (AAP) RedBook 2021-2024 cite that cryotherapy, curettage and cantharidin (compounded) have the most support for treatment.[2]

POLICY STATEMENT
Prior Authorization is recommended for medical benefit coverage of Ycanth. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ycanth is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Molluscum Contagiosum.** Approve Ycanth for 3 months if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient is ≥ 2 years of age; AND
   - **B)** Approve if patient meets ONE of the following (i or ii):
     - **i.** Patient is treating new lesions that have not previously been treated with Ycanth; OR
     - **ii.** Patient is treating lesions that have been previously treated with Ycanth for less than 4 treatment cycles; AND
   - **C)** Ycanth is being administered by a healthcare professional.

   Dosing. Approve two applicators per treatment, once every 21 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ycanth is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy		02/28/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Dermatology – Gene Therapy – Vyjuvek Utilization Management Medical Policy
- Vyjuvek™ (beremagene geperpavec-svdt topical gel – Krystal Biotech)

REVIEW DATE: 06/28/2023; selected revision 09/13/2023, 09/27/2023, 10/11/2023, and 01/24/2024

OVERVIEW

Vyjuvek, a herpes-simplex virus type-1 (HSV-1) vector-based gene therapy, is indicated for the treatment of wounds in patients ≥ 6 months of age with **dystrophic epidermolysis bullosa** (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene.[1]

Vyjuvek is a live, replication defective HSV-1-based vector that has been genetically modified to express the human type VII collagen (COL7) protein.[1] Mutation(s) in the COL7A1 gene result in reduced or absent levels of biologically active COL7 in patients with DEB. COL7 protein is a crucial component of anchoring fibrils that are essential for maintaining skin integrity. Application of Vyjuvek to wounds results in transcription of the encoded human COL7A1 and production and secretion of COL7 by the cell in its mature form. The COL7 molecules form anchoring fibrils that hold the epidermis and dermis together.

DEB usually presents at birth and is divided into two major types depending on the pattern of inheritance: recessive DEB (RDEB) and dominant DEB (DDEB).[6] All subtypes of DEB are caused by mutations in the gene coding COL7A1 leading to extreme skin fragility.[4,6] The hallmark of DEB is scarring of blisters, both on the skin and on other mucosal surfaces.[4]

Clinical Efficacy

GEM-3, a Phase III, double-blind, placebo-controlled, intrapatient randomized, pivotal study, assigned patients with DEB to treat two similarly sized wounds; one with Vyjuvek and one with placebo for 26 weeks (N = 31).[2] Eligible patients were ≥ 6 months of age presenting with a clinical diagnosis of DEB, characterized by blistering, wounds, and scarring and confirmed by genetic testing including COL7A1. The appearance of the wounds was to be clean with adequate granulation tissue, excellent vascularization, and to not appear infected. Patients receiving immunotherapy, chemotherapy, or other investigational products were not included. In addition, wound sites with current evidence or a history of squamous-cell carcinoma or active infection were excluded as sites for Vyjuvek (or placebo) application. Vyjuvek or placebo was applied only to open wounds. Wounds were evaluated weekly to determine continued application of Vyjuvek or placebo. If a healed wound reopened, application was resumed; if the wound remained closed, application was omitted. All but one patient had the recessive DEB genotype. At Month 6, significantly more Vyjuvek- vs. placebo-treated wounds were completely healed (67% vs. 22%, respectively; P = 0.002) [primary endpoint]. Similar results were observed at Month 3 favoring Vyjuvek vs. placebo for complete wound healing (71% vs. 20%, respectively; P < 0.001). Durability (complete wound healing at both Months 3 and 6) was seen in 50% vs. 7% of Vyjuvek- vs. placebo-treated wounds, respectively (difference 43%; 95% confidence interval: 23%, 63%). One patient had a chronic secondary wound of the back measuring > 100 cm^2 that had been open for > 10 years. Following Vyjuvek treatment, the patient was able to resume activities of daily living, including showering, which had not previously been possible due to the open nature of the wound.

Dosing Information

Only a healthcare professional should apply Vyjuvek either in a healthcare setting (e.g., clinic) or the home setting.[1] The recommended dose is based on age (see Table 1) and applied topically to wound(s) once weekly. It may not be possible to apply Vyjuvek to all the wounds at each treatment visit. Vyjuvek should be applied to wounds until they are closed before selecting new wound(s) to treat. Prioritize weekly treatment to previously treated wounds if they re-open. If a dose is missed, apply Vyjuvek as soon as possible and resume weekly dosing thereafter. Vyjuvek is applied to the selected wound(s) in droplets spaced evenly within the wound, approximately 1 cm x 1 cm apart. The resulting droplet pattern should loosely resemble a grid. Table 2 provides a reference dose based on wound size. A hydrophobic dressing is placed on top the Vyjuvek droplets, and a standard dressing is placed on top of the hydrophobic dressing. The wound dressing should not be changed for approximately 24 hours after Vyjuvek gel administration.

Table 1. Maximum Weekly Dose by Age.[1]

Age Range	Maximum Weekly Dose	Maximum Weekly Volume*
≥ 6 months to < 3 years	1.6 x 10^9 PFUs	0.8 mL
≥ 3 years	3.2 x 10^9 PFUs	1.6 mL

* Maximum weekly volume after mixing Vyjuvek biological suspension with excipient gel; PFUs – Plaque forming units.

Table 2. Reference Dose by Wound Size.[1]

Area	Dose	Volume
< 20 cm^2	4 x 10^8 PFUs	0.2 mL
≥ 20 cm^2 to < 40 cm^2	8 x 10^8 PFUs	0.4 mL
≥ 40 cm^2 to ≤ 60 cm^2	1.2 x 10^9 PFUs	0.6 mL

PFUs – Plaque forming units.

Guidelines

Vyjuvek is not addressed in available guidelines. According to a position statement by the **European Reference Network for Rare Skin Diseases** (2021), wound care is the cornerstone of treatment for patients with DEB.[5] Careful and complete skin and wound assessment should be undertaken regularly, at least every 6 months. The healing rate of chronic wounds should be closely monitored, by checking wound edges.

The diagnosis of DEB is based on a combination of clinical features, family history, and laboratory findings.[5] Laboratory techniques include immunofluorescence mapping, transmission electron microscopy, and molecular genetic testing. Whenever possible, laboratory diagnosis should be performed in a specialized DEB center. Genetic testing is the gold standard for the diagnosis of DEB, since it provides a definitive diagnosis and classification of the major DEB type and in many cases the subtype.

An **international consensus best practice guideline** on skin and wound care in epidermolysis bullosa (EB) [2017] notes that EB is a lifelong disease that requires specialist intervention and consideration to minimize complications and improve quality of life.[6] Management should take place in a specialized center by a multi-disciplinary team, ideally. Definitive diagnosis is most commonly made from analysis of a skin biopsy using positive immunofluorescence, antigenic mapping, and transmission electron microscopy. These key diagnostic tools help confirm diagnosis and indicate the particular subtype of EB. Due to the rarity of expertise and facilities, diagnosis is generally made using immunofluorescence and antigen mapping. Some laboratories are moving towards molecular diagnosis from exome sequencing of a panel of known skin fragility genes. Experienced clinicians can often make a provisional diagnosis on clinical observations, but a definitive diagnosis will always be required.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Vyjuvek. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vyjuvek as well as the monitoring required for adverse events and long-term efficacy, approval requires Vyjuvek to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Vyjuvek as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vyjuvek is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Dystrophic Epidermolysis Bullosa.** Approve for the duration outlined below if the patient meets ONE of the following (A or B):
   Note: For new wound(s) the patient is directed to Initial Therapy criteria. If the patient is continuing to treat the same wound(s) the patient is directed to criteria for Patient Currently Receiving Vyjuvek on Previously Treated Wound(s).
   - **A)** Initial Therapy: Approve for 6 months if the patient meets the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 6 months of age; AND
     - **ii.** The diagnosis is confirmed by genetic testing showing a pathogenic mutation in the collagen type VII alpha 1 chain (COL7A1) gene **[documentation required]**; AND
     - **iii.** Patient meets ALL of the following (a, b, and c):
       - **a)** Patient has at least one clinical feature of dystrophic epidermolysis bullosa **[documentation required]**; AND
         Note: Examples of clinical features of dystrophic epidermolysis bullosa include but are not limited to blistering, wounds, and scarring.
       - **b)** Patient has one or more open wound(s) that will be treated (i.e., "target wound[s]); AND
       - **c)** Target wound(s) meets the following, according to the prescriber [(1), (2), and (3)]:
         - **(1)** Target wound(s) is clean in appearance and does not appear to be infected; AND
         - **(2)** Target wound(s) has adequate granulation tissue and vascularization; AND
         - **(3)** Squamous cell carcinoma has been ruled out for the target wound(s); AND
     - **iv.** The medication is prescribed by or in consultation with a dermatologist or wound care specialist.

B) Patient is Currently Receiving Vyjuvek on **Previously Treated Wound(s)**: Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
Note: If the patient is treating a new wound(s) not previously treated with Vyjuvek or a reopened recurrent wound(s), then refer to Initial Therapy criteria above.
- **i.** According to the prescriber, the target wound(s) remains open; AND
- **ii.** According to the prescriber, the target wound(s) has decreased in size from baseline; AND
- **iii.** The medication is prescribed by or in consultation with a dermatologist or wound care specialist.

Dosing. Approve one of the following dosing regimens (A or B):

A) Patient is ≥ 6 months to < 3 years of age: Approve up to 0.8 mL (1.6×10^9 plaque forming units) topically once weekly.
Note: This is the maximum weekly volume after mixing Vyjuvek biological suspension with excipient gel.

B) Patient is ≥ 3 years of age: Approve up to 1.6 mL (3.2×10^9 plaque forming units) topically once weekly.
Note: This is the maximum weekly volume after mixing Vyjuvek biological suspension with excipient gel.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vyjuvek is not recommended in the following situations:

1. **Combination use with Filsuvez (birch triterpenes topical gel).** Combination use of Vyjuvek and Filsuvez have not been studied.[7]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	06/28/2023
Selected Revision	**Dystrophic Epidermolysis Bullosa.** Criteria were divided into "Initial Therapy" and "Patient is Currently Receiving Vyjuvek". The approval duration for initial and continuation therapy are 3 months, previously criteria approved all patients for 6 months. Initial Therapy A documentation requirement was added to criteria for the confirmation of the diagnosis by genetic testing showing a pathogenic mutation in the collagen type VII alpha 1 chain (COL7A1) gene. A documentation requirement was added to criteria for one clinical feature of dystrophic epidermolysis bullosa. Criteria for one or more open wound(s) were clarified to address such wound(s) would be treated (referred to as "target wound[s]") and that, according to the prescriber, the target wound(s) meets all of the following criteria: is clean in appearance and does not appear to be infected, has adequate granulation tissue and vascularization, and squamous cell carcinoma has been ruled out. Patient is Currently Receiving Vyjuvek on Previously Treated Wound(s) Patients currently receiving Vyjuvek on previously treated wounds are required to have a target wound(s) that remains open, according to the prescriber and has decreased in size from baseline as demonstrated by wound measurements or photographs, according to the prescriber. The medication must also be prescribed by or in consultation with a dermatologist or wound care specialist with expertise in the management of dystrophic epidermolysis bullosa. Of note, if the patient is treating a new wound(s) not previously treated with Vyjuvek or reopened recurrent wound(s) the patient is directed to Initial Therapy criteria.	09/13/2023
Selected Revision	**Dystrophic Epidermolysis Bullosa.** Initial Therapy: The approval duration was changed to 6 months. Patient is Currently Receiving Vyjuvek on Previously Treated Wound(s): The approval duration was changed to 6 months.	09/27/2023
Selected Revision	**Dystrophic Epidermolysis Bullosa.** Patient is Currently Receiving Vyjuvek on Previously Treated Wound(s): The criterion requiring that the target wound(s) has decreased in size from baseline as demonstrated by wound measurements or photographs, according to the prescriber was modified to remove the requirement of wound measurements or photographs. The criterion now requires that according to the prescriber, the target wound(s) has decreased in size from baseline.	10/11/2023
Selected Revision	**Dystrophic Epidermolysis Bullosa:** Initial Therapy and Patient is Currently Receiving Vyjuvek on Previously Treated Wound(s). The criterion requiring that the medication is prescribed by or in consultation with a dermatologist or wound care specialist with expertise in the management of dystrophic epidermolysis bullosa was modified to remove the requirement of expertise in the management of dystrophic epidermolysis bullosa. The requirement now reads that the medication is prescribed by or in consultation with a dermatologist or wound care specialist. **Combination use with Filsuvez (birch triterpenes topical gel).** This condition was added to the Conditions Not Recommended for Approval.	01/24/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Diabetes – Tzield Utilization Management Medical Policy
- Tzield™ (teplizumab-mzwv intravenous infusion – Provention/Sanofi)

REVIEW DATE: 11/15/2023

OVERVIEW

Tzield, an anti-CD3 monoclonal antibody, is indicated to **delay the onset of Stage 3 type 1 diabetes** in adults and pediatric patients ≥ 8 years of age with Stage 2 type 1 diabetes.

Tzield is administered by intravenous infusion (over a minimum of 30 minutes) using body surface area-based dosing, once daily for 14 consecutive days.[1] Prior to initiating Tzield, obtain a complete blood count and liver enzyme tests. Use of Tzield is not recommended in patients with certain laboratory abnormalities, including lymphopenia, anemia, thrombocytopenia, neutropenia, or increased liver enzymes. Refer to the prescribing information for specific thresholds. Additionally, patients with laboratory or clinical evidence of acute infection with Epstein-Barr virus or cytomegalovirus should not receive Tzield, nor should patients with active serious infection or chronic active infection other than localized skin infections.

Clinical Efficacy

Efficacy of Tzield among patients at risk for development of type 1 diabetes was evaluated in one pivotal study called TN-10 (published) [n = 76].[2] Eligible patients were non-diabetic relatives of patients with type 1 diabetes and were ≥ 8 years of age at the time of randomization. Patients were also required to have two or more diabetes-related autoantibodies, confirmed on at least two occasions, within 6 months before randomization. In addition, patients were required to have had evidence of dysglycemia during an oral glucose tolerance test (OGTT). An abnormal OGTT was defined as meeting one of the following: fasting plasma glucose ≥ 110 to < 126 mg/dL; 2-hour postprandial plasma glucose ≥ 140 to < 200 mg/dL; or 30-, 60-, or 90-minute postprandial plasma glucose ≥ 200 mg/dL. Initially, two OGTTs were required within 52 days of enrollment; however, a protocol amendment was put in place requiring only one abnormal glucose tolerance test result for patients < 18 years of age.

Guidelines

American Diabetes Association (ADA) Standards of Care (2023) state that Tzield should be considered in selected individuals ≥ 8 years with stage 2 type 1 diabetes to delay the onset of symptomatic type 1 diabetes.[3] Management should be in a specialized setting with appropriately trained personnel. According to the ADA Standards, screening for pre-symptomatic type 1 diabetes may be done by detection of autoantibodies to insulin, glutamic acid decarboxylase (GAD, GAD65), islet antigen 2 (IA-2 and IA-2b), or zinc transporter 8 (Level B recommendation).[3] The presence of multiple islet autoantibodies is a risk factor for clinical diabetes. Testing for dysglycemia may be used to further forecast near-term risk. When multiple islet autoantibodies are identified, referral to a specialized center for further evaluation and/or consideration of a clinical trial or approved therapy to potentially delay the development clinical diabetes should be considered (Level B recommendation).

According to the ADA Standards, three distinct stages of type 1 diabetes can be identified, which serve as a framework for future research and regulatory decision-making.[3] Clinical type 1 diabetes is referred to as "Stage 3 type 1 diabetes" and is characterized by overt hyperglycemia and the presence of symptoms. Diagnostic criteria include involve one of the following: fasting plasma glucose (FPG) ≥ 126 mg/dL; 2-hour postprandial glucose ≥ 200 mg/dL during an OGTT (75 grams); hemoglobin A_{1c} (HbA_{1c}) ≥ 6.5%; or

random plasma glucose ≥ 200 mg/dL for a patient with classic symptoms of hyperglycemia or hyperglycemic crisis. "Stage 1 type 1 diabetes" and "Stage 2 type 1 diabetes" are pre-symptomatic states characterized by autoimmunity (i.e., multiple autoantibodies) but no overt diabetes symptoms. In Stage 1 disease, glycemia is normal. In Stage 2 disease, dysglycemia is present but below the threshold considered overt for Stage 3 type 1 diabetes. Dysglycemia in Stage 2 type 1 diabetes involves FPG 100 to 125 mg/dL; 2-hour postprandial glucose 140 to 199 mg/dL; HbA_{1c} 5.7% to 6.4%; or a ≥ 10% increase in HbA_{1c}.

Screening for Type 1 Diabetes Risk

Multiple studies indicate that measuring islet autoantibodies in relatives of those with type 1 diabetes or in children from the general population can effectively identify those who will develop type 1 diabetes.[3] A study reported the risk of progression to type 1 diabetes from the time of seroconversion to autoantibody positivity in pediatric cohorts from three countries. Of the 585 children who developed more than two autoantibodies, nearly 70% developed type 1 diabetes within 10 years and 84% developed type 1 diabetes within 15 years. These findings are highly significant because while the one group of patients was recruited from children of parents with type 1 diabetes, the other two groups were recruited from the general population. The findings in all three groups were the same, suggesting that the same sequence of events led to clinical disease in both "sporadic" and familial cases of type 1 diabetes. The risk of type 1 diabetes increases as the number of relevant autoantibodies detected increases.

Family history of autoimmune diabetes and personal or family history of allergic diseases or other autoimmune diseases increases risk of autoimmune diabetes compared with the general population.[3] Individuals who test autoantibody positive should be either provided with or referred for counseling about the risk of developing diabetes, diabetes symptoms, diabetic ketoacidosis prevention, and consideration of additional testing as applicable to help determine if they meet criteria for intervention aimed at delaying progression.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Tzield. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tzield as well as the monitoring required for adverse events and long-term efficacy, approval requires Tzield to be prescribed by or in consultation with a physician who specializes in the condition being treated. For certain criteria, verification is required as noted by **[verification required by prescriber]**. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to chart notes, laboratory tests, claims records, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tzield is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Type 1 Diabetes (Clinical/Stage 3), Delay of Onset.** Approve for a one-time per lifetime course (14-day course) if the patient meets the following (A, B, C, D, E, F, G, H, I, J, and K):
   - **A)** Patient is ≥ 8 years of age; AND
   - **B)** Patient does NOT have a clinical diagnosis of type 1 diabetes (i.e., Stage 3 type 1 diabetes); AND
     Note: Clinical type 1 diabetes is also referred to as Stage 3 type 1 diabetes. "Stage 1 type 1 diabetes" and "Stage 2 type 1 diabetes" are considered preclinical states and would not fall into the category of clinical type 1 diabetes.
   - **C)** Patient does NOT have type 2 diabetes; AND
   - **D)** Patient has at least one biological relative with a diagnosis of type 1 diabetes; AND
     Note: Examples of relatives include first-degree relatives (e.g., parent, sibling) or other relatives (e.g., grandparent, aunt, uncle, cousin).
   - **E)** Patient has tested positive for at least TWO of the following type 1 diabetes-related autoantibodies on two separate occasions: anti-glutamic acid decarboxylase 65 (anti-GAD65); anti-islet antigen-2 (anti-IA-2); islet-cell autoantibody (ICA); micro insulin; anti-zinc transporter 8 (anti-ZnT8) **[documentation required]**.
     Note: The patient needs to have tested positive on two separate occasions, with at least two positive autoantibodies per occasion; however, the patient does not have to be positive for the same two antibodies on both occasions. For example, a positive test for anti-GAD65 and anti-IA-2 on one occasion, and positive test for ICA and micro insulin on another occasion would satisfy the requirement.
   - **F)** Patient meets ONE of the following (i, ii, or iii) **[documentation required]**:
     - **i.** Patient has a 2-hour postprandial glucose level ≥ 140 to < 200 mg/dL during an oral glucose tolerance test in the preceding 2 months; OR
     - **ii.** Patient has a fasting plasma glucose level ≥ 100 to < 126 mg/dL in the preceding 2 months; OR
     - **iii.** Patient has an HbA_{1c} ≥ 5.7% to < 6.5% in the preceding 2 months. AND
   - **G)** At baseline (prior to the initiation of Tzield), patient does NOT have evidence of hematologic compromise, as defined by meeting the following (i, ii, iii, and iv) **[documentation required]**:
     - **i.** Lymphocyte count ≥ 1,000 lymphocytes/mcL; AND
     - **ii.** Hemoglobin ≥ 10 g/dL; AND
     - **iii.** Platelet count ≥ 150,000 platelets/mcL; AND
     - **iv.** Absolute neutrophil count ≥ 1,500 neutrophils/mcL; AND
   - **H)** At baseline (prior to the initiation of Tzield), patient does NOT have evidence of hepatic compromise, as defined by meeting the following (i, ii, and iii) **[documentation required]**:
     - **i.** Alanine aminotransferase (ALT) ≤ 2 times the upper limit of normal (ULN); AND
     - **ii.** Aspartate aminotransferase (AST) ≤ 2 times the ULN; AND
     - **iii.** Bilirubin ≤ 1.5 times the ULN; AND
   - **I)** According to the prescriber, the patient does NOT have any of the following (i, ii, or iii):
     - **i.** Laboratory or clinical evidence of acute infection with Epstein-Barr Virus or cytomegalovirus; OR
     - **ii.** Active serious infection; OR
     - **iii.** Chronic active infection (other than localized skin infection); AND
   - **J)** Patient has NOT received Tzield in the past **[verification required by prescriber]**; AND
     Note: Verify through claims history that the patient has not previously received Tzield AND, if no claim for Tzield is present, the prescriber must attest that the patient has not previously received Tzield.
   - **K)** The medication will be prescribed by an endocrinologist.

Dosing. Approve a one-time, 14-day course of Tzield with the following regimen (A, B, C, D, and E):
A) 65 mcg/m^2 body surface area (BSA) given intravenously on Day 1; AND
B) 125 mcg/m^2 BSA given intravenously on Day 2; AND
C) 250 mcg/m^2 BSA given intravenously on Day 3; AND
D) 500 mcg/m^2 BSA given intravenously on Day 4; AND
E) 1,030 mcg/m^2 BSA given intravenously once daily on Days 5 through 14.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tzield is not recommended in the following situations:

1. **Type 1 Diabetes (Clinical/Stage 3), Treatment.** Note: Clinical type 1 diabetes is also referred to as Stage 3 type 1 diabetes. "Stage 1 type 1 diabetes" and "Stage 2 type 1 diabetes" are considered preclinical states and would not fall into the category of clinical type 1 diabetes.
   Tzield is not indicated for patients with a diagnosis of clinical type 1 diabetes (i.e., Stage 3 type 1 diabetes).

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Tzield™ intravenous infusion [prescribing information]. Red Bank, NJ: Provention; November 2022.
2. Herold KC, Bundy BN, Long SA, et al; Type 1 Diabetes TrialNet Study Group. An Anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. *N Engl J Med*. 2019 Aug 15;381(7):603-613.
3. American Diabetes Association. Standards of medical care in diabetes – 2023. *Diabetes Care*. 2023;46(Suppl 1):S1-S291.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	11/30/2022
Annual Revision	**Type 1 Diabetes (Clinical/Stage 3), Delay of Onset.** Glycemic criteria for the diagnosis of Stage 2, Type 1 diabetes was revised. The criterion related to fasting plasma glucose was modified to remove the requirement that the result of the test comes from an oral glucose tolerance test. Additionally, the definition of the fasting plasma glucose value was modified to ≥ 100 mg/dL to < 126 mg/dL (previously, fasting plasma glucose was defined as a value of ≥ 110 mg/dL to < 126 mg/dL). The criterion for an intervening postprandial glucose level at 30, 60, or 90 minutes of > 200 mg/dL based on an oral glucose tolerance test within the preceding 2 months was removed. A new criterion was added, such that an HbA_{1c} of ≥ 5.7% to < 6.5% in the preceding 2 months is an option for diagnosis. The updated set of glycemic criteria for the diagnosis of Stage 2, Type 1 diabetes now reads that the patient meets ONE of the following [documentation required]: Patient has a 2-hour postprandial glucose level ≥ 140 mg/dL to < 200 mg/dL during an oral glucose tolerance test in the preceding 2 months (no change to this criterion); OR, Patient has a fasting plasma glucose level of ≥ 100 mg/dL to < 126 mg/dL in the preceding 2 months (see change described above); OR, Patient has an HbA_{1c} of ≥ 5.7% to < 6.5% in the preceding 2 months (new criterion, see above).	11/15/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Aldurazyme Utilization Management Medical Policy
- Aldurazyme® (laronidase intravenous infusion – Genzyme)

REVIEW DATE: 04/24/2024

OVERVIEW

Aldurazyme, a human α-L-iduronidase, is indicated for **Hurler and Hurler-Scheie forms of Mucopolysaccharidosis type I (MPS I)** and in patients with the **Scheie form who have moderate to severe symptoms**.[1]

Disease Overview

MPS I is a rare autosomal recessive, lysosomal storage disease characterized by the deficiency of α-L-iduronidase.[2] Patients with MPS I are unable to degrade dermatan and heparin sulfate, resulting in the accumulation of glycosoaminoglycans within lysosomes. Over time, the accumulation of glycosoaminoglycans leads to progressive tissue damage,[3] ultimately resulting in multiorgan dysfunction.[2,3] Patients with MPS I commonly have a characteristic face, corneal clouding, cardiomyopathy, enlarged tongue, respiratory insufficiency, hepatosplenomegaly, hernias, dysostosis multiplex, joint stiffness, and cognitive impairment.[4,5] MPS I is commonly classified as three separate entities, Hurler syndrome (severe form), Hurler-Scheie syndrome (intermediate form) and Scheie syndrome (mild form).[2-4] However, this classification system is based on disease severity and age of onset, not on any biochemical differences between the three syndromes.[5] All three forms of the disease are the result of the same enzymatic deficiency and represent varying degrees of severity along the disease continuum. The definitive diagnosis of MPS I is based on demonstrating deficient α-L-iduronidase activity in fibroblasts, leukocytes, plasma, or serum.[2,3,5]

Specific treatments for MPS I include hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy.[2,4,5] HSCT is indicated for the severe forms of MPS I, in children < 2 years of age who are cognitively intact.[2,4] HSCT has been shown to preserve intellectual development, reverse some aspects of somatic disease and increase survival.[2,4,5] Enzyme replacement therapy (Aldurazyme) does not cross the blood-brain barrier and is unlikely to improve cognitive or neurologic function.[2] Therefore, Aldurazyme is appropriate in children < 2 years of age who have already experienced cognitive decline, or who are cognitively intact with severe physical disease prior to HSCT to improve their health. Aldurazyme is also recommended in older patients with or without cognitive or neurologic decline.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Aldurazyme. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Aldurazyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Aldurazyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Aldurazyme is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Mucopolysaccharidosis Type I (Hurler Syndrome, Hurler-Scheie Syndrome, and Scheie Syndrome).** Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** The diagnosis is established by ONE of the following (i or ii):
     - **i.** Patient has a laboratory test demonstrating deficient α-L-iduronidase activity in leukocytes, fibroblasts, plasma, or serum; OR
     - **ii.** Patient has a molecular genetic test demonstrating biallelic pathogenic or likely pathogenic α-L-iduronidase (*IDUA*) gene variants; AND
   - **B)** Aldurazyme is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

   Dosing. Each dose must not exceed 0.58 mg/kg administered intravenously no more frequently than once weekly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Aldurazyme is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Aldurazyme® intravenous infusion [prescribing information]. Novato, CA: Genzyme; December 2023.
2. Muenzer J, Wraith JE, Clarke LA, et al. Mucopolysaccharidosis I: Management and treatment guidelines. *Pediatrics*. 2009;123:19-29.
3. Clarke LA, Atherton AM, Burton BK, et al. Mucopolysaccharidosis type I newborn screening: Best practices for diagnosis and management. *J Pediatr*. 2017;182:363-370.
4. Giugliani R, Federhen A, Munoz Rojas MV, et al. Mucopolysaccharidosis I, II, and VI: Brief review and guidelines for treatment. *Genet Mol Biol*. 2010;33:589-604.
5. Martins AM, Dualibi AP, Norato D, et al. Guidelines for the management of mucopolysaccharidosis type I. *J Pediatr*. 2009;155(Suppl 2):S32-S46.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/12/2023
Annual Revision	**Mucopolysaccharidosis Type I**: Confirmation of a genetic mutation in the alpha-L-iduronidase gene was revised to more specifically state, "genetic testing demonstrating biallelic pathogenic or likely pathogenic alpha-L-iduronidase gene variants".	04/24/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Elaprase Utilization Management Medical Policy
- Elaprase® (idursulfase intravenous infusion – Shire Human Genetic Therapies)

REVIEW DATE: 04/24/2024

OVERVIEW

Elaprase, human iduronate-2-sulfatase (idursulfase), is indicated for **Hunter syndrome** (**Mucopolysaccharidosis type II** [MPS II]).[1]

Disease Overview

MPS II or Hunter syndrome, is a rare, X-linked lysosomal storage disorder characterized by a deficiency of iduronate-2-sulfatase leading to the accumulation of glycosaminoglycans dermatan sulfate and heparin sulfate.[2,3] Males are almost exclusively affected, although there have been a few case reports of females with Hunter syndrome.[3,4] The onset, progression, and severity of MPS II is variable.[2-4] Most of the patients with MPS II have a severe form with neurologic involvement leading to cognitive impairment and neurologic regression.[3,4] Other manifestations of Hunter syndrome include course facial features, hepatosplenomegaly, cardiac and respiratory disease, short stature, and stiff joints and contractures.[2,3] The definitive diagnosis of MPS II is established by demonstrating deficient iduronate-2-sulfatase activity in leukocytes, fibroblasts, serum, or plasma; or mutations in the iduronate-2-sulfatase gene.[2,5] Definitive treatment of MPS II consists of enzyme replacement therapy with Elaprase.[2-4,6] Hematopoietic stem cell transplantation has not demonstrated clear neurological benefit to date and is not recommended for MPS II due to the high rate of morbidity and mortality associated with this therapy.[2,4]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Elaprase. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Elaprase as well as the monitoring required for adverse events and long-term efficacy, approval requires Elaprase to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Elaprase is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Mucopolysaccharidosis Type II (Hunter Syndrome).** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) The diagnosis is established by ONE of the following (i or ii):

i. Patient has a laboratory test demonstrating deficient iduronate-2-sulfatase activity in leukocytes, fibroblasts, serum, or plasma; OR

ii. Patient has a molecular genetic test demonstrating an iduronate-2-sulfatase gene variant; AND

B) Elaprase is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

Dosing. Each dose must not exceed 0.5 mg/kg administered intravenously no more frequently than once a week.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Elaprase is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Elaprase® intravenous infusion [prescribing information]. Lexington, MA: Shire Human Genetic Therapies; October 2021.
2. Scarpa M, Almassy Z, Beck M, et al. Mucopolysaccharidosis type II: European recommendations for the diagnosis and multidisciplinary management of a rare disease. *Orphanet J Rare Dis*. 2011;6:72.
3. Muenzer J, Beck M, Eng CM, et al. Multidisciplinary management of Hunter syndrome. *Pediatrics*. 2009;124:e1228-e1239.
4. Giugliani R, Federhen A, Munoz Rojas MV, et al. Mucopolysaccharidosis I, II, and VI: Brief review and guidelines for treatment. *Genet Mol Biol*. 2010;33:589-604.
5. D'Avanzo F, Rigon L, Zanetti A, Tomanin R. Mucopolysaccharidosis type II: One hundred years of research, diagnosis, and treatment. *Int J Mol Sci*. 2020;21:E1258.
6. McBride KL, Berry SA, Braverman N; ACMG Therapeutics Committee. Treatment of mucopolysaccharidosis type II (Hunter syndrome): a Delphi derived practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2020 Nov;22(11):1735-1742.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/12/2023
Annual Revision	**Mucopolysaccharidosis Type II (Hunter Syndrome)**: For diagnosis confirmed by molecular genetic testing, the term "mutation" was rephrased to "variant".	04/24/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Fabrazyme Utilization Management Medical Policy
- Fabrazyme® (agalsidase intravenous infusion – Genzyme)

REVIEW DATE: 04/19/2024

OVERVIEW

Fabrazyme, a human α-galactosidase A (α-Gal), is indicated for **Fabry disease**.[1] It is the same amino acid sequence as the native enzyme and is produced in Chinese hamster ovary cells via recombinant DNA technology. Fabrazyme catalyzes the breakdown of globotriaosylceramide (GL-3) and other α-galactyl-terminated neutral glycosphingolipids to ceramide and galactose and reduces the deposition of GL-3 in the capillary endothelium of the kidney and certain other cell types.

Disease Overview

Fabry disease is a rare inherited X-linked lysosomal storage disorder due to absent or significantly reduced α-Gal activity leading to the accumulation of GL-3 in a wide variety of cells throughout the body.[2-4] The accumulation of GL-3 leads to progressive multisystem disease, primarily impacting the kidney, heart, and nervous system.[3,4] The incidence of Fabry disease is estimated to be about 1:117,000 live male births.[2] Fabry disease can be divided into two phenotypes. A severe, classical phenotype typically occurs in men without α-Gal activity, whereas a generally milder non-classical phenotype is found in men and women with some residual α-Gal activity.[2,3] The diagnosis of Fabry disease can be confirmed in males by demonstrating a deficiency in α-Gal activity, and in all patients by identifying a Fabry disease causing gene mutation.[4] Long-term consequences of Fabry disease include hypertrophic cardiomyopathy, arrhythmias, renal failure, and stroke.[3] The kidney disease that occurs in Fabry disease is associated with progressive proteinuria and a decline in glomerular filtration rate, which over time, leads to end-stage renal disease requiring dialysis and ultimately, kidney transplantation.[2] Treatment with Fabrazyme reduces the accumulation of GL-3 in the kidney (and in other organs), with the goal of stopping or slowing the decline in kidney function.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Fabrazyme. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Fabrazyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Fabrazyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Fabrazyme is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Fabry Disease.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** The diagnosis is established by ONE of the following (i or ii):
     - **i.** Patient has a laboratory test demonstrating deficient α-galactosidase A activity in leukocytes or fibroblasts; OR
     - **ii.** Patient has a molecular genetic test demonstrating a pathogenic variant in the galactosidase alpha gene (*GLA*); AND
   - **B)** Fabrazyme is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

   Dosing. Each dose must not exceed 1 mg/kg administered intravenously no more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Fabrazyme is not recommended in the following situations:

1. **Concurrent Use with Galafold® (migalastat oral capsules)**. One small study (n = 23) assessed a single dose of Galafold (150 mg or 450 mg) used concurrently with Fabrazyme or agalsidase alpha.[5] While a single dose of Galafold significantly increased α-Gal activity, the long-term safety and efficacy of concurrent use of Galafold and Fabrazyme has not been established. Galafold is not FDA approved for concurrent use with Fabrazyme.

2. **Concurrent Use with Elfabrio® (pegunigalsidase alfa intravenous infusion)**.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Fabrazyme® intravenous infusion [prescribing information]. Cambridge, MA: Genzyme; May 2024.
2. Schiffmann R. Fabry Disease. *Handb Clin Neurol*. 2015;132:231-248.
3. Arends M, Wanner C, Hughes D, et al. Characterization of Classical and Nonclassical Fabry Disease: A Multinational Study. *J Am Soc Nephrol*. 2017;28:1631-1641.
4. Laney DA, Bennett RL, Clarke V, et al. Fabry Disease Practice Guidelines: Recommendations of the National Society of Genetic Counselors. *J Genet Counsel*. 2013;22:555-564.
5. Warnock DG, Bichet DG, Holida M, et al. Oral Migalastat HCl Leads to Greater Systemic Exposure and Tissue Levels of Active α-Galactosidase A in Fabry Patients when Co-Administered with Infused Agalsidase. *PLoS ONE*. 2015;10: e0134341.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/12/2023
Annual Revision	**Fabry Disease**: For diagnosis confirmed by genetic testing, the term "mutation" was rephrased to "pathogenic variant." Conditions not recommended for approval were added and include concurrent use with Galafold® (migalastat oral capsules) and concurrent use with Elfabrio® (pegunigalsidase alfa intravenous infusion).	04/19/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Kanuma Utilization Management Medical Policy
- Kanuma® (sebelipase alfa intravenous infusion – Alexion)

REVIEW DATE: 04/24/2024

OVERVIEW

Kanuma, a human lysosomal acid lipase (LAL), indicated for the treatment of **LAL deficiency**.[1] It is produced in the egg white of genetically engineered chickens via recombinant DNA technology. LAL catalyzes the breakdown of cholesteryl esters to free cholesterol and fatty acids, and the breakdown of triglycerides to glycerol and free fatty acids.

Disease Overview

LAL deficiency is a rare lysosomal storage disorder characterized by absent or deficient LAL activity leading to the accumulation of cholesterol and triglycerides in the liver and other organs.[2,3] Patients with LAL deficiency often have dyslipidemias, cardiovascular disease, and progressive liver disease.[2] The disorder has a heterogeneous presentation ranging from a rapidly progressive form occurring in infants which leads to death in the first year of life, to a childhood/adult-onset form with milder signs and symptoms. Almost all patients with childhood/adult-onset LAL deficiency have hepatomegaly with elevated liver transaminases and have an increased risk of developing fibrosis and cirrhosis.[3] The diagnosis of LAL deficiency is established by demonstrating deficient LAL activity in leukocytes, fibroblasts, or liver tissue; or by genetic testing.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Kanuma. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). Because of the specialized skills required for evaluation and diagnosis of patients treated with Kanuma as well as the monitoring required for adverse events and long-term efficacy, approval requires Kanuma to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kanuma is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Lysosomal Acid Lipase Deficiency.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) The diagnosis is established by ONE of the following (i or ii):

i. Patient has a laboratory test demonstrating deficient lysosomal acid lipase activity in leukocytes, fibroblasts, or liver tissue; OR
ii. Patient has a molecular genetic test demonstrating biallelic pathogenic or likely pathogenic lysosomal acid lipase (*LAL*) gene variants; AND

B) Kanuma is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

Dosing. Each dose must not exceed 5 mg/kg administered intravenously no more frequently than once per week.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kanuma is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Kanuma® intravenous infusion [prescribing information]. Cheshire, CT: Alexion; November 2021.
2. Reiner Z, Guardamagna O, Nair D, et al. Lysosomal acid lipase deficiency – an under-recognized cause of dyslipidaemia and liver dysfunction. *Atherosclerosis*. 2014;235:21-30.
3. Erwin AL. The role of sebelipase alfa in the treatment of lysosomal acid lipase deficiency. *Ther Adv Gastroenterol*. 2017;10:553-562.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/12/2023
Annual Revision	**Lysosomal Acid Lipase Deficiency**: Confirmation of a genetic mutation in the lysosomal acid lipase gene was revised to more specifically state, "genetic testing demonstrating biallelic pathogenic or likely pathogenic lysosomal acid lipase gene variants".	04/24/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Lamzede Utilization Management Medical Policy
- Lamzede® (velmanase alfa-tycv intravenous infusion – Chiesi)

REVIEW DATE: 03/06/2024

OVERVIEW

Lamzede, a recombinant human lysosomal alpha-mannosidase, is indicated for the treatment of **non-central nervous system manifestations of alpha-mannosidosis** in adult and pediatric patients.[1]

Disease Overview

Alpha-mannosidosis is an ultra-rare autosomal recessive lysosomal storage disease. It is estimated to occur in 1 to 2:1,000,000 live births.[2] Alpha-mannosidosis results from reduced activity of the lysosomal enzyme, alpha-mannosidase, which is caused by gene variants in Mannosidase Alpha Class 2B Member 1 (*MAN2B1*). This results in accumulation of mannose-rich oligosaccharides in various tissues, which leads to significant and diverse multi-systemic manifestations. This can include progressive motor function disturbances and physical disability, hearing and speech impairment, intellectual disability, and immune deficiency. Lamzede is the first and only enzyme replacement therapy approved for alpha-mannosidosis in the United States. There are no other FDA approved therapies for alpha-mannosidosis. Treatment is generally targeted towards management of the various clinical manifestations of the disease. Hematopoietic stem cell transplantation (HSCT) has been used to prevent cognitive decline, preserve neurocognitive function, and prevent early death.[2-4] However, not all patients are eligible for HSCT and it is associated with the risk of mortality and complications. Lamzede has been approved by the European Medicines Agency (EMA) in 2018. Diagnosis of alpha-mannosidosis is confirmed by molecular genetic testing and identification of biallelic pathogenic variants in *MAN2B1*.[5] Alpha-mannosidase enzyme activity in peripheral blood leukocytes is 5% to 10% of normal activity in affected individuals.

Clinical Efficacy

The efficacy of Lamzede in adult and pediatric patients with alpha-mannosidosis was established in two pivotal studies (rhLAMAN-05 and rhLAMAN-08) and one non-pivotal trial (rhLAMAN-10).[2-4] Patients with a confirmed diagnosis of alpha-mannosidosis, defined as alpha-mannosidase activity less than 10% of normal activity in blood leukocytes were enrolled. Lamzede demonstrated a statistically significant clearance of serum oligosaccharides vs. placebo in the pivotal trials. Lamzede also demonstrated improvement in endurance, pulmonary function, motor proficiency testing, and a decrease in serum immunoglobulins.

Dosing Information

The recommended dosage of Lamzede is 1 mg/kg (actual body weight) administered once every week as an intravenous infusion.[1] The total volume of infusion is determined by the patient's actual body weight and should be administered over a minimum of 60 minutes for patients weighing up to 49 kg. Patients weighing ≥ 50 kg should be infused at a maximum infusion rate of 25 mL/hour to control the protein load.

Safety

Lamzede has a Boxed Warning for hypersensitivity reactions, including anaphylaxis.[1] Other Warnings/Precautions for Lamzede include infusion-associated reactions and embryofetal toxicity.

Pretreatment with antihistamines, antipyretics, and/or corticosteroids should be considered to reduce the risk of hypersensitivity and infusion-related reactions.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Lamzede. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lamzede as well as the monitoring required for adverse events and long-term efficacy, approval requires Lamzede to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lamzede is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Alpha-mannosidosis.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Patient has a confirmed diagnosis of alpha-mannosidosis, defined as alpha-mannosidase activity less than 10% of normal activity in blood leukocytes; AND
   - **B)** Patient has non-central nervous system manifestations; AND
     Note: Examples of non-central nervous system manifestations include progressive motor function disturbances, physical disability, hearing and speech impairment, skeletal abnormalities, and immune deficiency.
   - **C)** Patient has biallelic pathogenic variants in Mannosidase Alpha Class 2B Member 1 (*MAN2B1)* as confirmed by mutation testing; AND
   - **D)** The medication is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

   Dosing. Approve up to 1 mg/kg (actual body weight) administered by intravenous infusion no more frequently than every week.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lamzede is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Lamzede® intravenous infusion [prescribing information]. Cary, NC: Chiesi USA; February 2023.
2. Borgwardt L, Guffon N, Amraoui Y, et al. Efficacy and safety of velmanase alfa in the treatment of patients with alpha-mannosidosis: results from the core and extension phase analysis of a phase III multicentre, double-blind, randomised, placebo-controlled trial. *J Inherit Metab Dis*. 2018;41(6):1215-1223.
3. Guffon N, Konstantopoulou V, Hennermann JB, et al. Long-term safety and efficacy of velmanase alpha (VA) treatment in children under 6 years of age with alpha-mannosidosis (AM). Presented at: 14th International Congress of Inborn Errors of Metabolism (ICIEM 2021); Sydney, Australia; November 21-23, 2021.
4. Lund A, Borgwardt L, Cattaneo F, et al. Comprehensive long-term efficacy and safety of recombinant human alpha-mannosidase (velmanase alfa) treatment in patients with alpha-mannosidosis. *J Inherit Metab Dis*. 2018;41:1225-1233.
5. Guffon N, Tylki-Szymanska A, Borgwardt L, et al. Recognition of alpha-mannosidosis in paediatric and adult patients: Presentation of a diagnostic algorithm from an international working group. *Mol Genet Metab*. 2019;126(4):470-474.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/08/2023
Selected Revision	**Alpha-mannosidosis:** The following criteria was added "Patient has biallelic pathogenic variants in Mannosidase Alpha Class 2B Member 1 (*MAN2B1)* as confirmed by mutation testing."	03/22/2023
Annual Revision	No criteria changes.	03/06/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Mepsevii Utilization Management Medical Policy
- Mepsevii® (vestronidase alfa-vjbk intravenous infusion – Ultragenyx)

REVIEW DATE: 04/24/2024

OVERVIEW

Mepsevii, a lysosomal beta glucuronidase (GUS), is indicated for the treatment of **Mucopolysaccharidosis type VII** ([MPS VII], Sly syndrome).[1] It is produced in a Chinese hamster ovary cell line via recombinant DNA technology. It has the same amino acid sequence as human GUS and catabolizes accumulated glycosaminoglycans in lysosomes in affected tissues.

Disease Overview

MPS VII or Sly syndrome is an extremely rare lysosomal storage disorder characterized by deficient GUS activity.[2] In MPS VII, the partially catabolized glycosaminoglycans, chondroitin sulfate, dermatan sulfate, and heparin sulfate accumulate in the lysosomes, ultimately leading to the signs and symptoms of the disease.[2,3] The onset, severity, and rate of progression of MPS VII is heterogeneous. Patients may present at birth with hydrops fetalis and only survive a few months while others may have milder disease and survive into their 40s.[2] However, most patients have mental retardation, hepatosplenomegaly, and musculoskeletal issues including short stature, course facial features, loss of range of motion, restricted mobility, scoliosis, and kyphosis. The diagnosis of MPS VII is established by demonstrating deficient GUS activity in leukocytes, fibroblasts, or serum; or by genetic testing.[3] Treatment for MPS VII includes enzyme replacement therapy with Mepsevii and hematopoietic stem cell transplantation.[2]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Mepsevii. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Mepsevii as well as the monitoring required for adverse events and long-term efficacy, approval requires Mepsevii to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mepsevii is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. Mucopolysaccharidosis Type VII (Sly Syndrome). Approve for 1 year if the patient meets BOTH of the following (A and B):

A) The diagnosis is established by ONE of the following (i or ii):

i. Patient has a laboratory test demonstrating deficient beta-glucuronidase activity in leukocytes, fibroblasts, or serum; OR

ii. Patient has a molecular genetic test demonstrating biallelic pathogenic or likely pathogenic glucuronidase (*GUS*) gene variants; AND

B) Mepsevii is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

Dosing. Each dose must not exceed 4 mg/kg administered intravenously no more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mepsevii is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Mepsevii® intravenous infusion [prescribing information]. Novato, CA: Ultragenyx; December 2020.
2. Montano AM, Lock-Hock N, Steiner RD, et al. Clinical course of sly syndrome (mucopolysaccharidosis type VII). *J Med Genet*. 2016;53:403-418.
3. Tomatsu S, Montano AM, Dung VC, et al. Mutations and polymorphisms in GUSB gene in mucopolysaccharidosis VII (Sly syndrome). *Hum Mutat*. 2009;30:511-519.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/12/2023
Annual Revision	**Mucopolysaccharidosis Type VII (Sly Syndrome)**: Confirmation of a genetic mutation in the glucuronidase gene was revised to more specifically state, "genetic testing demonstrating biallelic pathogenic or likely pathogenic glucuronidase gene variants".	04/24/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Naglazyme Utilization Management Medical Policy
- Naglazyme® (galsulfase intravenous infusion – BioMarin)

REVIEW DATE: 04/24/2024

OVERVIEW

Naglazyme, a human *N*-acetylgalactosamine 4-sulfatase, is indicated for **Mucopolysaccharidosis type VI** (Maroteaux – Lamy syndrome [MPS VI]).[1] It is produced in a Chinese hamster ovary cell line via recombinant DNA technology. The enzyme catalyzes the hydrolysis of the sulfate ester from the glycosaminoglycans, chondroitin 4-sulfate and dermatan sulfate. Naglazyme has been shown to improve walking and stair climbing capacity.

Disease Overview

MPS VI, or Maroteaux – Lamy syndrome, is a rare lysosomal storage disorder characterized by a deficiency of *N*-acetylgalactosamine 4-sulfatase (arylsulfatase B).[2,3] The enzyme deficiency results in the accumulation of partially hydrolyzed dermatan sulfate and chondroitin 4-sulfate in lysosomes leading to the signs and symptoms of the disease.[2,3] The onset, severity, and rate of progression of MPS VI is heterogeneous; however, most patients are severely affected with a rapidly progressive form.[3] Clinical manifestations include course facial features, short stature, kyphoscoliosis, joint stiffness, pulmonary insufficiency, cardiac disease, hepatosplenomegaly, corneal clouding, and hernias.[2,3] The definitive diagnosis of MPS VI is established by demonstrating deficient arylsulfatase B enzyme activity in leukocytes or fibroblasts, or by genetic testing.[2,3] Definitive treatment of MPS VI consists of either enzyme replacement therapy with Naglazyme or hematopoietic stem cell transplantation. Due to the morbidity and mortality associated with hematopoietic stem cell transplantation, this therapy is typically reserved for patients who are intolerant of or do not respond to enzyme replacement therapy.[2]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Naglazyme. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Naglazyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Naglazyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Naglazyme is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Mucopolysaccharidosis Type VI (Maroteaux – Lamy Syndrome).** Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** The diagnosis is established by ONE of the following (i or ii):
     - **i.** Patient has a laboratory test demonstrating deficient *N*-acetylgalactosamine 4-sulfatase (arylsulfatase B) activity in leukocytes or fibroblasts; OR
     - **ii.** Patient has a molecular genetic test demonstrating biallelic pathogenic or likely pathogenic arylsulfatase B (*ARSB*) gene variants; AND
   - **B)** Naglazyme is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

   Dosing. Each dose must not exceed 1 mg/kg administered intravenously no more frequently than once weekly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Naglazyme is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Naglazyme® intravenous infusion [prescribing information]. Novato, CA: BioMarin; April 2020.
2. Harmatz PR, Shediac R. Mucopolysaccharidosis VI: Pathophysiology, diagnosis and treatment. *Front Biosci*. 2017;22:385-406.
3. Vairo F, Federhen A, Baldo G, et al. Diagnostic and treatment strategies in mucopolysaccharidosis VI. *Appl Clin Genet*. 2015;8:245-255.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/12/2023
Annual Revision	**Mucopolysaccharidosis Type VI (Maroteaux – Lamy Syndrome)**: Confirmation of a genetic mutation in the arylsulfatase B gene was revised to more specifically state, "genetic testing confirmation of biallelic pathogenic or likely pathogenic arylsulfatase gene variants".	04/24/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Nexviazyme Utilization Management Medical Policy
- Nexviazyme® (avalglucosidase alfa-ngpt intravenous infusion – Genzyme)

REVIEW DATE: 08/23/2023

OVERVIEW

Nexviazyme, a hydrolytic lysosomal glycogen-specific recombinant human α-glucosidase enzyme, is indicated for **late-onset Pompe disease** (lysosomal acid α-glucosidase deficiency) in patients ≥ 1 year of age.[1]

Disease Overview

Pompe disease (glycogen storage disease type II, or acid maltase deficiency), is a rare lysosomal storage disorder characterized by a deficiency in acid α-glucosidase activity leading to the accumulation of glycogen, particularly in muscle.[2,3] The onset, progression and severity of Pompe disease is variable. Infantile-onset Pompe disease usually manifests in the first few months of life and death often occurs in the first year of life, if left untreated.[2] Clinical manifestations of infantile-onset Pompe disease includes hypotonia, difficulty feeding, and cardiopulmonary failure.[4] Late-onset Pompe disease has a more variable clinical course and can manifest any time after 12 months of age.[3,4] Patients typically present with progressive muscle weakness which can progress to respiratory insufficiency. The diagnosis of Pompe disease is established by demonstrating decreased acid α-glucosidase activity in blood, fibroblasts, or muscle tissue, or by genetic testing.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Nexviazyme. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nexviazyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Nexviazyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nexviazyme is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Acid Alpha-Glucosidase Deficiency (Pompe Disease).** Approve for 1 year if the patient meets the following (A, B, C, and D):
   - **A)** Patient is ≥ 1 year of age; AND
   - **B)** Patient has late-onset acid alpha-glucosidase deficiency (late-onset Pompe disease); AND

C) The diagnosis is established by one of the following (i or ii):
- **i.** Patient has a laboratory test demonstrating deficient acid alpha-glucosidase activity in blood, fibroblasts, or muscle tissue; OR
- **ii.** Patient has a molecular genetic test demonstrating acid alpha-glucosidase gene mutation; AND

D) The medication is prescribed by or in consultation with a geneticist, neurologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

Dosing. Approve one of the following dosing regimens (A or B):

A) Patient ≥ 30 kg: Dose is 20 mg/kg administered by intravenous infusion once every 2 weeks; OR

B) Patient < 30 kg: Dose is 40 mg/kg administered by intravenous infusion once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nexviazyme is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Nexviazyme® intravenous infusion [prescribing information]. Cambridge, MA: Genzyme; April 2023.
2. Chien YH, Hwu WL, Lee NC. Pompe disease: Early diagnosis and early treatment make a difference. *Pediatr Neonatol*. 2013;54:219-227.
3. Llerena Junior JC, Nascimento OJM, Oliveira ASB, et al. Guidelines for the diagnosis, treatment and clinical monitoring of patients with juvenile and adult Pompe disease. *Arq Neuropsiquiatr*. 2016;74:166-176.
4. Cupler EJ, Berger KI, Leshner RT, et al. Consensus treatment recommendations for late-onset Pompe disease. *Muscle Nerve*. 2012;45:319-333.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/10/2022
Annual Revision	No criteria changes.	08/23/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Revcovi Utilization Management Medical Policy
- Revcovi® (elapegademase-lvlr intramuscular injection – Chiesi)

REVIEW DATE: 12/13/2023

OVERVIEW

Revcovi, a recombinant adenosine deaminase, is indicated for the treatment of **adenosine deaminase severe combined immune deficiency (ADA-SCID)** in pediatric and adult patients.[1]

Disease Overview

ADA-SCID is an ultra-rare, autosomal recessive genetic disorder of purine metabolism affecting lymphocyte development, viability, and function.[1,2] It is estimated to occur in 1:200,000 to 1:1,000,000 live births. ADA is a purine salvage enzyme which metabolizes deoxyadenosine (dAdo) and adenosine (Ado) into deoxyinosine and inosine, respectively.[3] When ADA is deficient, dAdo accumulates in intracellular and extracellular compartments, along with its metabolite, deoxyadenosinetriphosphate (dATP). The buildup of both dAdo and dATP negatively impacts lymphocyte development and function by impeding DNA replication and repair, inducing apoptosis, and inhibiting lymphocyte activation.

There are a variety of phenotypes of ADA deficiency; ADA-SCID is the most severe and typically diagnosed before 1 year of age.[2] Infants with typical ADA-SCID have failure to thrive and opportunistic infections associated with marked depletion of B, T, and NK lymphocytes. Manifestations include persistent diarrhea, extensive dermatitis, recurrent pneumonia, and other life-threatening illnesses caused by opportunistic infections. Growth failure and other physical manifestations, including hepatic and neurologic abnormalities, may also be present. Without treatment, patients with ADA-SCID rarely survive beyond 1 to 2 years of age.

Guidelines

According to a consensus statement for management of ADA-SCID (2018) and updated guidelines in 2023, diagnosis is usually established by demonstrating absent or very low (< 1 % of normal) ADA catalytic activity, accompanied by elevated Ado or dAdo in plasma, urine, or dried blood spots.[3,4] This should be followed by genetic testing to confirm bi-allelic mutations in the *ADA* gene. Enzyme replacement therapy (ERT) is recommended by the consensus panel for all patients newly diagnosed with ADA-SCID as an immediate stabilizing measure. The ideal duration of ERT has not been established. The consensus recommends that most patients use ERT as a "bridge" for a few months to approximately 2 years, prior to undergoing curative therapy with a hematopoietic stem cell transplant (HSCT) or hematopoietic stem cell gene therapy. Long-term use of ERT has declined in the past 30 years and has not been systematically studied. Lymphocyte counts and function may deteriorate over time, contributing to increased risk of infections and malignancy. Therefore, ERT longer than 5 to 8 years should be avoided and employed on a continuous basis only when neither HSCT nor gene therapy have been available or effective. The consensus also suggests ERT use for patients with later-onset phenotypes who may not be ideal candidates for curative processes.

Dosing Considerations

Dosing is provided in the Prescribing Information for patients who are naïve to Adagen® (pegademase bovine injection for intramuscular use), as well as for patients who are Adagen-experienced.[1] For Adagen-naïve patients, the starting weekly dose of Revcovi is 0.4 mg/kg (divided into two doses) by the

intramuscular route. This dose is continued for at least 12 to 24 weeks until immune reconstitution is achieved. Thereafter, the dose may be gradually adjusted down for maintenance (adjusted based on laboratory values). Lower starting doses are generally recommended for Adagen-experienced patients; the Prescribing Information provides a conversion factor for calculating the Revcovi dose based on the prior Adagen dose. The Prescribing Information notes that the optimal long-term dose and schedule of administration are individualized; total weekly doses may be divided into multiple intramuscular injections during a week. The dosing provided in this policy is intended to provide a sufficient maximum weekly dose for the majority of patients; exceptions will be reviewed by a clinician on a case-by-case basis.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Revcovi. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Revcovi, approval requires it to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Revcovi is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID).** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient has a diagnosis of ADA-SCID confirmed by one of the following (i or ii):
     - **i.** At baseline (i.e., prior to initiating enzyme replacement therapy), the patient has had absent or very low (< 1% of normal) adenosine deaminase (ADA) catalytic activity; OR
     - **ii.** Patient has had molecular genetic testing confirming bi-allelic mutations in the *ADA* gene; AND
   - **B)** The medication is prescribed by or in consultation with an immunologist, hematologist/oncologist, or physician who specializes in ADA-SCID or related disorders.

   Dosing. Approve up to a maximum weekly dose of 0.4 mg/kg by the intramuscular route.
   Note: Doses may be divided into multiple injections as long as weekly cumulative maximum of 0.4 mg/kg is not exceeded.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Revcovi is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Revcovi® injection [prescribing information]. Cary, NC: Chiesi; August 2022.
2. Hershfield M. GeneReviews [Internet]. Updated March 16, 2017. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1483/. Accessed on November 28, 2023.
3. Kohn DB, Hershfield MS, Puck JM, et al. Consensus approach for the management of severe combined immune deficiency caused by adenosine deaminase deficiency. *J Allergy Clin Immunol*. 2019;143(3):852-863.
4. Grunebaum E, Booth C, Cuvelier GDE, et al. Updated Management Guidelines for Adenosine Deaminase Deficiency. *J Allergy Clin Immunol Pract.* 2023 Jun;11(6):1665-1675.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/16/2022
Annual Revision	No criteria changes.	12/13/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Vimizim Utilization Management Medical Policy
- Vimizim® (elosulfase alfa intravenous infusion – BioMarin)

REVIEW DATE: 04/24/2024

OVERVIEW

Vimizim, a human *N*-acetylgalactosamine-6-sulfatase, is indicated for **Mucopolysaccharidosis type IVA** (Morquio A syndrome [MPS IVA]).[1] It is produced in Chinese hamster ovary cells via recombinant DNA technology. Vimizim is a hydrolytic lysosomal enzyme which is taken up by lysosomes and hydrolyzes sulfate from the non-reduced ends of the glycosaminoglycans keratan sulfate and chondroitin-6-sulfate.

Disease Overview

MPS IVA (Morquio A syndrome) is a rare lysosomal storage disorder characterized by deficient *N*-acetylgalactosamine-6-sulfatase activity leading to the accumulation of chondroitin-6-sulfate and keratan sulfate in lysosomes in bone, cartilage, and ligaments.[2,3] The clinical course, onset, and severity of MPS IVA is heterogeneous.[2] Manifestations of MPS IVA include short trunk dwarfism with short neck, kyphoscoliosis, odontoid dysplasia, knock-knee, cervical spinal cord compression, hypermobile joints, cardiac disease, respiratory insufficiency, obstructive sleep apnea, corneal clouding, and dental abnormalities.[2-4] MPS IVA has not been associated with cognitive decline.[2] The definitive diagnosis of MPS IVA is established by demonstrating deficient *N*-acetylgalactosamine-6-sulfatase activity in leukocytes or fibroblasts; or by genetic testing.[2] Definitive treatment for MPS IVA consists of enzyme replacement therapy with Vimizim. Hematopoietic stem cell transplantation is not recommended for MPS IVA.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Vimizim. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vimizim as well as the monitoring required for adverse events and long-term efficacy, approval requires Vimizim to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vimizim is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Mucopolysaccharidosis Type IVA (Morquio A Syndrome).** Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** The diagnosis is established by ONE of the following (i or ii):
     - **i.** Patient has a laboratory test demonstrating deficient *N*-acetylgalactosamine-6-sulfatase activity in leukocytes or fibroblasts; OR
     - **ii.** Patient has a molecular genetic test demonstrating biallelic pathogenic or likely pathogenic *N*-acetylgalactosamine-6-sulfatase (*GALNS*) gene variants; AND
   - **B)** Vimizim is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

   Dosing. Approve up to 2 mg/kg of body weight administered intravenously no more frequently than once a week.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vimizim is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Vimizim® intravenous infusion [prescribing information]. Novato, CA: BioMarin; January 2021.
2. Akyol MU, et al. MPS Consensus Programme Co-Chairs. Recommendations for the management of MPS IVA: systematic evidence- and consensus-based guidance. *Orphanet J Rare Dis*. 2019 Jun 13;14(1):137.
3. Tomatsu S, Yasuda E, Patel P, et al. Morquio A syndrome: Diagnosis and current and future therapies. *Pediatr Endocrinol Rev*. 2014;12:141-151.
4. Regier DS, Tanpaiboon P. Role of elosulfase alfa in mucopolysaccharidosis IVA. *Appl Clin Genet*. 2016;9:67-74.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/12/2023
Annual Revision	**Mucopolysaccharidosis Type IVA (Morquio A Syndrome)**: Confirmation of a genetic mutation in the *N*-acetylgalactosamine-6-sulfatase gene was revised to more specifically state, "genetic testing demonstrating biallelic pathogenic or likely pathogenic *N*-acetylgalactosamine-6-sulfatase gene variants".	04/24/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Xenpozyme Utilization Management Medical Policy
- Xenpozyme™ (olipudase alfa-rpcp intravenous infusion – Genzyme)

REVIEW DATE: 09/13/2023

OVERVIEW

Xenpozyme, a hydrolytic lysosomal sphingomyelin-specific enzyme, is indicated for the treatment of **non-central nervous system (CNS) manifestations of acid sphingomyelinase deficiency (ASMD)** in adult and pediatric patients.[1]

Disease Overview

ASMD is an autosomal recessive lysosomal storage disease that results from reduced activity of the enzyme acid sphingomyelinase (ASM), caused by pathogenic variants in the sphingomyelin phosphodiesterase 1 gene.[1,2] ASM degrades sphingomyelin to ceramide and phosphocholine.[1] The deficiency of ASM causes an intra-lysosomal accumulation of sphingomyelin (as well as cholesterol and other cell membrane lipids) in various tissues. Xenpozyme provides an exogenous source of ASM. Xenpozyme is not expected to cross the blood-brain barrier or modulate the CNS manifestations of ASMD.

ASMD has historically been known as Niemann-Pick disease type A and/or B and is associated with a spectrum of disease phenotypes.[2] ASMD type B (also known as chronic visceral ASMD or Niemann-Pick type B disease) and ASMD type A/B (chronic neurovisceral ASMD, Niemann-Pick disease type A/B, or intermediate phenotype) have disease onset from childhood to early adulthood. ASMD type B has minimal to no CNS involvement, while ASMB type A/B has less severe neurologic manifestations than those observed in ASMD type A, which is fatal in early childhood. Visceral manifestations in ASMD include interstitial lung disease with decreased diffusing capacity of the lung, hepatosplenomegaly, progressive liver disease with cirrhosis or fibrosis, dyslipidemia, osteopenia, and thrombocytopenia. The leading causes of early mortality in adults with ASMD are lung disease/infections, liver failure, and bleeding.

Dosing Information

Dosing is weight-based.[1] For patients with a body mass index (BMI) of ≤ 30 kg/m^2, actual body weight is used. For patients with a BMI > 30 kg/m^2 adjusted body weight is used (adjusted body weight in kg = [actual height in meters]^2 x 30). Home infusion of Xenpozyme under the supervision of a healthcare provider may be considered for patients on a maintenance dose and who are tolerating the infusion well. The decision to have patients moved to home infusion should be made after evaluation and recommendation by a physician.

The recommended starting dose in adults is 0.1 mg/kg via intravenous (IV) infusion.[1] The dose is titrated every 2 weeks over a period of 14 weeks to a maintenance dose of 3 mg/kg every 2 weeks (Table 1). In pediatric patients, the recommended starting dose is 0.03 mg/kg via IV infusion. The dose is titrated every 2 weeks over a period of 16 weeks to a maintenance dose of 3 mg/kg every 2 weeks (Table 2). To reduce the risk of hypersensitivity and infusion-related reactions or elevated transaminase levels, the dose escalation regimen outlined in Tables 1 and 2 below should be followed. A dose is considered "missed" when it is not administered within 3 days of the scheduled date. Refer to Table 3 for missed doses.

Table 1. Xenpozyme Dose Escalation Regimen for Adults (≥ 18 Years of Age).[1]

First dose (Day 1/Week 0)	0.1 mg/kg
Second dose (Week 2)	0.3 mg/kg
Third dose (Week 4)	0.3 mg/kg
Fourth dose (Week 6)	0.6 mg/kg
Fifth dose (Week 8)	0.6 mg/kg
Sixth dose (Week 10)	1 mg/kg
Seventh dose (Week 12)	2 mg/kg
Eighth dose (Week 14)†	3 mg/kg

† The dose escalation phase includes the first 3 mg/kg dose.

Table 2. Xenpozyme Dose Escalation Regimen for Pediatric Patients.[1]

First dose (Day 1/Week 0)	0.03 mg/kg
Second dose (Week 2)	0.1 mg/kg
Third dose (Week 4)	0.3 mg/kg
Fourth dose (Week 6)	0.3 mg/kg
Fifth dose (Week 8)	0.6 mg/kg
Sixth dose (Week 10)	0.6 mg/kg
Seventh dose (Week 12)	1 mg/kg
Eighth dose (Week 14)†	2 mg/kg
Ninth dose (Week 16) †	3 mg/kg

† The dose escalation phase includes the first 3 mg/kg dose.

Table 3. Dosing Recommendations for Xenpozyme Missed Doses*.[1]

Consecutive Missed Doses In:	Escalation Phase	Maintenance Phase
1 missed dose	First dose after a missed dose: Administer last tolerated dose. Second and subsequent doses after missed dose: Resume dose escalation at next infusion according to Table 1 for adult patients or Table 2 for pediatric patients.	First and subsequent doses after missed dose: Administer maintenance dose.
2 consecutive missed doses	First dose after missed dose: Administer 1 dose below the last tolerated dose. Second and subsequent doses after missed dose: Resume dose escalation according to Table 1 for adults or Table 2 for pediatric patients.	First dose after missed dose: Administer 1 dose below the maintenance dose. Second and subsequent doses after missed dose: Resume the maintenance dose.
≥ 3 consecutive missed doses	First and subsequent doses after missed doses: Resume dose escalation at 0.3 mg/kg and follow Table 1 for adults or Table 2 for pediatric patients.	First and subsequent doses after missed doses: Restart dosing at 0.3 mg/kg and follow Table 1 for adult patients or Table 2 for pediatric patients.

*At scheduled infusion after a missed dose, if the dose administered is 0.3 mg/kg or 0.6 mg/kg, administer that dose twice as per Table 1 and 2.

Clinical Efficacy

The efficacy of Xenpozyme in adults and pediatric patients with ASMD was established in two pivotal trials (ASCEND and ASCEND-PEDS, respectively).[2,3] The pivotal trials enrolled patients with ASMD types B or A/B, but not type A. Eligible patients also had splenomegaly (spleen volumes ≥ 5 multiples of normal [MN] in pediatric patients and ≥ 6 MN in adults). In adults and children, Xenpozyme treatment improved spleen and liver volume as well as diffusing capacity of the lungs for carbon monoxide.

Guidelines

A consensus guideline for ASMD diagnosis has been developed by an international expert panel.[4] When there is a suspicion of ASMD, an ASM enzyme assay should be performed followed by gene sequencing if

the enzymatic test is indicative of ASMD. Whenever possible, an enzyme assay for ASM and glucocerebrosidase activity should be performed in parallel to distinguish ASMD from Gaucher disease. Gene sequencing can be conducted after diagnosis based on ASM activity, but is not diagnostic on its own because of the high number of genetic variants of unknown significance. Biomarkers, while useful in disease monitoring, should not be considered sufficient for ASMD diagnosis (i.e., these include plasma chitotriosidase, plasma lyso-sphingolipids, and oxysterols). Physicians should perform clinical assessments to predict the phenotype and clinical course of the disease upon identification of sphingomyelin phosphodiesterase-1 (SMPD1) pathogenic variants of unknown pathogenicity in pediatric patients.

Safety

Xenpozyme has a Boxed Warning for hypersensitivity reactions, including anaphylaxis.[1] Prior to administration, pretreatment with antihistamines, antipyretics, and/or corticosteroids should be considered and appropriate medical measures, including cardiopulmonary resuscitation equipment should be readily available during Xenpozyme administration.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Xenpozyme. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Xenpozyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Xenpozyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xenpozyme is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. **Acid Sphingomyelinase Deficiency (ASMD).** Approve for 1 year if the patient meets the following (A, B, C, and D):
   Note: ASMD has historically been known as Niemann-Pick Disease.
   - **A)** The diagnosis of ASMD meets ALL of the following (i, ii, and iii):
     - **i.** The diagnosis of ASMD has been established by acid sphingomylinase (ASM) enzymatic assay testing; AND
     - **ii.** The diagnosis of ASMD has been confirmed by mutation testing; AND
     - **iii.** A diagnosis of Gaucher disease has been excluded; AND
   - **B)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has ASMD type B; OR
     - **ii.** Patient has ASMD type A/B; AND
   - **C)** Patient has two or more non-central nervous system signs of ASMD type B or type A/B according to the prescriber; AND
     Note: Examples of non-central nervous system signs of ASMD type B or type A/B include but are not limited to hepatosplenomegaly, interstitial lung disease, decreased diffusing capacity of the

lungs, progressive liver disease with cirrhosis or fibrosis, dyslipidemia, osteopenia, thrombocytopenia, anemia, leukopenia.

D) The medication is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

Dosing. Approve up to 3 mg/kg administered by intravenous infusion no more frequently than once every 2 weeks.
Note: For patients with a body mass index (BMI) of ≤ 30 kg/m^2, actual body weight is used. For patients with a BMI > 30 kg/m^2 adjusted body weight is used. To calculate adjusted body weight, use the following equation: adjusted body weight in kg = (actual height in meters)^2 x 30.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xenpozyme is not recommended in the following situations:

1. **Acid Sphingomyelinase Deficiency (ASMD), Type A.** Xenpozyme is indicated for non-central nervous system manifestations of ASMD. Xenpozyme is not expected to cross the blood-brain barrier or modulate the central nervous system manifestations of ASMD.[1] Patients with ASMD type A were excluded from the pivotal trials with Xenpozyme.[2,3]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Xenpozyme™ intravenous infusion [prescribing information]. Cambridge, MA: Genzyme; August 2022.
2. Wasserstein M, Lachmann R, Hollack C, et al. A randomized, placebo-controlled clinical trial evaluating olipudase alfa enzyme replacement for chronic acid sphingomyelinase deficiency (ASMD) in adults: One-year results. *Genet Med.* 2022;24(7):1425-1436.
3. Diaz GA, Jones SA, Scarpa M, et al. One-year results of a clinical trial of olipudase alfa enzyme replacement therapy in pediatric patients with acid sphingomyelinase deficiency. *Genet Med.* 2021;23:154-1550.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	**Acid Sphingomylinase Deficiency (ASMD).** Criteria for the diagnosis of ASMD were expanded to additionally require that the diagnosis be confirmed by mutation testing and that Gaucher disease be excluded as a diagnosis. Previously, the diagnosis was required to be established by enzymatic assay alone. Criteria requiring patients have AMSD type B or A/B was revised to clarify that patients have two or more non-central nervous system sign of ASMD type B or type A/B, examples of non-central nervous system signs were moved to a note.	11/09/2022
Annual Revision	No criteria changes.	09/13/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Erythropoiesis-Stimulating Agents – Aranesp Utilization Management Medical Policy
- Aranesp® (darbepoetin alfa intravenous or subcutaneous injection – Amgen)

REVIEW DATE: 07/19/2023

OVERVIEW

Aranesp, an erythropoiesis-stimulating agent (ESA), is indicated for the following uses:[1]
- **Anemia due to chronic kidney disease** (CKD), including patients on dialysis and patients not on dialysis.
- **Anemia due to chemotherapy in patients with cancer,** in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

Aranesp has not been shown to improve quality of life, fatigue, or patient well-being.[1] Aranesp is not indicated for the following uses:
- In patients with cancer receiving hormonal agents, biologic products, or radiotherapy unless also receiving concomitant myelosuppressive chemotherapy.
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- In patients with cancer receiving myelosuppressive chemotherapy in whom anemia can be managed by transfusion.
- As a substitute for red blood cell (RBC) transfusions in those who require immediate correction of anemia.

Therapy should be initiated for **adults with CKD on dialysis** when the hemoglobin (Hb) level is < 10.0 g/dL and if the Hb level approaches or exceeds 11.0 g/dL, reduce or interrupt the Aranesp dose.[1] For **adults with CKD not on dialysis**, consider initiating Aranesp only when Hb is < 10.0 g/dL and other considerations apply (e.g., rate of Hb decline indicates patient is likely to need RBC transfusion and reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal). If the Hb level exceeds 10.0 g/dL, reduce or interrupt the Aranesp dose and use the lowest dose sufficient to reduce the need for RBC transfusions. For **pediatric patients with CKD**, initiate Aranesp when the Hb < 10.0 g/dL and if the Hb level approaches 12.0 g/dL, reduce or interrupt the dose of Aranesp. Initiate Aranesp for patients on cancer chemotherapy only if the Hb is < 10.0 g/dL and if there is a minimum of two additional months of planned chemotherapy. Use the lowest dose of Aranesp to avoid RBC transfusions.

Dosing Information

Doses of Aranesp are titrated based on Hb values. Refer to the prescribing information regarding increasing, reducing, interrupting, or conversion dosing. Use the lowest dose sufficient to reduce the need for RBC transfusions.

Guidelines

The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for anemia in CKD (2012) state that for adults with CKD on dialysis, ESA therapy should be used to avoid having the Hb concentration fall below 9.0 g/dL by initiating ESA therapy when the Hb is between 9.0 and 10.0 g/dL.[2] The guidelines recommend against ESA therapy for adult patients with CKD who are not on dialysis when

Hb levels are ≥ 10.0 g/dL. For adult patients with CKD who are not on dialysis with Hb levels < 10.0 g/dL, the decision whether to initiate ESA therapy should be individualized based on many factors (e.g., prior response to iron therapy, the risk of needing a transfusion, presence of symptoms). In general, ESAs should not be used to maintain Hb concentrations above 11.5 g/dL in adult patients with CKD. For pediatric patients with CKD, the Hb concentration in which ESAs should be initiated in the individual patient should be considered while being aware of the potential benefits and potential harms. In all pediatric patients with CKD receiving ESA therapy, the selected Hb concentration should be in the range of 11.0 to 12.0 g/dL. Iron supplementation can improve response to ESA therapy. Baseline and periodic monitoring (e.g., iron, total iron-binding capacity, transferrin saturation, or ferritin levels) and instituting iron replacement when needed may be useful in limiting the need for ESAs, maximizing symptomatic improvement in patients, and determining the reason for inadequate response to ESAs. Iron deficiency can occur following continued ESA use. Therefore, iron supplementation is required in most patients to maintain an optimal response.

Aranesp is recommended in several guidelines from the National Comprehensive Cancer Network (NCCN):

- **Myelodysplastic Syndrome (MDS):** NCCN guidelines (version 1.2023 – September 12, 2022) list Aranesp and epoetin alfa products as having utility in anemic, symptomatic patients with MDS if serum erythropoietin levels are ≤ 500 mU/mL.[3] Iron stores should be adequate. Due to safety issues, the guidelines suggest that ESAs be used in the management of symptomatic anemia in patients with MDS and to aim for a target Hb range of 10 to 12.0 g/dL but not to exceed 12.0 g/dL.
- **Myeloproliferative Neoplasms:** The NCCN guidelines (version 1.2023 – May 19, 2023) address Aranesp and epoetin alfa products as options for treatment of patients with anemia related to myelofibrosis having a serum erythropoietin level < 500 mU/mL.[4] Iron stores should be adequate. The guidelines also advise that ESAs are not effective for the management of transfusion-dependent anemia.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Aranesp in patients with conditions other than CKD who are on dialysis. The intent of this policy is to provide recommendations for uses other than anemia in patients with CKD who are on dialysis. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Aranesp as well as the monitoring required for adverse events and long-term efficacy, approval requires Aranesp to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

*Indications and/or approval conditions noted with **[eviCore]** are managed by eviCore healthcare for those clients who use eviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to eviCore at www.eviCore.com.*

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Aranesp is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. Anemia in a Patient with Chronic Kidney Disease who is on Dialysis. Approve for 3 years.

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2. Anemia in a Patient with Chronic Kidney Disease who is not on Dialysis. Approve for 1 year if the patient meets the following (A or B):

A) Initial Therapy. Approve if the patient meets the following (i and ii):
- **i.** Patient meets one of the following (a or b):
  - **a)** Patient is ≥ 18 years of age with a hemoglobin < 10.0 g/dL; OR
  - **b)** Patient is < 18 years of age with a hemoglobin ≤ 11.0 g/dL; AND
- **ii.** Patient meets one of the following (a or b):
  - **a)** Patient is currently receiving iron therapy; OR
  - **b)** Patient has adequate iron stores according to the prescriber; OR

B) Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve if the patient meets the following (i and ii):
Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit), a darbepoetin alfa product (e.g., Aranesp), or a methoxy polyethylene glycol-epoetin beta product (e.g., Mircera).
- **i.** Patient has a hemoglobin ≤ 12.0 g/dL; AND
- **ii.** Patient meets one of the following (a or b):
  - **a)** Patient is currently receiving iron therapy; OR
  - **b)** Patient has adequate iron stores according to the prescriber.

Dosing. Approve one of the following dosing regimens (A or B):

A) Patient is ≥ 18 years of age. Approve if the dose meets the following (i and ii):
- **i.** Each dose is ≤ 0.45 mcg/kg; AND
- **ii.** Each dose is given no more frequently than once every 4 weeks; OR

B) Patient is < 18 years of age. Approve if the dose meets the following (i and ii):
- **i.** Each dose is ≤ 0.75 mcg/kg; AND
- **ii.** Each dose is given no more frequently than once every 2 weeks.

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3. Anemia in a Patient with Cancer due to Cancer Chemotherapy. ***[eviCore]*** Approve for 6 months if the patient meets the following (A or B):

A) Initial Therapy. Approve if the patient meets the following (i, ii, and iii):
- **i.** Patient has a hemoglobin < 10.0 g/dL; AND
- **ii.** Patient meets BOTH of the following (a and b):
  - **a)** Patient is currently receiving myelosuppressive chemotherapy; AND
  - **b)** According to the prescriber, myelosuppressive chemotherapy is considered non-curative; AND
- **iii.** Patient meets one of the following (a or b):
  - **a)** Patient is currently receiving iron therapy; OR
  - **b)** Patient has adequate iron stores according to the prescriber; OR

B) Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve if the patient meets the following (i, ii, and iii):

Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit) or a darbepoetin alfa product (e.g., Aranesp).
- **i.** Patient has a hemoglobin ≤ 12.0 g/dL; AND
- **ii.** Patient meets BOTH of the following (a and b):
  - **a)** Patient is currently receiving myelosuppressive chemotherapy; AND
  - **b)** According to the prescriber, myelosuppressive chemotherapy is considered non-curative; AND
- **iii.** Patient meets one of the following (a or b):
  - **a)** Patient is currently receiving iron therapy; OR
  - **b)** Patient has adequate iron stores according to the prescriber.

Dosing. Approve one of the following dosing regimens (A or B):
- **A)** Patient is ≥ 18 years of age. Approve if the dose meets the following (i and ii):
  - **i.** Each dose is ≤ 500 mcg; AND
  - **ii.** Each dose is given no more frequently than once every week; OR
- **B)** Patient is < 18 years of age. Approve if the dose meets the following (i and ii):
  - **i.** Each dose is ≤ 2.25 mcg/kg; AND
  - **ii.** Each dose is given no more frequently than once every week.

Other Uses with Supportive Evidence

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4. Anemia Associated with Myelodysplastic Syndrome. ***[eviCore]*** Approve for 1 year if the patient meets the following (A or B):
- **A)** Initial Therapy. Approve if the patient meets the following (i, ii, iii, and iv):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** Patient meets one of the following (a or b):
    - **a)** Patient has a hemoglobin < 10.0 g/dL; OR
    - **b)** Patient has a serum erythropoietin level ≤ 500 mU/mL; AND
  - **iii.** Patient meets one of the following (a or b):
    - **a)** Patient is currently receiving iron therapy; OR
    - **b)** Patient has adequate iron stores according to the prescriber; AND
  - **iv.** The medication is prescribed by or in consultation with a hematologist or oncologist.
- **B)** Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve if the patient meets the following (i, ii, iii, and iv):
  Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit) or a darbepoetin alfa product (e.g., Aranesp).
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** Patient has a hemoglobin ≤ 12.0 g/dL; AND
  - **iii.** Patient meets one of the following (a or b):
    - **a)** Patient is currently receiving iron therapy; OR
    - **b)** Patient has adequate iron stores according to the prescriber; AND
  - **iv.** The medication is prescribed by or in consultation with a hematologist or oncologist.

Dosing. Approve if the dose meets the following (A and B):
- **A)** Each dose is ≤ 500 mcg; AND
- **B)** Each dose is given no more frequently than once every 2 weeks.

5. **Anemia Associated with Myelofibrosis.** *[eviCore]* Approve for the duration noted below if the patient meets the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets the following (i, ii, and iii):
     - **i.** Patient meets one of the following (a or b):
       - **a)** Patient has a hemoglobin < 10.0 g/dL; OR
       - **b)** Patient has a serum erythropoietin level ≤ 500 mU/mL; AND
     - **ii.** Patient meets one of the following (a or b):
       - **a)** Patient is currently receiving iron therapy; OR
       - **b)** Patient has adequate iron stores according to the prescriber; AND
     - **iii.** The medication is prescribed by or in consultation with a hematologist or oncologist.
   - **B)** Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):
     Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit) or a darbepoetin alfa product (e.g., Aranesp).
     - **i.** Patient has a hemoglobin ≤ 12.0 g/dL; AND
     - **ii.** Patient meets one of the following (a or b):
       - **a)** Patient is currently receiving iron therapy; OR
       - **b)** Patient has adequate iron stores according to the prescriber; AND
     - **iii.** According to the prescriber, patient has responded to therapy defined as hemoglobin ≥ 10 g/dL or a hemoglobin increase of ≥ 2 g/dL; AND
     - **iv.** The medication is prescribed by or in consultation with a hematologist or oncologist.

   Dosing. Approve if the dose meets the following (A and B):
   - **A)** Each dose is ≤ 500 mcg; AND
   - **B)** Each dose is given no more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Aranesp is not recommended in the following situations:

1. **Anemia Associated with Cancer in a Patient not Receiving Myelosuppressive Cancer Chemotherapy.** *[eviCore]* Aranesp is not indicated in patients with cancer who are not receiving cancer chemotherapy.[1]

2. **Anemia Associated with Acute Myelogenous Leukemias (AML), Chronic Myelogenous Leukemias (CML) or other Myeloid Cancers.** *[eviCore]* Aranesp is indicated for use in non-myeloid cancers. AML and CML are examples of myeloid cancers.[1]

3. **Anemia Associated with Radiotherapy in Cancer.** *[eviCore]* Aranesp is not indicated for use in patients with cancer who are given only radiation therapy.[1]

4. **To Enhance Athletic Performance.** Aranesp is not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

5. **Anemia due to Acute Blood Loss.** Use of Aranesp is not appropriate in these types of situations.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Aranesp® intravenous or subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; January 2019.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	07/20/2022
Selected Revision	**Anemia in a Patient with Cancer due to Cancer Chemotherapy:** A non-curative treatment, according to the prescriber was added to the criterion for a patient to be currently receiving myelosuppressive chemotherapy.	09/28/2022
Selected Revision	**Anemia in a Patient with Chronic Kidney Disease who is not on Dialysis:** For a Patient Currently Receiving an Erythropoiesis-Stimulating Agent, the criterion regarding a patient who is ≥ 18 years of age, the hemoglobin level was changed from < 11.5 to ≤ 12.0 g/dL. Since the criterion is now the same as a patient < 18 years of age, the delineation of age was also removed from criteria.	03/22/2023
Annual Revision	No criteria changes.	07/19/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Erythropoiesis-Stimulating Agents – Mircera Utilization Management Medical Policy
- Mircera® (methoxy polyethylene glycol-epoetin beta intravenous or subcutaneous injection – Vifor)

REVIEW DATE: 07/19/2023

OVERVIEW

Mircera, an erythropoiesis-stimulating agent (ESA), is indicated for **anemia due to chronic kidney disease** (CKD), including adults on dialysis, adults not on dialysis, and pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA.

Mircera has not been shown to improve symptoms, physical functioning, or health-related quality of life.[1] Mircera is not indicated for the following uses:
- Treatment of anemia due to cancer chemotherapy.
- As a substitute for red blood cell (RBC) transfusions in those who require immediate correction of anemia.

Therapy should be initiated for adults with CKD on dialysis when the Hb level is < 10.0 g/dL and if the Hb level approaches or exceeds 11.0 g/dL, reduce or interrupt the dose of Mircera.[1] For adults with CKD not on dialysis, consider initiating Mircera only when the Hb is < 10.0 g/dL and other considerations apply (e.g., rate of Hb decline indicates patient is likely to need RBC transfusion and reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal). If the Hb exceeds 10.0 g/dL, reduce or interrupt the Mircera dose and use the lowest dose sufficient to reduce the need for RBC transfusions.

Guidelines

The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for anemia in CKD (2012) state that for adults with CKD on dialysis ESA therapy should be used to avoid having the Hb concentration fall below 9.0 g/dL by initiating ESA therapy when the Hb is between 9.0 and 10.0 g/dL.[2] The guidelines recommend against ESA therapy for adult patients with CKD who are not on dialysis when Hb levels are ≥ 10.0 g/dL. For adult patients with CKD who are not on dialysis with Hb levels < 10.0 g/dL, the decision whether to initiate ESA therapy should be individualized based on many factors (e.g., prior response to iron therapy, the risk of needing a transfusion, presence of symptoms). In general, ESAs should not be used to maintain Hb concentrations above 11.5 g/dL in adult patients with CKD. For pediatric patients with CKD, the Hb concentration in which ESAs should be initiated in the individual patient should be considered while being aware of the potential benefits and potential harms. In all pediatric patients with CKD receiving ESA therapy, the selected Hb concentration should be in the range of 11.0 to 12.0 g/dL. Iron supplementation can improve response to ESA therapy. Baseline and periodic monitoring (e.g., iron, total iron-binding capacity, transferrin saturation, or ferritin levels) and instituting iron replacement when needed may be useful in limiting the need for ESAs, maximizing symptomatic improvement in patients, and determining the reason for inadequate response to ESAs. Iron deficiency can occur following continued ESA use. Therefore, iron supplementation is required in most patients to maintain an optimal response.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Mircera in patients with conditions other than CKD who are on dialysis. The intent of this policy is to provide recommendations for uses other than anemia in patients with CKD who are on dialysis. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mircera is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. Anemia in a Patient with Chronic Kidney Disease who is on Dialysis. Approve for 3 years.

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2. Anemia in a Patient with Chronic Kidney Disease who is not on Dialysis. Approve for 1 year if the patient meets the following (A or B):

A) Initial Therapy. Approve if the patient meets the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has a hemoglobin < 10.0 g/dL; AND
- **iii.** Patient meets one of the following (a or b):
  - **a)** Patient is currently receiving iron therapy; OR
  - **b)** Patient has adequate iron stores according to the prescriber; OR

B) Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve if the patient meets the following (i, ii, and iii):

Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit), a darbepoetin alfa product (e.g., Aranesp), or a methoxy polyethylene glycol-epoetin beta product (e.g., Mircera).
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has a hemoglobin ≤ 12.0 g/dL; AND
- **iii.** Patient meets one of the following (a or b):
  - **a)** Patient is currently receiving iron therapy; OR
  - **b)** Patient has adequate iron stores according to the prescriber.

Dosing. Approve one of the following dosing regimens (A or B):

A) Approve if the dose meets the following (i and ii):
- **i.** Each dose is ≤ 180 mcg; AND
- **ii.** Each dose is given no more frequently than once every 2 weeks; OR

B) Approve if the dose meets the following (i and ii):
- **i.** Each dose is ≤ 360 mcg; AND
- **ii.** Each dose is given no more frequently than once monthly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mircera is not recommended in the following situations:

1. **Anemia Associated with Cancer in a Patient Receiving Myelosuppressive Cancer Chemotherapy.** Mircera is not indicated and not recommended for the treatment of anemia due to cancer chemotherapy.[1]

2. **To Enhance Athletic Performance.** Mircera is not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

3. **Anemia due to Acute Blood Loss.** Use of Mircera is not appropriate in these types of situations.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Mircera® intravenous or subcutaneous injection [prescribing information]. Basking Ridge, NJ: Vifor Pharma; March 2023.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int*. 2012; 2(Suppl):279-335.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	07/20/2022
Selected Revision	**Anemia in a Patient with Chronic Kidney Disease who is <u>not</u> on Dialysis**: For a Patient Currently Receiving an Erythropoiesis-Stimulating Agent, the hemoglobin level was changed from < 11.5 to ≤ 12.0 g/dL.	03/22/2023
Annual Revision	No criteria changes.	07/19/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Gamifant Utilization Management Medical Policy
- Gamifant® (emapalumab-lzsg intravenous infusion – Sobi)

REVIEW DATE: 02/14/2024

OVERVIEW

Gamifant, an anti-interferon gamma (IFN-γ) antibody, is indicated for the treatment of **primary hemophagocytic lymphohistiocytosis** (HLH) in adult and pediatric patients with refractory, recurrent, or progressive disease, or intolerance with conventional HLH therapy.[1]

Disease Overview

HLH is a syndrome characterized by signs and symptoms of extreme inflammation, caused by defects in cytotoxic function (cytotoxic T cells and natural killer cells).[2] The incidence is estimated at 1.2 cases per million individuals per year, but this is likely an underestimate.[3] In healthy individuals, cytotoxic function is important to terminate immune responses when appropriate by targeting and destroying activated immune cells. Deficiencies in cytotoxic function lead to an unchecked immune response and hyper-inflammation. Primary HLH has a clear genetic cause, whereas secondary HLH is triggered by a concomitant infection or medical condition, such as Epstein-Barr virus infection, malignancy, or rheumatologic disorders. IFN-γ normally has both pro-inflammatory functions (e.g., macrophage activation) and anti-inflammatory functions (e.g., activation of cytotoxic cells).[4,5] However, in HLH, the anti-inflammatory action of IFN-γ is ineffective due to impaired cytotoxic cell activity; thus, pro-inflammatory effects predominate.

Guidelines

The HLH-2004 treatment protocol, developed by the Histiocyte Society, is the current standard of care for diagnostic and therapeutic guidelines.[6] Gamifant is not addressed in the 2004 protocol. To establish a diagnosis of HLH, patients must either have a molecular diagnosis consistent with HLH or must meet five out of eight diagnostic criteria. A backbone of etoposide and systemic dexamethasone is the conventional standard of care to induce symptomatic resolution; cyclosporine A and anti-thymocyte globulin have also demonstrated efficacy. Although chemotherapy prolongs survival in primary HLH, a hematopoietic stem cell transplant (HSCT) is needed for cure. Patients with primary HLH should continue chemotherapy (usually with etoposide, cyclosporine A, and dexamethasone) until HSCT can be performed. Myelotoxicity due to chemotherapy is a concern, especially since patients with HLH can have severe cytopenias and immunodeficiency at baseline.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Gamifant. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Gamifant, approval requires it to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Gamifant is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Hemophagocytic Lymphohistiocytosis, Primary.** Approve Gamifant for 6 months if the patient meets the following (A, B, C, and D):
   - **A)** Patient has a diagnosis of hemophagocytic lymphohistiocytosis determined by at least one of the following (i or ii):
     - **i.** Patient has a molecular genetic diagnosis consistent with hemophagocytic lymphohistiocytosis; OR
     - **ii.** Prior to treatment, the patient meets at least FIVE of the following diagnostic criteria at baseline (FIVE of a, b, c, d, e, f, g, or h):
       - **a)** Fever ≥ 38.5° C;
       - **b)** Splenomegaly;
       - **c)** Cytopenias defined as at least TWO of the following (TWO of 1, 2, or 3):
         - **1)** Hemoglobin < 9 g/dL (or < 10 g/dL in infants less than 4 weeks of age);
         - **2)** Platelets < 100 x 10^9/L;
         - **3)** Neutrophils < 1.0 x 10^9/L;
       - **d)** Patient meets ONE of the following (1 or 2):
         - **1)** Fasting triglycerides ≥ 265 mg/dL; OR
         - **2)** Fibrinogen ≤ 1.5 g/L;
       - **e)** Hemophagocytosis in bone marrow, spleen, or lymph nodes;
       - **f)** Low or absent natural killer cell activity (according to local laboratory reference);
       - **g)** Ferritin ≥ 500 mcg/L;
       - **h)** Soluble CD25 (i.e., soluble interleukin-2 receptor) ≥ 2,400 U/mL; AND
   - **B)** Patient has tried at least one conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); AND
   - **C)** According to the prescriber, the patient has experienced at least one of the following (i or ii):
     - **i.** Refractory, recurrent, or progressive disease during conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); OR
     - **ii.** Intolerance to conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); AND
   - **D)** The medication is prescribed by or in consultation with a hematologist, oncologist, immunologist, transplant specialist, or physician who specializes in hemophagocytic lymphohistiocytosis or related disorders.

   Dosing. Approve up to a maximum dose of 10 mg/kg by intravenous infusion, not more frequently than twice weekly (once every 3 to 4 days).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Gamifant is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Gamifant® intravenous infusion [prescribing information]. Waltham, MA: Sobi; May 2022.
2. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood*. 2011;118(15):4041-4052.
3. Weitzman S. Approach to hemophagocytic syndromes. *Hematology Am Soc Hematol Edu Program.* 2011;2011:178-183.
4. Avau A, Matthys P. Therapeutic potential of interferon-γ and its antagonists in autoinflammation: lessons from murine models of systemic juvenile idiopathic arthritis and macrophage activation syndrome. *Pharmaceuticals.* 2015;8:793-815.
5. Osinska I, Popko K, Demkow U. Perforin: an important player in immune response. *Centr Eur J Immunol*. 2014;39(1):109-115.
6. Henter J, Horne A, Aricó M, et al. HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48:124-131.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	01/04/2023
Annual Revision	No criteria changes.	02/14/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Gaucher Disease – Enzyme Replacement Therapy – Cerezyme Utilization Management Medical Policy
- Cerezyme® (imiglucerase intravenous infusion – Genzyme)

REVIEW DATE: 04/10/2024

OVERVIEW

Cerezyme, an analogue of β-glucocerebrosidase, is indicated for the treatment of a confirmed diagnosis of **Type 1 Gaucher disease** in patients ≥ 2 years of age that results in at least one of the following: anemia, thrombocytopenia, bone disease, hepatomegaly, or splenomegaly.[1]

Cerezyme is produced via recombinant DNA technology in Chinese hamster ovary cells and differs from human placental glucocerebrosidase by one amino acid at position 495.[1] Cerezyme catalyzes the breakdown of glucocerebroside to glucose and ceramide.

Disease Overview

Gaucher disease is a rare autosomal recessive, inherited, lysosomal storage disorder caused by a deficiency of the lysosomal enzyme β-glucocerebrosidase.[2-4] Glucocerebrosidase is responsible for the breakdown of glucosylcerebroside (GluCer) into glucose and ceramide. A deficiency of this enzyme is characterized by an excessive accumulation of GluCer in the visceral organs such as the liver, spleen, and bone marrow. GluCer remains stored within lysosomes causing enlarged lipid-laden macrophages called "Gaucher cells".

Gaucher disease is classified into three phenotypes (Types 1 through 3).[2-5] Type 1 is a non-neuropathic variant with asymptomatic or symptomatic clinical manifestations of splenomegaly, hepatomegaly, anemia, thrombocytopenia, skeletal complications, and occasional lung involvement. Type 2 is an acute neuropathic form characterized by an early onset (3 to 6 months of age) of rapidly progressive neurological disease with visceral manifestations; death generally occurs by the time patients reach 1 to 2 years of age. Type 3 is characterized by neurological symptoms and visceral symptoms with a later onset and includes abnormal eye movements, ataxia, seizures, and dementia. Type 1 is most prevalent in the Western world, accounting for an estimated 94% of patients with Gaucher disease.[2,6] Types 2 and 3 represent < 1% and 5%, respectively, in Europe, North America, and Israel.[2,5] The diagnosis of Gaucher disease is established by demonstrating deficient β-glucocerebrosidase activity in leukocytes or fibroblasts, or mutations in the glucocerebrosidase gene.[7,8]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Cerezyme. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cerezyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Cerezyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cerezyme is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. **Gaucher Disease.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient has Type 1 Gaucher disease; AND
   - **B)** The diagnosis is established by ONE of the following (i or ii):
     - **i.** Demonstration of deficient β-glucocerebrosidase activity in leukocytes or fibroblasts; OR
     - **ii.** Molecular genetic testing documenting glucocerebrosidase gene mutation; AND
   - **C)** Cerezyme is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

   Dosing. Each individual dose must not exceed 60 U/kg administered intravenously no more frequently than three times per week.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cerezyme is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Cerezyme® intravenous infusion [prescribing information]. Cambridge, MA: Genzyme; December 2022.
2. Burrow TA, Barnes S, and Grabowski GA. Prevalence and management of Gaucher disease. *Pediatric Health Med Ther*. 2011;2:59-73.
3. Cox T. Gaucher disease: clinical profile and therapeutic development. *Biologics*. 2010;4:299-313.
4. Jmoudiak, M. and Futerman, AH. Gaucher disease: Pathological mechanisms and modern management. *Br J Haematol*. 2005;129(2):178–188.
5. Grabowski GA. Lysosomal storage disease 1- phenotype, diagnosis, and treatment of Gaucher's disease. *Lancet*. 2008;372:1263-1271.
6. Zimran A. How I treat Gaucher disease. *Blood*. 2011;118:1463-1471.
7. Stirnemann J, Belmatoug N, Camou F, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. *Int J Mol Sci*. 2017;18:441.
8. Baris HN, Cohen IJ, Mistry PK. Gaucher disease: The metabolic defect, pathophysiology, phenotypes and natural history. *Pediatr Endocrinol Rev*. 2014;12:72-81.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/05/2023
Annual Revision	No criteria changes.	04/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Gaucher Disease – Enzyme Replacement Therapy – Elelyso Utilization Management Medical Policy
- Elelyso® (taliglucerase intravenous infusion – Pfizer)

REVIEW DATE: 04/10/2024

OVERVIEW

Elelyso, an analogue of β-glucocerebrosidase, is indicated for the treatment of a confirmed diagnosis of **Type 1 Gaucher disease** in patients ≥ 4 years of age.[1]

Elelyso is produced via recombinant DNA technology in genetically modified carrot plant root cells.[1] Elelyso differs from human glucocerebrosidase by two amino acids at the N terminal and seven amino acids at the C terminal end of the protein. Elelyso catalyzes the breakdown of glucocerebroside to glucose and ceramide.

Disease Overview

Gaucher disease is a rare autosomal recessive, inherited, lysosomal storage disorder caused by a deficiency of the lysosomal enzyme β-glucocerebrosidase.[2-4] Glucocerebrosidase is responsible for the breakdown of glucosylcerebroside (GluCer) into glucose and ceramide. A deficiency of this enzyme is characterized by an excessive accumulation of GluCer in the visceral organs such as the liver, spleen, and bone marrow. GluCer remains stored within lysosomes causing enlarged lipid-laden macrophages called "Gaucher cells".

Gaucher disease is classified into three phenotypes (Types 1 through 3).[2-5] Type 1 is a non-neuropathic variant with asymptomatic or symptomatic clinical manifestations of splenomegaly, hepatomegaly, anemia, thrombocytopenia, skeletal complications, and occasional lung involvement. Type 2 is an acute neuropathic form characterized by an early onset (3 to 6 months of age) of rapidly progressive neurological disease with visceral manifestations; death generally occurs by the time patients reach 1 to 2 years of age. Type 3 is characterized by neurological symptoms and visceral symptoms with a later onset and includes abnormal eye movements, ataxia, seizures, and dementia. Type 1 is most prevalent in the Western world, accounting for an estimated 94% of patients with Gaucher disease.[2,6] Types 2 and 3 represent < 1% and 5%, respectively, in Europe, North America, and Israel.[2,5] The diagnosis of Gaucher disease is established by demonstrating deficient β-glucocerebrosidase activity in leukocytes or fibroblasts, or mutations in the glucocerebrosidase gene.[7,8]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Elelyso. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Elelyso as well as the monitoring required for adverse events and long-term efficacy, approval requires Elelyso to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Elelyso is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Gaucher Disease.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Patient has Type 1 Gaucher disease; AND
   - **B)** Patient is ≥ 4 years of age; AND
   - **C)** The diagnosis is established by ONE of the following (i or ii):
     - **i.** Demonstration of deficient β-glucocerebrosidase activity in leukocytes or fibroblasts; OR
     - **ii.** Molecular genetic testing documenting glucocerebrosidase gene mutation; AND
   - **D)** Elelyso is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

   Dosing. Each individual dose must not exceed 60 U/kg administered intravenously no more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Elelyso is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Elelyso® intravenous infusion [prescribing information]. New York, NY: Pfizer; May 2023.
2. Burrow TA, Barnes S, and Grabowski GA. Prevalence and management of Gaucher disease. *Pediatric Health Med Ther*. 2011;2:59-73.
3. Cox T. Gaucher disease: clinical profile and therapeutic development. *Biologics*. 2010;4:299-313.
4. Jmoudiak, M and Futerman, AH. Gaucher disease: Pathological mechanisms and modern management. *Br J Haematol*. 2005;129(2):178–188.
5. Grabowski GA. Lysosomal storage disease 1- phenotype, diagnosis, and treatment of Gaucher's disease. *Lancet*. 2008;372:1263-1271.
6. Zimran A. How I treat Gaucher disease. *Blood*. 2011;118:1463-1471.
7. Stirnemann J, Belmatoug N, Camou F, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. *Int J Mol Sci*. 2017;18:441.
8. Baris HN, Cohen IJ, Mistry PK. Gaucher disease: The metabolic defect, pathophysiology, phenotypes and natural history. *Pediatr Endocrinol Rev*. 2014;12:72-81.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/05/2023
Annual Revision	No criteria changes.	04/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Gaucher Disease – Enzyme Replacement Therapy – Vpriv Utilization Management Medical Policy
- Vpriv® (velaglucerase intravenous infusion – Shire Human Genetic Therapies)

REVIEW DATE: 04/10/2024

OVERVIEW

Vpriv, an analogue of β-glucocerebrosidase, is indicated for long-term enzyme replacement therapy for patients with **Type 1 Gaucher disease**.[1]

Vpriv is produced via gene activation technology in a human fibroblast cell line.[1] Vpriv has the same amino acid sequence as the naturally occurring human glucocerebrosidase. Vpriv catalyzes the breakdown of glucocerebroside to glucose and ceramide.

Disease Overview

Gaucher disease is a rare autosomal recessive, inherited, lysosomal storage disorder caused by a deficiency of the lysosomal enzyme β-glucocerebrosidase.[2-4] Glucocerebrosidase is responsible for the breakdown of glucosylcerebroside (GluCer) into glucose and ceramide. A deficiency of this enzyme is characterized by an excessive accumulation of GluCer in the visceral organs such as the liver, spleen, and bone marrow. GluCer remains stored within lysosomes causing enlarged lipid-laden macrophages called "Gaucher cells".

Gaucher disease is classified into three phenotypes (Types 1 through 3).[2-5] Type 1 is a non-neuropathic variant with asymptomatic or symptomatic clinical manifestations of splenomegaly, hepatomegaly, anemia, thrombocytopenia, skeletal complications, and occasional lung involvement. Type 2 is an acute neuropathic form characterized by an early onset (3 to 6 months of age) of rapidly progressive neurological disease with visceral manifestations; death generally occurs by the time patients reach 1 to 2 years of age. Type 3 is characterized by neurological symptoms and visceral symptoms with a later onset and includes abnormal eye movements, ataxia, seizures, and dementia. Type 1 is most prevalent in the Western world, accounting for an estimated 94% of patients with Gaucher disease.[2,6] Types 2 and 3 represent < 1% and 5%, respectively, in Europe, North America, and Israel.[2,5] The diagnosis of Gaucher disease is established by demonstrating deficient β-glucocerebrosidase activity in leukocytes or fibroblasts, or mutations in the glucocerebrosidase gene.[7,8]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Vpriv. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vpriv as well as the monitoring required for adverse events and long-term efficacy, approval requires Vpriv to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vpriv is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Gaucher Disease.** Approve for 1 year if the patient meets ALL the following (A, B, and C):
   - **A)** Patient has Type 1 Gaucher disease; AND
   - **B)** The diagnosis is established by ONE of the following (i or ii):
     - **i.** Demonstration of deficient β-glucocerebrosidase activity in leukocytes or fibroblasts; OR
     - **ii.** Molecular genetic testing documenting glucocerebrosidase gene mutation; AND
   - **C)** Vpriv is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

   Dosing. Each individual dose must not exceed 60 U/kg administered intravenously no more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vpriv is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Vpriv® intravenous infusion [prescribing information]. Lexington, MA: Shire Human Genetic Therapies; September 2021.
2. Burrow TA, Barnes S, and Grabowski GA. Prevalence and management of Gaucher disease. *Pediatric Health Med Ther.* 2011;2:59-73.
3. Cox T. Gaucher disease: clinical profile and therapeutic development. *Biologics*. 2010;4:299-313.
4. Jmoudiak, M and Futerman, AH. Gaucher disease: Pathological mechanisms and modern management. *Br J Haematol*. 2005;129(2):178–188.
5. Grabowski GA. Lysosomal storage disease 1- phenotype, diagnosis, and treatment of Gaucher's disease. *Lancet*. 2008;372:1263-1271.
6. Zimran A. How I treat Gaucher disease. *Blood*. 2011;118:1463-1471.
7. Stirnemann J, Belmatoug N, Camou F, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. *Int J Mol Sci*. 2017;18:441.
8. Baris HN, Cohen IJ, Mistry PK. Gaucher disease: The metabolic defect, pathophysiology, phenotypes and natural history. *Pediatr Endocrinol Rev*. 2014;12:72-81.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/05/2023
Annual Revision	No criteria changes.	04/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Gonadotropin-Releasing Hormone Agonists – Central Precocious Puberty Utilization Management Medical Policy

- Fensolvi® (leuprolide acetate subcutaneous injection, extended-release – Tolmar)
- Lupron Depot-Ped® (leuprolide acetate depot intramuscular injection – AbbVie)
- Triptodur™ (triptorelin intramuscular injection, extended-release – Azurity)

REVIEW DATE : 11/08/2023

OVERVIEW

Fensolvi, Lupron Depot-Ped, and Triptodur are gonadotropin-releasing hormone (GnRH) agonists indicated for the **treatment of pediatric patients with central precocious puberty**.[1-3]

GnRH agonists can also be used off-label for the **treatment of gender-dysphoric/gender-incongruent persons** to suppress physical changes of puberty and gonadal function.[7,8] Pubertal hormonal suppression should typically be initiated after the adolescent first exhibits physical changes of puberty (Tanner stages G2/B2). Long-acting GnRH analogs are the currently preferred treatment option. An advantage to using a GnRH analog is that the effects can be reversed; pubertal suppression can be discontinued if the individual no longer wishes to transition. Upon discontinuation of therapy, spontaneous pubertal development has been shown to resume. GnRH analogs can also be used in patients during late puberty to suppress the hypothalamic-pituitary-gonadal axis to allow for lower doses of cross-sex hormones.[9] In addition to use in adolescents, GnRH analog therapy is also used in adults, particularly male-to-female patients.[10]

Dosing Information

Fensolvi is administered by a subcutaneous injection and both Lupron Depot-Ped and Triptodur are administered by intramuscular injection.[1-3] Fensolvi is administered once every 6 months, Lupron Depot-Ped is administered once a month, once every 3 months (12 weeks), or once every 6 months (24 weeks), and Triptodur is administered once every 24 weeks. There are no specific dosing recommendations for off-label use of Fensolvi, Lupron Depot-Ped, or Triptodur. Therefore, the FDA-approved dosing in the product labeling for approved uses has been cited for off-label uses. Treatment decisions, including duration of therapy, are individualized with careful consideration of the risks and benefit of the selected regimen.

Guidelines

The standard of care for central precocious puberty is GnRH agonists.[4-6] The European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society convened a consensus conference to review the use of GnRH agonists in pediatric patients with central precocious puberty (2009).[4] The panel noted that the available GnRH agonists (including leuprolide and triptorelin) are effective, despite different routes of administration, dosing, and duration of action. In addition, the various GnRH agonists are well-tolerated in children and adolescents. An update by an International Consortium (2019) notes the lack of prospective comparative studies to establish differences in efficacy (if any) among the various GnRH agonists.[5] The Consortium does not prefer one GnRH agonist over another. Discontinuation of GnRH agonist therapy should be individualized, based on the patient's readiness for resumption of puberty, recent growth rates, and shifts in height prediction.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of the gonadotropin-releasing hormone agonists (Fensolvi, Lupron Depot-Ped, and Triptodur). Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of gender-dysphoric/gender-incongruent patients treated with Fensolvi, Lupron Depot-Ped, or Triptodur, as well as the monitoring requested for adverse events and long-term efficacy, approval requires that the product be prescribed by or in consultation with a physician who specializes in this condition.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of a gonadotropin-releasing hormone agonist (Fensolvi, Lupron Depot-Ped, and Triptodur) is recommended in those who meet one of the following criteria:

FDA-Approved Indication

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1. Central Precocious Puberty. Approve for 1 year.

Dosing. Approve one of the following dosing regimens (A, B, or C):

A) Fensolvi: Approve up to one injection (45 mg) given subcutaneously once every 6 months; OR

B) Lupron Depot-Ped: Approve ONE of the following doses (i, ii, iii, iv, or v); OR

- **i.** 1-month depot, ≤ 25 kg: Approve up to one 1-month depot (7.5 mg) given intramuscularly (IM) once every month; OR
- **ii.** 1-month depot, > 25 to 37.5 kg: Approve up to one 1-month depot (11.25 mg) given IM once every month; OR
- **iii.** 1-month depot, > 37.5 kg: Approve up to one 1-month depot (15 mg) given IM once every month; OR
- **iv.** 3-month depot: Approve up to one 3-month depot (11.25 mg or 30 mg) given IM once every 3 months (12 weeks); OR
- **v.** 6-month depot: Approve up to one 6-month depot (45 mg) given IM once every 6 months (24 weeks).

C) Triptodur: Approve up to one injection (22.5 mg) given IM once every 24 weeks.

Other Uses with Supportive Evidence

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2. Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Gender Reassignment (Female-to-Male or Male-to-Female). Approve for 1 year if prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.

Dosing. Approve ONE of the following dosing regimen (A, B, or C):

A) Fensolvi: Approve up to one injection (45 mg) given subcutaneously once every 6 months; OR

B) Lupron Depot-Ped: Approve ONE of the following doses (i, ii, or iii); OR

i. 1-month depot: Approve up to one 1-month depot (7.5 mg, 11.25 mg, or 15 mg) given intramuscularly (IM) once every month; OR
ii. 3-month depot: Approve up to one 3-month depot (11.25 mg or 30 mg) given IM once every 3 months (12 weeks); OR
iii. 6-month depot: Approve up to one 6-month depot (45 mg) given IM once every 6 months (24 weeks).

C) Triptodur: Approve up to one injection (22.5 mg) given IM once every 24 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of a gonadotropin-releasing hormone agonist (Fensolvi, Lupron Depot-Ped, and Triptodur) is not recommended in the following situations:

1. **Peripheral Precocious Puberty (Also Known As GnRH-Independent Precocious Puberty)**. Children with peripheral precocious puberty do not respond to GnRH agonist therapy.[4] Treatment is directed at removing or blocking the production and/or response to the excess sex steroids, depending on the cause (e.g., surgically removing human chorionic gonadotropin-secreting tumors or using glucocorticoids to treat defects in adrenal steroidogenesis [such as classic congenital adrenal hyperplasia]).

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Lupron Depot-Ped® [prescribing information]. North Chicago, IL; AbbVie; April 2023.
2. Triptodur™ [prescribing information]. Woburn, MA: Azurity; December 2022.
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9. Rosenthal SM. Approach to the patient: transgender youth: endocrine considerations. *J Clin Endocrine Metab*. 2014;99:4379-4389.
10. Spack NP. Management of transgenderism. *JAMA*. 2013;309:478-484.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/02/2022
Annual Revision	Lupron Depot-Ped dosage (for each indication): Updated frequency to also include 12 weeks on the 3-month depot. Added the following dosage regimen: 6-month depot: Approve up to one 6-month depot (45 mg) given IM once every 6 months (24 weeks).	11/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Gonadotropin-Releasing Hormone Agonists – Implants Utilization Management Medical Policy
- Supprelin® LA (histrelin acetate subcutaneous implant – Endo)
- Vantas® (histrelin acetate subcutaneous implant – Endo [discontinued])
- Zoladex® (goserelin acetate subcutaneous implant – TerSera Therapeutics)

REVIEW DATE: 02/21/2024

OVERVIEW

Supprelin LA, Vantas, and Zoladex are gonadotropin-releasing hormone (GnRH) agonists implants.[1-4]

Supprelin LA is indicated for the treatment of **central precocious puberty** in children.[1]

Vantas is indicated for the palliative treatment of **advanced prostate cancer**.[2] Although Vantas is not indicated for use in children with central precocious puberty, it contains the same chemical entity as that of Supprelin LA, and can be used for this condition. Endo discontinued the manufacturing of Vantas as of 9/21/2021.[10]

Zoladex is indicated for the following conditions:[3,4] Zoladex 3.6 mg (equivalent to 3.8 mg goserelin acetate) is approved for all the diagnoses below. Zoladex 10.8 mg (equivalent to 11.3 mg goserelin acetate) is only indicated for prostate cancer.
- **Breast cancer**, palliative treatment of advanced breast cancer in pre- and perimenopausal women (Zoladex 3.6 mg implant only).
- **Endometrial-thinning**, use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding (Zoladex 3.6 mg implant only).
- **Endometriosis**, including pain relief and reduction of endometriotic lesions for the duration of therapy (Zoladex 3.6 mg implant only). Labeling notes that experience with Zoladex for this indication has been limited to women ≥ 18 years of age.[3]
- **Prostate cancer**, in combination with flutamide for the management of locally confined Stage T2b-T4 (Stage B2-C).
- **Prostate cancer**, advanced carcinoma or palliative treatment.

Guidelines

The GnRH agonists are addressed in treatment guidelines:
- **Breast cancer:** The National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 1.2024 – January 25, 2024) note that candidates for ovarian suppression plus endocrine therapy include: 1) premenopausal women, and 2) endocrine sensitive tumors with high enough recurrence risk where the additional absolute decrease in recurrence compared with tamoxifen alone is worth the additional toxicity (young age, high-grade tumor, lymph node involvement).[5] Goserelin doses for breast cancer are recommended at 3.6 mg subcutaneous every 4 weeks or 10.8 mg subcutaneous every 12 weeks. Guidelines also note that GnRH agonists (e.g., goserelin) administered prior to initiating chemotherapy protect against ovarian failure and reduce the risk of early menopause. Ovarian suppression may be recommended in patients who are premenopausal at diagnosis.

- **Central precocious puberty**, also known as gonadotropin-dependent precocious puberty, is caused by early maturation of the hypothalamic-pituitary-gonadal axis.[6] The standard of care for central precocious puberty is GnRH agonists. The European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society convened a consensus conference (2009) to review the use of GnRH agonists in pediatric patients with central precocious puberty.[7] The panel noted that the available GnRH agonists (including leuprolide, triptorelin, and histrelin implants) are effective despite different routes of administration, dosing, and duration of action. An update by the International Consortium (2019) reiterates the use of GnRH agonists (e.g., leuprolide, triptorelin, and histrelin implants) for the treatment of central precocious puberty.[8] GnRH agonists are generally well-tolerated in children and adolescents.
- **Head and neck cancer – salivary gland tumors:** The NCCN head and neck cancer guidelines (version 2.2024 – December 08, 2023) notes that goserelin (category 2B) is useful for androgen receptor positive salivary gland tumors which are recurrent, unresectable, or metastatic.[11,13] Dosing used in NCCN references was 3.6 mg subcutaneously once every 28 days.
- **Ovarian cancer, including fallopian tube cancer and primary peritoneal cancer:** The NCCN ovarian cancer guidelines (version 1.2024 – January 17, 2024) notes goserelin as other hormone therapy options for endometrioid carcinoma, low-grade serous carcinoma, and malignant sex cord stromal tumors.[11,14]
- **Prostate cancer:** The NCCN prostate cancer guidelines (version 4.2023 – September 7, 2023) list goserelin, leuprolide, and triptorelin as androgen deprivation therapy options for use in various settings: clinically localized disease, regional disease, prostate specific antigen persistence/recurrence after radical prostatectomy or external beam radiation therapy (castration-sensitive disease), and metastatic castration-sensitive disease.[9]
- **Uterine cancer:** The NCCN uterine neoplasm guidelines (version 1.2024 – September 20, 2023) notes that GnRH analogs are included as a category 2B option for endometrial stromal sarcoma, adenosarcoma without sarcomatous overgrowth, and estrogen receptor-progesterone receptor positive uterine sarcomas.[11,12]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Supprelin LA, Vantas, and Zoladex. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vantas and Zoladex as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated. Note that as with Supprelin LA, when Vantas is prescribed for use in children with central precocious puberty, it does not need to be prescribed by or in consultation with a specialist.

Automation: None.

*Indications and/or approval conditions noted with **[eviCore]** are managed by eviCore healthcare for those clients who use eviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to eviCore at www.eviCore.com.*

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Supprelin LA is recommended in patients who meet the following criteria:

FDA-Approved Indication

1. Central Precocious Puberty. Approve for 1 year.

Dosing. Approve one implant (50 mg) once every 12 months (inserted subcutaneously in the upper arm).

II. Coverage of Vantas is recommended in patients who meet one of the following criteria:

FDA-Approved Indication

1. Prostate Cancer. ***[eviCore].*** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

Dosing. Approve one implant (50 mg) once every 12 months (inserted subcutaneously in the upper arm).

Other Uses with Supportive Evidence

1. Central Precocious Puberty. Approve for 1 year.

Dosing. Approve one implant (50 mg) once every 12 months (inserted subcutaneously in the upper arm).

III. Coverage of Zoladex is recommended in patients who meet one of the following criteria:

FDA-Approved Indications

1. Abnormal Uterine Bleeding. Approve for 2 months if the patient meets the following (A and B):
- **A)** Zoladex is used as an endometrial-thinning agent prior to endometrial ablation; AND
- **B)** The medication is prescribed by or in consultation with an obstetrician-gynecologist or a health care practitioner who specializes in the treatment of women's health.

Dosing. Approve Zoladex 3.6 mg implant once every 28 days (inserted subcutaneously into the anterior abdominal wall).

2. Breast Cancer. ***[eviCore].*** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosage regiments (inserted subcutaneously into the anterior abdominal wall) [A or B]:
- **A)** Zoladex 3.6 mg implant once every 28 days; OR
- **B)** Zoladex 10.8 mg implant once every 12 weeks.

3. **Endometriosis.** Approve for 6 months if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) The medication is prescribed by or in consultation with an obstetrician-gynecologist or a health care practitioner who specializes in the treatment of women's health.

   Dosing. Approve Zoladex 3.6 mg implant once every 28 days (inserted subcutaneously into the anterior abdominal wall).

4. **Head and Neck Cancer – Salivary Gland Tumors**. ***[eviCore].*** Approve for 1 year if the patient meets the following (A, B, and C):
   A) Patient has recurrent, unresectable, or metastatic disease; AND
   B) Patient has androgen receptor-positive disease; AND
   C) The medication is prescribed by or in consultation with an oncologist.

   Dosing. Approve Zoladex 3.6 mg implant once every 28 days (inserted subcutaneously into the anterior abdominal wall).

5. **Ovarian Cancer, including Fallopian Tube Cancer and Primary Peritoneal Cancer**. ***[eviCore].*** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

   Dosing. Approve Zoladex 3.6 mg implant once every 28 days (inserted subcutaneously into the anterior abdominal wall).

6. **Prostate Cancer**. ***[eviCore].*** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

   Dosing. Approve ONE of the following dosage regimens (inserted subcutaneously into the anterior abdominal wall) [A or B]:
   A) Zoladex 3.6 mg implant once every 28 days; OR
   B) Zoladex 10.8 mg implant once every 12 weeks.

7. **Uterine Cancer**. ***[eviCore].*** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

   Dosing. Approve Zoladex 3.6 mg implant once every 28 days (inserted subcutaneously into the anterior abdominal wall).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Supprelin LA, Vantas, and Zoladex is not recommended in the following situations:

1. **Peripheral Precocious Puberty (also known as GnRH-independent precocious puberty)**.
   Children with peripheral precocious puberty do not respond to GnRH agonist therapy.[8] Treatment is directed at removing or blocking the production and/or response to the excess sex steroids, depending on the cause (e.g., surgically removing human chorionic gonadotropin-secreting tumors or using

glucocorticoids to treat defects in adrenal steroidogenesis [such as classic congenital adrenal hyperplasia]).

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Supprelin® LA [prescribing information]. Malvern, PA: Endo; April 2022.
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13. The NCCN Head and Neck Cancers Clinical Practice Guidelines in Oncology (version 2.2024 – December 08, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 6, 2024.
14. The NCCN Ovarian Cancer Clinical Practice Guidelines in Oncology (version 1.2024 – January 17, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 6, 2024.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	02/15/2023
Annual Revision	**Head and Neck Cancer – Salivary Gland Tumors; Ovarian Cancer, including Fallopian Tube Cancer and Primary Peritoneal Cancer; Uterine Cancer.** These new conditions and criteria were added to the policy. **Breast Cancer:** Removal of criteria related to premenopausal or perimenopausal women. Added the following dosing regimen for approval: Zoladex 10.8 mg every 12 weeks.	02/21/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products Utilization Management Medical Policy
- Lupron Depot® (leuprolide acetate suspension for intramuscular injection – AbbVie)
- Lupaneta Pack® (leuprolide acetate for depo suspension; norethindrone acetate tablets co-packaged for intramuscular use and oral use, respectively – AbbVie) [discontinued]

REVIEW DATE: 02/21/2024

Overview

Lupaneta Pack is indicated for the initial management of the painful symptoms of **endometriosis** and for management of recurrence of symptoms.[1,2] Lupaneta Pack was discontinued in 2021.

Lupron Depot (3.75 mg intramuscular [IM] injection every month, 11.25 mg IM injection every 3 months) is indicated for the following conditions:[3,4]
- **Anemia caused by uterine leiomyomata** (fibroids), preoperative hematologic improvement in women for whom 3 months of hormonal suppression is deemed necessary. (Lupron Depot in combination with iron therapy).
- **Endometriosis**, including pain relief and reduction of endometriotic lesions (Lupron Depot monotherapy).
- **Endometriosis**, initial management of the painful symptoms of endometriosis and management of recurrence of symptoms (Lupron Depot and norethindrone acetate 5 mg daily).

Lupron Depot (7.5 mg IM injection every month, 22.5 mg IM injection every 3 months, 30 mg IM injection every 4 months, and 45 mg IM injection every 6 months) is indicated for the palliative treatment of **advanced prostate cancer**.[5]

Duration of Treatment:
- Lupaneta Pack: Initial treatment course is limited to 6 months; a single retreatment course of up to 6 months is allowed. Total duration of treatment is limited to 12 months.[1,2]
- Lupron Depot 3.75 mg and 11.25 mg:[3,4]
  - Endometriosis: For the first 6 months of treatment, Lupron Depot may be used as monotherapy or in combination with norethindrone acetate. If retreatment is needed, Lupron Depot must be used in combination with norethindrone acetate (for 6 months). Total duration of treatment is limited to 12 months.
  - Uterine leiomyomata (fibroids): Recommended duration of treatment is up to 3 months.
- Lupron Depot 7.5 mg, 22.5 mg, 30 mg, and 45 mg: Labeling does not specify a treatment duration.

Guidelines

Abnormal Uterine Bleeding/Uterine Leiomyomata (Fibroids)

The American College of Obstetricians and Gynecologists (ACOG) [2021] practice bulletin regarding the management of symptomatic uterine leiomyomas discuss that gonadotropin-releasing hormone (GnRH) agonists (either with or without add-back hormonal therapy) are recommended for bleeding associated with fibroids, uterine enlargement associated with fibroids, and as a bridge to other treatment strategies (such as surgical management, menopause, or other medical therapies).[6] Add-back hormonal therapy (such as low-dose estrogen or progestin, or both) may help mitigate the hypoestrogenic effects of GnRH agonists, such

as decreased bone mineral density. The guidelines state that the type, dose, and route of delivery of add-back therapy depend on patient preference and the severity of symptoms.

GnRH agonists can also be used for acute abnormal uterine bleeding with an aromatase inhibitor or antagonist to prevent initial estrogen flare and for the treatment of heavy menstrual bleeding caused by leiomyoma-associated hormonal imbalance.[7] A clinical practice guideline from the Society of Obstetricians and Gynaecologists of Canada notes that leuprolide acetate or combined hormonal contraception should be considered highly effective in preventing abnormal uterine bleeding when initiated prior to cancer treatment in premenopausal women at risk of thrombocytopenia.[8] The ACOG committee opinion on options for prevention and management of menstrual bleeding in adolescent patients undergoing cancer treatment states that GnRH agonists are an option for menstrual suppression.[9]

Endometriosis

According to the ACOG practice bulletin on the management of endometriosis (2010, reaffirmed 2018), empiric therapy with a 3-month course of a GnRH agonist is appropriate after an appropriate pretreatment evaluation (to exclude other causes of chronic pelvic pain) and failure of initial treatment with oral contraceptives and nonsteroidal anti-inflammatory drugs.[10] The ACOG committee opinion on dysmenorrhea and endometriosis in the adolescent (2018) notes that patients with endometriosis who have pain after conservative surgical therapy and suppressive hormonal therapy may benefit from at least 6 months of GnRH agonist therapy with add-back medicine.[11]

Other Uses With Supportive Evidence

ACOG practice guideline (2023) suggests GnRH agonists with adjunctive combined hormonal add-back therapy for adults with severe, refractory premenstrual symptoms.[27] Premenstrual disorders include the conditions of premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD). The symptoms associated with these conditions can be physical and/or affective and may interfere with daily functioning. GnRH agonists are not recommended as first-line therapy and should be reserved for adult patients who have severe symptoms. GnRH agonists are not generally used to treat premenstrual symptoms in adolescents because of the lack of efficacy data in this population and concern for long-term effects on bone health. ACOG recommends selective serotonin reuptake inhibitors for the management of affective premenstrual symptoms and combined oral contraceptives for the management of overall premenstrual symptoms.

The Endocrine Society Guideline (2017) for the Treatment of Gender-Dysphoric/Gender-Incongruent Persons note that persons who fulfill criteria for treatment and who request treatment should initially undergo treatment to suppress physical changes of puberty.[12] Pubertal hormonal suppression should typically be initiated after the adolescent first exhibits physical changes of puberty (Tanner stages G2/B2). However, there may be compelling reasons to initiate hormone treatment before the age of 16 years in some adolescents. The guidelines note suppression of pubertal development and gonadal function can be effectively achieved via gonadotropin suppression using GnRH analogs. Long-acting GnRH analogs are the currently preferred treatment option. An advantage to using a GnRH analog is that the effects can be reversed; pubertal suppression can be discontinued if the individual no longer wishes to transition. Upon discontinuation of therapy, spontaneous pubertal development has been shown to resume. The World Professional Association for Transgender Health (WPATH) Standards of Care (version 8) document also recommends the use of GnRH analogs to suppress endogenous sex hormones in transgender and gender diverse people for whom pubery blocking is indicated.[13] GnRH can also be used in patients during late puberty to suppress the hypothalamic-pituitary-gonadal axis to allow for lower doses of cross-sex hormones.[14] In addition to use in adolescents, GnRH analog therapy is also used in adults, particularly male-to-female patients.[15]

In addition to the approved indications, GnRH agonists such as long-acting leuprolide, have been used for other conditions. The National Comprehensive Cancer Network (NCCN) guidelines address the use of GnRH agonists in a number of guidelines:

- **Adolescent and young adult oncology** (version 2.2024 – July 9, 2023) guidelines note GnRH agonists may be used in (oncology) protocols that are predicted to cause prolonged thrombocytopenia and present a risk for menorrhagia.[16] There are some limited data on GnRH agonists to preserve ovarian function during chemotherapy and some have shown that GnRH agonists may be beneficial for fertility preservation, although the guidelines note further investigation is needed and other fertility preservation modalities should still be pursued.
- **Breast cancer** (version 1.2024 – January 25, 2024) guidelines note that luteinizing hormone-releasing hormone agonists, such as leuprolide, can be used for ovarian suppression.[17] Leuprolide dosing per NCCN includes 3.75 mg to 7.5 mg every 4 weeks or 11.25 mg to 22.5 mg every 12 weeks. The guidelines further note that randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with breast tumors (regardless of hormone receptor status) may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea.
- **Head and neck cancer** (version 2.2024 – December 08, 2023) guidelines note that a significant number of advanced salivary gland tumors with distant metastases are androgen receptor-positive (AR+), and therefore, the panel recommends patients with tumors that are AR+ receive androgen receptor therapy (i.e., leuprolide, bicalutamide).[18]
- **Ovarian cancer, including fallopian tube cancer and primary peritoneal cancer** (version 1.2024 – January 17, 2024) recommend leuprolide as a hormonal therapy option in various settings (e.g., primary therapy, adjuvant therapy, recurrence).[19]
- **Uterine neoplasm** guidelines (version 1.2024 – September 20, 2023) notes that GnRH analogs are included as a category 2B option for endometrial stroma sarcoma, adenosarcoma without sarcomatous overgrowth, and estrogen receptor-progesterone receptor positive uterine sarcomas.[20,23]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Lupron Depot and Lupaneta Pack. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria. All approvals are provided for the durations noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lupaneta Pack and Lupron-Depot as well as the monitoring required for adverse events and long-term efficacy, approval for some of the conditions requires Lupaneta Pack or Lupron-Depot to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

*Indications and/or approval conditions noted with **[eviCore]** apply to Lupron Depot only and are managed by eviCore healthcare for those clients who use eviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to eviCore at www.eviCore.com. Indications and/or approval conditions for Lupaneta Pack should not be directed to eviCore.*

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lupron Depot or Lupaneta Pack are recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. Endometriosis. Approve Lupron Depot or Lupaneta Pack for 1 year if the patient has tried ONE of the following, unless contraindicated (A, B, or C):

A) A contraceptive (e.g., combination oral contraceptives, levonorgestrel-releasing intrauterine systems [e.g., Mirena®, Liletta®]), OR

B) An oral progesterone (e.g., norethindrone tablets), OR

C) A depo-medroxyprogesterone injection.

Note: An exception to the requirement for a trial of the above therapies can be made if the patient has previously used a gonadotropin-releasing hormone [GnRH] agonist (e.g., Lupron-Depot) or antagonist (e.g., Orilissa).

Dosing. Approve ONE of the following dosing regimens (A or B):

A) For Lupaneta Pack: Approve ONE of the following dosage regimens (i or ii):

i. 3.75 mg IM once every month with norethindrone 5 mg orally once daily; OR

ii. 11.25 mg IM once every 3 months with norethindrone 5 mg orally once daily; OR

B) For Lupron Depot: Approve ONE of the following dosage regimens (i or ii):

i. 3.75 mg IM once every month; OR

ii. 11.25 mg IM once every 3 months.

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2. Prostate Cancer. ***[eviCore]*** Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, C, or D):

A) 45 mg IM once every 6 months; OR

B) 30 mg IM once every 4 months; OR

C) 22.5 mg IM once every 3 months; OR

D) 7.5 mg IM once every month.

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3. Uterine Leiomyomata (fibroids). Approve Lupron Depot for 3 months.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) 3.75 mg IM once every month; OR

B) 11.25 mg IM once every 3 months.

Other Uses with Supportive Evidence

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4. Abnormal Uterine Bleeding. Approve Lupron Depot for 6 months.

Dosing. Approve ONE of the following dosage regimens (A or B):

A) 3.75 IM once every month; OR

B) 11.25 IM once every 3 months.

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5. **Breast Cancer.** *[eviCore]* Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

   Dosing. Approve ONE of the following dosage regimens (A or B):
   A) 3.75 mg or 7.5 mg IM once every month; OR
   B) 11.25 mg or 22.5 mg IM once every 3 months.

6. **Gender Dysphoric/Gender-Incongruent Persons; Persons Undergoing Gender Reassignment (Female-To-Male [FTM] or Male-to-Female [MTF]).** Approve Lupron Depot for 1 year if prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.

   Dosing. Approve ONE of the following dosage regimens (A, B, C, or D):
   A) 3.75 or 7.5 mg IM once every month; OR
   B) 11.25 or 22.5 mg IM once every 3 months; OR
   C) 30 mg IM once every 4 months; OR
   D) 45 mg IM once every 6 months.

7. **Head and Neck Cancer – Salivary Gland Tumors.** *[eviCore]* Approve Lupron Depot for 1 year if the patient meets ALL of the following criteria (A, B, and C):
   A) Patient has recurrent, unresectable, or metastatic disease; AND
   B) Patient has androgen receptor-positive disease; AND
   C) The medication is prescribed by or in consultation with an oncologist.

   Dosing. Approve ONE of the following dosage regimens (A or B):
   A) 3.75 mg or 7.5 mg IM every month; OR
   B) 11.25 mg or 22.5 mg IM once every 3 months.

8. **Ovarian Cancer, including Fallopian Tube Cancer and Primary Peritoneal Cancer.** *[eviCore]* Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

   Dosing. Approve ONE of the following dosage regimens (A or B):
   A) 3.75 mg or 7.5 mg IM once every month; OR
   B) 11.25 mg or 22.5 mg IM once every 3 months

9. **Premenstrual Disorders, including Premenstrual Syndrome and Premenstrual Dysphoric Disorder.** Approve for 1 yeear if the patient meets ALL of the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) According to the prescriber, the patient has severe, refractory premenstrual symptoms; AND
   C) Patient has tried ONE of the following therapies (i or ii):
      i. A selective serotonin reuptake inhibitor (SSRI); OR
      Note: Examples of SSRI include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.

ii. A combined oral contraceptive.

Dosing. Approve ONE of the following dosage regimens (A or B):
A) 3.75 mg IM once every month; OR
B) 11.25 mg IM once every 3 months.

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10. Preservation of Ovarian Function/Fertility in Patients undergoing Chemotherapy. *[eviCore]* Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosage regimens (A or B):
A) 3.75 mg IM once every month; OR
B) 11.25 mg IM once every 3 months.

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11. Prophylaxis or Treatment of Uterine Bleeding or Menstrual Suppression in Patients with Hematologic Malignancy, or Undergoing Cancer Treatment, or Prior to Bone Marrow/Stem Cell Transplantation (BMT/SCT). *[eviCore]* Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosage regimens (A or B):
A) 3.75 mg IM once every month; OR
B) 11.25 mg IM once every 3 months.

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12. Uterine Cancer. *[eviCore]* Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosage regimens (A, B, C, or D):
A) 7.5 mg IM once every month; OR
B) 22.5 mg IM once every 3 months; OR
C) 30 mg IM once every 4 months; OR
D) 45 mg IM once every 6 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lupron Depot and Lupaneta Pack is not recommended in the following situations:

1. **Menstrual Migraine**. A review article notes that GnRH analogs are effective in eliminating menstrual migraines, but their use is limited due to the significant adverse effects of estrogen deficiency, including severe vasomotor symptoms, sleep disruption, and a marked reduction in bone density.[21,22]

2. **Polycystic Ovarian Syndrome (PCOS)**. Review articles do not recommend GnRH agonists as a treatment modality. [24,25] Additionally, the International Evidence-based Guideline for the Assesment and Management of Polycystic Ovary Syndrome (2018) only mention GnRH products as they relate to infertility and assisted reproductive technology procedures.[26]

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Head and Neck Cancer – Salivary Gland Tumors**: "Patient has advanced salivary gland tumors with distant metastases" was reworded to "Patient has recurrent, unresectable, or metastatic disease." Also, coverage of strengths 3.75 mg and 11.25 mg were added for this diagnosis.	2/22/2023
Annual Revision	**Breast Cancer.** Added coverage for strengths 7.5 mg and 22.5 mg of Lupron Depot. **Ovarian Cancer.** Wording was updated to Ovarian Cancer, including Fallopian Tube Cancer and Primary Peritoneal Cancer. **Premenstrual Syndrome (PMS)** was removed from Conditions Not Recommended for Approval. **Premenstrual Disorders, including Premenstrual Syndrome and Premenstrual Dysphoric Disorder** was added as a new coverage condition for Lupron Depot 3.75 mg and 11.25 mg. **Uterine Cancer** was added as a new coverage condition for Lupron Depot 7.5 mg, 22.5 mg, 30 mg, and 45 mg. **Hirsutism** was removed from Conditions Not Recommended for Approval.	02/21/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Gout – Krystexxa Utilization Management Medical Policy
- Krystexxa® (pegloticase intravenous infusion – Horizon)

REVIEW DATE: 05/15/2024

OVERVIEW

Krystexxa, a PEGylated uric acid specific enzyme, is indicated for treatment of **chronic gout refractory to conventional therapy**, in adult patients.[1] Krystexxa should be co-administered with methotrexate to increase effectiveness, prevent the formation of antibodies, and reduce infusion reactions. It is recommended that patients discontinue oral urate-lowering medications while on Krystexxa therapy due to the potential blunting of the rise of serum uric acid levels with concomitant use. Krystexxa has a Boxed Warning due to concerns for anaphylaxis and infusion reactions, and glucose-6-phosphate dehydrogenase (G6PD) deficiency associated hemolysis and methemoglobinemia.

Krystexxa is specifically labeled for use with methotrexate; however, data are also available to support concomitant use of Krystexxa with azathioprine, leflunomide, or mycophenolate mofetil.[4-6]

Disease Overview

Gout is a form of inflammatory arthritis and results from a metabolic disorder called hyperuricemia caused by an overproduction or underexcretion of uric acid; however, asymptomatic patients with elevated uric acid levels do not have gout and do not require treatment.[2,3] Excessive amounts of uric acid in the blood lead to deposits of crystals in the joints and connective tissues and may cause excruciating pain. Lumps of urate crystals (tophi) may develop in soft tissues such as the elbow, ear, or distal finger joints. Some patients fail to normalize serum uric acid and have inadequate control of the signs and symptoms of gout with maximum medically appropriate doses or have a contraindication to urate-lowering therapies. Treatment-failure should be differentiated as those who are under-treated for gout or are non-compliant with gout therapy. Those with treatment-failure gout generally have a high prevalence of tophi, frequent and disabling gout flares, deforming arthropathy, diminished quality of life, and disability.

Guidelines

The American College of Rheumatology provides guidelines (2020) for the management of gout. Allopurinol is the preferred first-line urate-lowering therapy, including patients with moderate to severe gout.[3] Febuxostat and probenecid are conditionally recommended as alternative first-line therapies for specific patient populations. Titration of urate-lowering therapy should be guided by serum uric acid concentrations, with a target of < 6 mg/dL. In patients with refractory disease, effective therapeutic options include combination therapy with a xanthine oxidase inhibitor (e.g., allopurinol or febuxostat) and a uricosuric agent (e.g., probenecid, fenofibrate, or losartan). Krystexxa is not recommended as first-line therapy, however it is appropriate in patients with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral urate-lowering therapies.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Krystexxa. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director

or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Krystexxa as well as the monitoring required for adverse events and long-term efficacy, approval requires Krystexxa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Krystexxa is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Gout, Chronic.** Approve for the duration noted below if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, and vi):
     - **i.** Patient meets ONE of the following (a or b):
       - **a)** Patient has at least one tophus; OR
       - **b)** Patient has a history of 2 previous gout flares in the past year (prior to the current flare); AND
     - **ii.** Patient meets ONE of the following (a or b):
       - **a)** Patient had an inadequate response, defined as serum uric acid level that remained > 6 mg/dL following a 3-month trial of a xanthine oxidase inhibitor; OR
         Note: Examples of xanthine oxidase inhibitors include allopurinol, febuxostat.
       - **b)** Patient has a contraindication or has had an intolerance to a trial of allopurinol, as determined by the prescriber; AND
     - **iii.** Patient meets ONE of the following (a or b):
       - **a)** Patient had an inadequate response, defined as serum uric acid level that remained > 6 mg/dL following a 3-month trial of a uricosuric agent; OR
         Note: Examples of uricosuric agents include probenecid, fenofibrate, losartan.
       - **b)** According to the prescriber, the patient has renal insufficiency (e.g., decreased glomerular filtration rate); AND
     - **iv.** Krystexxa will be used in combination with ONE of the following (a, b, c, or d):
       - **a)** Methotrexate; OR
       - **b)** Leflunomide; OR
       - **c)** Mycophenolate mofetil; OR
       - **d)** Azathioprine; AND
     - **v.** Krystexxa will not be used in combination with another uric acid lowering drug; AND
       Note: Examples of uric acid lower drugs include allopurinol, febuxostat, probenecid.
     - **vi.** Krystexxa is prescribed by or in consultation with a rheumatologist or a nephrologist.
   - **B)** Patient is Currently Receiving Krystexxa. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, iv, and v):
     - **i.** Patient is continuing therapy with Krystexxa to maintain response/remission; AND
     - **ii.** Patient has responded to therapy with evidence of serum uric acid level < 6 mg/dL with continued Krystexxa treatments; AND
     - **iii.** Krystexxa is being used in combination with ONE of the following (a, b, c, or d):
       - **a)** Methotrexate; OR

b) Leflunomide; OR
c) Mycophenolate mofetil; OR
d) Azathioprine; AND

iv. Krystexxa is not being used in combination with another uric acid lowering drug.
Note: Examples of uric lower drugs include allopurinol, febuxostat, probenecid.

v. Krystexxa is prescribed by or in consultation with a rheumatologist or a nephrologist.

Dosing. Approve 8 mg as an intravenous infusion every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Krystexxa is not recommended in the following situations:

1. **Known Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency.** Because of risks of hemolysis and methemoglobinemia, Krystexxa is contraindicated in G6PD deficiency.[1] Patients at increased risk of this deficiency (e.g., those of African or Mediterranean ancestry) should be screened prior to initiation of therapy.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	05/17/2023
Annual Revision	**Gout, Chronic**: Mycophenolate mofetil was added as immunosuppressive agent option to be used in combination with Krystexxa in addition to the existing options of methotrexate, leflunomide, or azathioprine.	05/15/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Adzynma Utilization Management Medical Policy
- Adzynma™ (ADAMTS13 recombinant-krhn intravenous infusion – Takeda)

REVIEW DATE: 12/06/2023

Overview
Adzynma, a human recombinant "A disintegrin and metalloproteinase with thrombospondin motifs 13" (ADAMTS13) product, is indicated for prophylactic or on demand enzyme replacement therapy for the management of congenital thrombotic thrombocytopenia purpura in adult and pediatric patients.[1]

Disease Overview
Congenital thrombotic thrombocytopenic purpura is a very rare, inherited blood clotting disorder.[2,3] It is due to a mutation in the ADAMTS13 gene that makes a key enzyme, also named ADAMTS13, that regulates blood clotting. A deficiency in this enzyme causes blood clots to form in the small blood vessels throughout the body. The disease impacts fewer than 1,000 people in the US. Symptoms typically start in infancy or early childhood, but in some cases may develop in adulthood and can initially manifest during pregnancy. Patients with congenital thrombotic thrombocytopenic purpura may experience severe bleeding episodes, strokes, and damage to vital organs. The condition can be fatal if not managed. Treatment for congenital thrombotic thrombocytopenic purpura currently involves prophylactic plasma-based therapy to reduce the risk of clotting/bleeding by replenishing the absent/low ADAMTS13 enzyme; on-demand therapy can also be given.

Guidelines
Adzynma has not been specifically addressed in guidelines post FDA-approval.[4] The International Society on Thrombosis and Haemostasis (ISTH) has guidelines for the treatment of thrombotic thrombocytopenic purpura (2020). For patients with congenital thrombotic thrombocytopenic purpura who are in remission, the panel suggests either plasma infusion or a watch and wait strategy. For patients with congenital thrombotic thrombocytopenic purpura who are pregnant, the panel recommends prophylactic treatment over no prophylactic treatment. In this clinical scenario, plasma infusion is recommended over Factor VIII products.

The British Society of Haemtology published guidelines for the diagnosis and management of thrombotic thrombocytopenic purpura and thrombotic microangiopathies.[5] The diagnosis of congenital thrombotic thrombocytopenic purpura is defined by ADAMTS13 activity < 10 IU/dL, no anti-ADAMTS13 antibodies, and confirmation of homozygous or compound heterozygous variants in the ADAMTS13 gene. For an acute episode, solvent detergent plasma infusion is recommended. ADAMTS13 prophylaxis should be considered for all patients with an individualized approach to dose and frequency according to symptoms, whether overt or non-overt. For pregnant women with congenital thrombotic thrombocytopenic purpura, regular solvent/detergent fresh frozen plasma replacement therapy should be given prophylactically to prevent clinical relapse.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Adzynma. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). Because of the specialized skills required for evaluation and diagnosis of patients treated with Adzynma as well as the monitoring required for adverse events and long-term efficacy, approval requires Adzynma to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Adzynma as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory data, genetic test results, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Adzynma is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Congenital Thrombotic Thrombocytopenic Purpura.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   - **A)** At baseline (prior to therapy) ADAMTS13 activity is < 10% (< 10 IU/dL) **[documentation required]**; AND
     Note: Baseline refers to before any treatment was received, such as Adzynma or plasma-based therapies.
   - **B)** Patient does not have anti-ADAMTS13 autoantibodies as determined by a diagnostic test **[documentation required]**; AND
   - **C)** Patient has a pathogenic variant or a mutation in the ADAMTS13 gene **[documentation required]**; AND
     Note: Pathogenic variants or gene mutations are usually homozygous or compound heterozygous.
   - **D)** Medication is prescribed by or in consultation with a hematologist.

   Dosing. Approve the following dosing regimens (A and/or B):
   - **A)** Routine prophylaxis: approve up to 40 IU/kg by intravenous infusion once weekly; AND/OR
   - **B)** On demand therapy: approve up to 135 IU/kg by intravenous infusion per week as needed for the treatment of acute event(s).
     Note: On demand therapy is given as a daily dose until 2 days after the acute event resolves; however, the total weekly dose should not exceed 135 IU/kg.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Adzynma is not recommended in the following situations.

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/06/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Aphexda Utilization Management Medical Policy
- Aphexda™ (motixafortide subcutaneous injection – BioLineRx)

REVIEW DATE: 11/15/2023

OVERVIEW

Aphexda, a hematopoietic stem cell mobilizer, is indicated in combination with filgrastim (granulocyte colony stimulating factor) to **mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with multiple myeloma**.[1]

Disease Overview

Multiple myeloma is a cancer formed by malignant plasma cells found in the bone marrow.[2,3] In 2023, it is estimated that there will be approximately 35,730 new cases of multiple myeloma and 12,590 deaths due to the disease. There are many therapies available for multiple myeloma. Autologous stem cell transplantation (ASCT) has a vital role in the treatment of multiple myeloma. The outcomes of ASCT relies on the collection of sufficient hematopoietic stem and progenitor cells, usually from peripheral blood.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Aphexda. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Aphexda, as well as the monitoring required for adverse events and long-term efficacy, the agent is required to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Aphexda is recommended for patients who meet the following criteria:

FDA-Approved Indication

1. Multiple Myeloma. Approve for 1 month if the patient meets the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The agent is utilized for mobilization of hematopoietic stem cells for subsequent autologous transplantation; AND
- **C)** Use is in combination with filgrastim; AND
  Note: Examples of filgrastim products include Granix (tbo-filgrastim subcutaneous injection) and Neupogen (filgrastim subcutaneous injection and intravenous infusion), as well as related biosimilars.

D) Medication is prescribed by a hematologist and/or a stem cell transplant specialist physician.

Dosing. Approve up to two doses at 1.25 mg/kg given by subcutaneous injection.
Note: Aphexda is given 10 to 14 hours prior to the initiation of apheresis. A second dose can be administered 10 to 14 hours before a third apheresis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Aphexda is not recommended in the following situations:

1. **Leukemia.** Aphexda may cause mobilization of leukemia cells and subsequent contamination of the apheresis product.[1] Aphexda is not intended for hematopoietic stem cell mobilization and harvest in patients with leukemia.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Aphexda™ subcutaneous injection [prescribing information]. Waltham, MA and Modi'in, Israel: BioLineRx; September 2023.
2. Cowan AJ, Green DJ, Kwok M, et al. Diagnosis and management of multiple myeloma. A review. *JAMA*. 2022;327(5):464-477.
3. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 4.2023 – August 25, 2023). © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 7, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	11/15/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Cablivi Utilization Management Medical Policy
- Cablivi® (caplacizumab-yhdp intravenous infusion and subcutaneous injection – Genzyme/Sanofi)

REVIEW DATE: 02/21/2024

Overview
Cablivi, a von Willebrand factor (vWF)-directed antibody fragment, is indicated for the treatment of **acquired thrombotic thrombocytopenic purpura** (aTTP) in adults, in combination with plasma exchange and immunosuppressive therapy.[1]

Disease Overview
Thrombotic thrombocytopenic purpura (TTP) is a rare but potentially fatal blood disorder.[2-4] TTP may be caused by an inherited severe deficiency of plasma ADAMTS13 (A Disintegrin And Metalloproteinase with ThromboSpondin-1 motif, member 13)activity resulting from mutations; this is referred to as hereditary or congenital TTP. More commonly, TTP is acquired and due to autoantibodies that inhibit plasma ADAMTS13 activity, referred to as immune-mediated (or acquired) TTP (iTTP). Reduced ADAMTS13 activity leads to accumulation of ultra-large vWF multimers in the blood, which bind to platelets and lead to excessive platelet clumping in the microvasculature, resulting in multi-organ failure and death.[2-5] Cablivi is a nanobody that targets the ultra-large vWF and inhibits the interaction between vWF and platelets, thereby preventing vWF platelet adhesion and consumption.[1,5,6]

Dosing Information
Two doses of Cablivi are given on the first day of plasma exchange, followed by one dose of Cablivi per day during plasma exchange; treatment is continued for 30 days after the last plasma exchange session.[1] If, after the initial treatment course, there are signs of persistent underlying disease such as suppressed ADAMTS13 levels, Cablivi therapy may be extended for a maximum of 28 days. Cablivi should be discontinued if the patient experiences more than two recurrences of aTTP while on Cablivi.

Guidelines/Recommendations
The standard of care for treatment of aTTP is plasma exchange and glucocorticoids.[7] Plasma exchange removes the ultra-large vWF and autoantibodies and replenishes ADAMTS13, and immunosuppressants inhibit autoantibody formation. Rituximab can also be added to the aTTP treatment regimen. Rituximab has been shown to reduce the incidence of aTTP relapse by diminishing the production of anti-ADAMTS13 antibodies and restoring ADAMTS13 activity.[2]

The International Society on Thrombosis and Haemostasis (ISTH) formed a multidisciplinary panel including hematologists and pathologists with clinical expertise in the diagnosis and management of TTP, clinicians from other relevant disciplines, and patient representatives to issue recommendations about treatment of TTP (2020).[8] For patients with aTTP or iTTP experiencing an acute event (first event or relapse), the panel suggests using Cablivi over not using Cablivi. The panel stressed that Cablivi should only be given under the guidance of an experienced clinician, ideally a TTP expert (e.g., a hematologist or pathologist specialized in transfusion medicine with previous experience in treating the disease).

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Cablivi. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for one course of treatment. Note that one course of treatment consists of Cablivi to be administered in conjunction with plasma exchange and Cablivi to be administered for up to 60 days (one dose per day) following the last plasma exchange session. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cablivi as well as the monitoring required for adverse events and long-term efficacy, approval requires Cablivi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cablivi is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Acquired Thrombotic Thrombocytopenic Purpura.** Approve for one course of treatment (up to 60 days following the last plasma exchange session) if the patient meets the following (A, B, C, D, and E):
   - **A)** Patient ≥ 18 years of age; AND
   - **B)** Cablivi was initiated in the inpatient setting, in combination with plasma exchange therapy; AND
   - **C)** Patient is currently receiving at least one immunosuppressive therapy; AND
     Note: Examples include systemic corticosteroids, rituximab (or a rituximab product), cyclosporine, cyclophosphamide, mycophenolate mofetil, hydroxychloroquine, bortezomib.
   - **D)** If the patient has previously received Cablivi, he/she has not had more than two recurrences of acquired thrombotic thrombocytopenic purpura while on Cablivi; AND
   - **E)** The medication is prescribed by or in consultation with a hematologist.

   Dosing. Approve the following dosing regimens:
   - **A)** Day 1 of treatment with plasma exchange: Two doses of Cablivi (11 mg intravenous [IV] bolus prior to plasma exchange followed by an 11 mg subcutaneous [SC] dose after completion of plasma exchange); AND
   - **B)** 11 mg SC injection up to once daily; AND
   - **C)** Do not exceed 60 doses following the last plasma exchange session.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cablivi is not recommended in the following situations.

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Cablivi® intravenous solution and subcutaneous injection [prescribing information]. Cambridge, MA: Genzyme/Sanofi; February 2022.
2. Coppo P, Cuker A, George JN. Thrombotic thrombocytopenic purpura: toward targeted therapy and precision medicine. *Res Pract Thromb Haemost*. 2019;3:26-37.
3. Subhan M, Scully M. Advances in the management of TTP. *Blood Rev*. 2022;55:100945.
4. Zheng XL, Vesely SK, Cataland SR, et al. International Society on Thrombosis and Haemostasis (ISTH) guidelines for the diagnosis of thrombotic thrombocytopenic purpura. *J Thromb Haemost*. 2020;18:2486-2495.
5. Scully M, Cataland SR, Peyvandi F, et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. *N Engl J Med*. 2019;380:335-346.
6. Scully M, de la Rubia J, Pavenski K, et al. Long-term follow-up of patients treated with caplacizumab and safety and efficacy of repeat caplacizumab use: post-HERCULES study. *J Thromb Haemost*. 2022;20:2810-2822.
7. Scully M, Hunt BJ, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *Br J Haematol*. 2012;158:323-335.
8. Zheng XL, Vesely SK, Cataland SR, et al. International Society on Thrombosis and Haemostasis (ISTH) guidelines for the treatment of thrombotic thrombocytopenic purpura. *J Thromb Haemost*. 2020;18:2496-2502.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	02/22/2023
Annual Revision	No criteria changes.	02/21/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Ceprotin Utilization Management Medical Policy
- Ceprotin® (protein C concentrate [human] intravenous infusion – Baxalta/Shire)

REVIEW DATE: 11/08/2023

OVERVIEW

Ceprotin is indicated for pediatric and adult patients with **severe congenital protein C deficiency** for the prevention and treatment of venous thrombosis and purpura fulminans.[1]

Disease Overview

Mutations in the *PROC* gene lead to deficiency of protein C, which is a natural anticoagulant.[2] Individuals with heterozygous *PROC* mutation present with milder disease but are at risk for development of venous thromboembolism. Those who have mutations in both *PROC* genes develop severe symptoms within a few hours to days after birth. In severe protein C deficiency, a complication called purpura fulminans may arise in which blood clots form throughout the body. Blood clots affect the extremities most often but can become widespread (disseminated intravascular coagulation), leading to tissue necrosis.

Diagnosis is based on characteristic symptoms and detailed family history, in addition to measurement of protein C activity or antigen levels.[3,4] It is critical to exclude any acquired reason for protein C deficiency, which is more common than congenital protein C deficiency.[3] Potential causes of acquired deficiency include vitamin K antagonists (e.g., warfarin), vitamin K deficiency, chronic liver disease, recent thrombosis, recent surgery, or disseminated intravascular coagulation. Diagnostic recommendations from the International Society of Thrombosis and Hemostasis recommend waiting until 30 days after vitamin K antagonist treatment ends to perform protein C assay testing.[4] Molecular genetic testing is only available in a few research laboratories and is not routinely used in clinical diagnosis.[3]

Dosing Information

Dosing is highly individualized. Guidance specific to protein C deficiency is limited. The National Hemophilia Foundation Medical and Scientific Advisory Council (MASAC) provides recommendations regarding doses of clotting factor concentrate in the home (2016).[5] The number of required doses varies greatly and is dependent on the severity of the disorder and the prescribed regimen. Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough episodes in addition to the prophylactic doses used monthly. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for prophylactic dosing plus three days of acute episodes or perioperative management per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

Dosing considerations for individual indications are as follows:

- **Protein C Deficiency, Severe:** For routine prophylaxis, the maximum dose is 60 IU/kg once every 12 hours.[1] For acute episodes or perioperative prophylaxis, the prescribing information recommends a loading dose up to 120 IU/kg once, followed by 80 IU/kg every 6 hours for 3 doses, followed by 60 IU/kg every 6 hours thereafter.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Ceprotin. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ceprotin as well as the monitoring required for adverse events and long-term efficacy, approval requires Ceprotin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ceprotin is recommended in those who meet the following criteria:

FDA-Approved Indication

1. Protein C Deficiency, Severe. Approve for 1 year if the patient meets the following (A, B, C, and D)

- **A)** The diagnosis of protein C deficiency is confirmed by at least one of the following (i, ii, or iii):
  - **i.** Plasma protein C activity below the lower limit of normal based on the age-specific reference range for the reporting laboratory; OR
  - **ii.** Plasma protein C antigen below the lower limit of normal based on the age-specific reference range for the reporting laboratory; OR
  - **iii.** Genetic testing demonstrating biallelic mutations in the *PROC* gene; AND
- **B)** Acquired causes of protein C deficiency have been excluded; AND
  Note: Examples of acquired causes of protein C deficiency include recent use of vitamin K antagonists (e.g., warfarin) within 30 days, vitamin K deficiency, chronic liver disease, recent thrombosis, recent surgery, or disseminated intravascular coagulation.
- **C)** According to the prescriber, patient has a current or prior history of symptoms associated with severe protein C deficiency (e.g., purpura fulminans, thromboembolism); AND
- **D)** Ceprotin is being prescribed by or in consultation with a hematologist.

Dosing. Approve up to 4,440 IU/kg intravenously per 28 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ceprotin is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Ceprotin® intravenous infusion [prescribing information]. Lexington, MA: Baxalta/Shire; August 2021.
2. Protein C Deficiency. National Organization of Rare Disorders. Updated 2016. Available at: https://rarediseases.org/rare-diseases/protein-c-deficiency/. Accessed on November 5, 2023.
3. Dinarvand P, Moser KA. Protein C deficiency. *Arch Pathol Lab Med*. 2019;143(10):1281-1285.
4. Cooper PC, Pavlova A, Moore GW, et al. Recommendations for clinical laboratory testing for protein C deficiency, for the subcommittee on plasma coagulation inhibitors of the ISTH. *J Thromb Haemost*. 2020 Feb;18(2):271-277.
5. MASAC (Medical and Scientific Advisory Council) recommendations regarding doses of clotting factor concentrate used in the home. MASAC Document #242. Adopted on June 7, 2016. Available at: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations/MASAC-Recommendations-Regarding-Doses-of-Clotting-Factor-Concentrate-in-the-Home. Accessed on November 5, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/02/2022
Annual Revision	No criteria changes.	11/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Coagadex Utilization Management Medical Policy
- Coagadex® (coagulation Factor X [human] intravenous infusion – BPL)

REVIEW DATE: 11/08/2023

OVERVIEW

Coagadex, a plasma-derived coagulation Factor X product, is indicated for use in adults and children with hereditary Factor X deficiency for:[1-3]

- **On-demand treatment and control** of bleeding episodes.
- **Perioperative management** of bleeding in patients with mild and moderate hereditary Factor X deficiency.
- **Routine prophylaxis** to reduce the frequency of bleeding episodes.

Disease Overview

Factor X deficiency, a rare autosomal recessive inherited bleeding disorder, affects approximately 1 in 500,000 to 1,000,000 patients worldwide.[4,5] The Factor X protein has a key role to assist in activating the enzymes that are key in clot formation. In this condition, blood does not clot properly. Patients experience easy bruising, nose or mouth bleeds, and bleeding after trauma or surgery. Among patients with severe Factor X deficiency, umbilical cord bleeding can be one of the first signs; however, bleeding may present at any time. Serious bleeds include spontaneous head bleeds, spinal cord bleeds, and gastrointestinal bleeds. Women who have the condition may experience heavy menstrual bleeding or have menorrhagia. During pregnancy, women may miscarry during the first trimester or have other complications during labor and delivery. However, Factor X deficiency has an equal prevalence in men and women. It is recommended to maintain trough levels of around 20% to 30%. Other treatments include fresh frozen plasma, prothrombin complex concentrates, and Coagadex.

Guidelines

The National Hemophilia Foundation Medical and Scientific Advisory Council (MASAC) has guidelines for the treatment of hemophilia and other bleeding disorders (revised February 2022).[6] Coagadex is recommended in patients who have Factor X deficiency.

Dosing Considerations

Dosing of clotting factor concentrates is highly individualized. MASAC provides recommendations regarding doses of clotting factor concentrate in the home (2016).[7] The number of required doses varies greatly and is dependent on the severity of the disorder and the prescribed regimen. Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough bleeding in addition to the prophylactic doses used monthly. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for prophylactic dosing plus three days of acute bleeding or perioperative management per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage Coagadex. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Coagadex, as well as the monitoring required for adverse events and long-term efficacy, the agent is required to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Coagadex is recommended for patients who meet the following criteria:

FDA-Approved Indication

1. **Hereditary Factor X Deficiency.** Approve for 1 year if the agent is prescribed by or in consultation with a hematologist.

   Dosing. Approve up to 600 IU/kg by intravenous infusion no more frequently than once every 28 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Coagadex is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Coagadex® intravenous infusion [prescribing information]. Durham, NC: BPL; April 2023.
2. Escobar MA, Kavakli K. Plasma-derived human factor X concentrate for the treatment of patients with hereditary factor X deficiency. *Hemophilia*. 2023 Oct 30. [Online ahead of print].
3. Payne J, Batsuli G, Leavitt AD, et al. A review of the pharmacokinetics, efficacy, safety of high-purity factor X for the prophylactic treatment of hereditary factor X deficiency. *Haemophilia*. 2022;28(4):523-531.
4. Menegatti M, Peyvandi F. Treatment of rare factor deficiencies other than hemophilia. *Blood*. 2019;133(5):415-424.
5. Peyvandi F, Auerswald G, Austin SK, et al. Diagnosis, therapeutic advances, and key recommendations for the management of factor X deficiency. *Blood Rev*. 2021 Nov;50:100833.
6. National Bleeding Disorders Foundation. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system (August 2023). MASAC Document #280. Available at: https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed on November 5, 2023.
7. National Hemophilia Foundation. MASAC (Medical and Scientific Advisory Council) recommendations regarding doses of clotting factor concentrate in the home (Revised June 7, 2016). MASAC Document #242. Adopted on June 7, 2016. Available at: https://www.hemophilia.org/sites/default/files/document/files/242.pdf. Accessed on November 5, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	10/19/2022
Annual Revision	No criteria changes.	11/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Corifact Utilization Management Medical Policy
- Corifact® (Factor XIII Concentrate [human] intravenous infusion – CSL Behring)

REVIEW DATE: 11/08/2023

OVERVIEW

Corifact, a Factor XIII concentrate, is indicated for adult and pediatric patients with congenital Factor XIII deficiency for:[1]

- **Peri-operative management** of surgical bleeding.
- **Routine prophylactic** treatment.

Disease Overview

Congenital Factor XIII deficiency is caused by defects in both Factor XIIIA and Factor XIIIB genes.[2,3] However, most cases are due to genetic alterations on the Factor XIIIA gene. The estimated prevalence of Factor XIIIA deficiency is one case in 2 million patients. Clinical symptoms include delayed wound healing, bleeding of soft and subcutaneous tissue, recurrent spontaneous miscarriage, and central nervous system (CNS) bleeding, which may be life-threatening. If patients have severe Factor XIII deficiency, early manifestations include bleeding from the umbilical cord or CNS. Prospective data showed that a level of 30% Factor XIII clotting activity is an adequate therapeutic target for most patients. Treatment of Factor XIII deficiency involves use of fresh frozen plasma, cryoprecipitate, Corifact, or Tretten® (coagulation Factor XIIIA-Subunit [recombinant] intravenous infusion).

Guidelines

The National Bleeding Disorders Foundation Medical and Scientific Advisory Council has guidelines for the treatment of hemophilia and other bleeding disorders (revised August 2023).[4] Corifact is recommended in patients who have Factor XIII deficiency.

Dosing Considerations

Dosing of clotting factor concentrates is highly individualized. MASAC provides recommendations regarding doses of clotting factor concentrate in the home (2016).[5] The number of required doses varies greatly and is dependent on the severity of the disorder and the prescribed regimen. Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough bleeding in addition to the prophylactic doses used monthly. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for prophylactic dosing plus three days of acute bleeding or perioperative management per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage Corifact. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). Because of the specialized skills required for evaluation and diagnosis of patients treated

with Corifact, as well as the monitoring required for adverse events and long-term efficacy, the agent is required to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Corifact is recommended for patients who meet the following criteria:

FDA-Approved Indication

1. **Congenital Factor XIII Deficiency.** Approve for 1 year if the agent is prescribed by or in consultation with a hematologist.

   Dosing. Approve up to 160 IU/kg by intravenous infusion no more frequently than once every 28 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Corifact is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Corifact® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; September 2020.
2. Menegatti M, Peyvandi F. Treatment of rare factor deficiencies other than hemophilia. *Blood*. 2019;133(5):415-424.
3. Pelcovits A, Schiffman F, Niroula R. Factor XIII deficiency: a review of clinical presentation and management. *Hematol Oncol Clin North Am*. 2021;35(6):1171-1180.
4. National Bleeding Disorders Foundation. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system (August 2023). MASAC Document #280. Available at: https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed on November 5, 2023.
5. National Hemophilia Foundation. MASAC (Medical and Scientific Advisory Council) recommendations regarding doses of clotting factor concentrate in the home (Revised June 7, 2016). MASAC Document #242. Adopted on June 7, 2016. Available at: https://www.hemophilia.org/sites/default/files/document/files/242.pdf. Accessed on November 5, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	10/19/2022
Annual Revision	No criteria changes.	11/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Enjaymo Utilization Management Medical Policy
- Enjaymo® (sutimlimab-jome intravenous infusion – Bioverativ/Sanofi)

REVIEW DATE: 01/03/2024

OVERVIEW

Enjaymo, a classical complement inhibitor, is indicated for the treatment of hemolysis in **cold agglutinin disease** in adults.[1]

Disease Overview

Cold agglutinin disease is a rare autoimmune hemolytic anemia.[2-4] Primary cold agglutinin disease is a B-cell lymphoproliferative disorder in which autoantibodies are produced against erythrocyte surface antigens. Primary cold agglutinin disease is distinct from secondary disease, termed cold agglutinin syndrome, which can occur with underlying conditions such as malignancy, infection, and autoimmune diseases.[2,3] Diagnosis of cold agglutinin disease is defined by chronic hemolysis, a cold agglutinin titer ≥ 64 at 4°C, and typical findings on direct antibody test (DAT), which include strong positivity for complement protein C3d and negativity (or only weak positivity) for immunoglobulin G.[2-4] Secondary causes of cold agglutinin syndrome should be excluded. Importantly, patients without chronic hemolysis or circulatory symptoms do not have cold agglutinin disease, even in the presence of positive DAT.[2] Symptoms include cold-induced circulatory symptoms, which can range from slight acrocyanosis to severe Raynaud phenomena. Anemia is generally considered mild to moderate with a median hemoglobin (Hb) of 8.9 g/dL; however, the lower tertile Hb was 8.0 g/dL and ranged to as low as 4.5 g/dL.[2,4]

Clinical Efficacy

In the pivotal CARDINAL trial (published) [n = 24], patients were required to have a confirmed diagnosis of cold agglutinin disease based on chronic hemolysis, typical DAT findings, and a recent blood transfusion within the prior 6 months.[1,5-7] Patients were also required to have a baseline hemoglobin level < 10 g/dL and total bilirubin above normal. Approximately two-thirds of patients had failed other therapies (e.g., rituximab). The Phase III CADENZA trial (published) [n = 42] also required chronic hemolysis, as well as the DAT and cold agglutinin titer findings described above; however, recent history of blood transfusion was not required.[1,8]

Dosing Information

Dosing is weight-based and is provided for patients weighing ≥ 39 kg.[1] For a patient weighing 39 to < 75 kg, the recommended dose is 6,500 mg. For a patient weighing ≥ 75 kg, the dose is 7,500 mg. For all patients, the initial dosing frequency is once weekly for 2 weeks, with administration once every 2 weeks (Q2W) thereafter. However, if the interval between doses exceeds 17 days, Enjaymo should be administered once weekly for 2 weeks, returning to Q2W administration thereafter.

Guidelines

An international consensus guideline for autoimmune hemolytic anemias was published in 2020.[9] The guideline was published prior to the approval of Enjaymo and no formal recommendation is made regarding its place in therapy, although positive Phase I data are acknowledged. It is noted that clinical and histological assessment, as well as radiologic examinations as needed, are necessary to rule out cold agglutinin syndrome secondary to malignant disease. Treatment of cold agglutinin syndrome involves

supportive care and management of the underlying disease. For treatment of cold agglutinin disease, asymptomatic patients should be managed with watchful waiting. For symptomatic patients (i.e., those with anemia, transfusion, or circulatory symptoms), rituximab is the best-documented first-line treatment and may be given alone or in combination with bendamustine. For second-line treatment, the combination of rituximab plus bendamustine is recommended (if not given in the first-line setting). Alternatively, rituximab monotherapy may be repeated for patients who previously responded for at least 1 year. Rituximab plus fludarabine is an option for fit, elderly patients. There are no evidence-based therapies for the third-line setting.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Enjaymo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Enjaymo as well as the monitoring required for adverse events and long-term efficacy, approval requires Enjaymo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Enjaymo is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. **Cold Agglutinin Disease.** Approve for 1 year if the patient meets the following (A, B, C, D, E, F, G, and H):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient weighs ≥ 39 kg; AND
   - **C)** Patient has a history of at least one sign or symptom associated with cold agglutinin disease; AND
     Note: Examples include symptomatic anemia (e.g., anemia associated with fatigue, weakness, shortness of breath, heart palpitations, lightheadedness, chest pain), acrocyanosis, Raynaud's syndrome, hemoglobinuria, disabling circulatory symptoms, or a major adverse vascular event (e.g., thrombosis).
   - **D)** According to the prescriber, the patient has evidence of chronic hemolysis; AND
   - **E)** Patient meets the following diagnostic criteria (i and ii):
     - **i.** Direct antibody test strongly positive for C3d and negative or only weakly positive for immunoglobulin G; AND
     - **ii.** Cold agglutinin antibody titer ≥ 64 at 4°C (approximately 40°F); AND
   - **F)** At baseline (prior to the initiation of Enjaymo), patient meets both of the following (i and ii):
     - **i.** Hemoglobin ≤ 10 g/dL; AND
     - **ii.** Total bilirubin above the upper limit of normal, based on the reference range for the reporting laboratory; AND
   - **G)** According to the prescriber, secondary causes of cold agglutinin syndrome have been excluded; AND

Note: Examples of secondary causes of cold agglutinin syndrome include infection, rheumatologic diseases, and active hematologic malignancies.

H) Enjaymo is prescribed by or in consultation with a hematologist.

Dosing: Approve the following dosing regimens (A or B):

A) Patient weighs ≥ 75 kg: Approve 7,500 mg intravenously not more frequently than once weekly.

B) Patient weighs < 75 kg: Approve 6,500 mg intravenously not more frequently than once weekly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Enjaymo is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	No criteria changes.	01/11/2023
Update	02/20/2023: No criteria changes. Updated the wording of the indication.	NA
Annual Revision	No criteria changes	01/03/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Fibrinogen Products Utilization Management Medical Policy
- Fibryga® (fibrinogen [human] intravenous injection – Octapharma)
- RiaSTAP® (fibrinogen concentrate [human] intravenous injection – CSL Behring)

REVIEW DATE: 11/08/2023

OVERVIEW

Fibryga and RiaSTAP, human fibrinogen concentrates, are indicated for treatment of acute bleeding episodes in patients with **congenital fibrinogen deficiency**, including afibrinogenemia and hypofibrinogenemia.[1,2] Both the Fibryga and RiaSTAP prescribing information note that these agents are not indicated for dysfibrinogenemia.

Disease Overview

Congenital deficiencies in fibrinogen (also known as Factor I) can be quantitative or qualitative.[3,4] Quantitative disorders include afibrinogenemia (absence of circulating fibrinogen) and hypofibrinogenemia (low levels of circulating fibrinogen). By contrast, dysfibrinogenemia is a qualitative deficiency in which fibrinogen levels are adequate, but function is impaired. In all cases, clinical presentation is variable; however, bleeding and thromboembolism are possible.

Diagnosis is made by routine coagulation tests in addition to fibrinogen assays.[5] An accurate diagnosis is crucial to distinguish between quantitative and qualitative disorders and guide appropriate treatment. Treatment of fibrinogen deficiency is generally on-demand for acute bleeding episodes, although effective prophylaxis has been used in high-risk patients (e.g., secondary prevention after cerebral hemorrhage, primary prevention during pregnancy to prevent miscarriage).[6,7]

Guidelines

Guidelines are available from the British Committee for Standards in Haemotology (2014); the guideline was written prior to approval of Fibryga.[8] Regarding diagnosis, it is noted that afibrinogenemia and hypofibrinogenemia manifest as prolonged prothrombin time and activated partial thromboplastin time, as well as reduced fibrinogen activity and fibrinogen antigen. Fibrinogen concentrate (e.g., RiaSTAP) may be required to treat or prevent bleeding. Cryoprecipitate is noted to be similarly effective to fibrinogen concentrate but may be associated with transfusion reactions or volume overload.

Dosing Information

Dosing is highly individualized. Guidance specific to congenital fibrinogen deficiency is limited. The National Hemophilia Foundation Medical and Scientific Advisory Council (MASAC) provides recommendations regarding doses of clotting factor concentrate in the home (2016).[9] The number of required doses varies greatly and is dependent on the severity of the disorder and the prescribed regimen. Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough episodes in addition to the prophylactic doses used monthly. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for prophylactic dosing plus three days of acute episodes or perioperative management per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

Dosing considerations for individual indications are as follows:

- **Congenital Fibrinogen Deficiency, Including Afibrinogenemia and Hypofibrinogenemia:** Doses of Fibryga and RiaSTAP are individualized based on patient-specific characteristics (e.g., extent of bleeding, clinical condition, laboratory values).[1,2] Treatment with fibrinogen products is repeated as needed to maintain target levels. Based on the product half-lives of approximately three days[1,2], it is not anticipated that dosing more frequent than once daily would typically be needed. On-demand doses up to 100 mg/kg are supported.[7] Prophylactic dosing is not well established; doses up to 100 mg/kg and intervals as frequent as once weekly have been reported.[7]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of fibrinogen products (Fibryga, RiaSTAP). Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with fibrinogen products as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Fibryga and RiaSTAP is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Congenital Fibrinogen Deficiency (Factor I Deficiency), Including Afibrinogenemia and Hypofibrinogenemia.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** The diagnosis is confirmed by the following laboratory testing (i and ii):
     - **i.** Prolonged activated partial thromboplastin time and prothrombin time at baseline, as defined by the laboratory reference values; AND
     - **ii.** Lower than normal plasma functional and antigenic fibrinogen levels at baseline, as defined by the laboratory reference values; AND
   - **B)** The requested agent is prescribed by or in consultation with a hematologist.

   Dosing. Approve up to 700 mg/kg intravenously per 28 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Fibryga and RiaSTAP is not recommended in the following situations:

1. **Concomitant Use of Fibryga and RiaSTAP.** There are no data to support concomitant use of these products.

2. **Dysfibrinogenemia.** In dysfibrinogenemia, patients have adequate levels of fibrinogen but dysfunctional clotting.[3,4] Fibryga and RiaSTAP are not indicated for dysfibrinogenemia.[1,2]

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/02/2022
Annual Revision	No criteria changes.	11/08/2023

EXPRESS SCRIPTS®

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Gene Therapy – Casgevy UM Medical Policy
- Casgevy™ (exagamglogene autotemcel intravenous infusion – Vertex/CRISPR Therapeutics)

REVIEW DATE: 01/31/2024; selected revision 03/20/2024

OVERVIEW

Casgevy, an autologous hematopoietic stem cell-based gene therapy, is indicated for the following uses:[1]
- **Sickle cell disease** in patients ≥ 12 years of age with recurrent vaso-occlusive crises (VOCs).
- **Transfusion-dependent beta-thalassemia** (TDT) in patients ≥ 12 years of age.

Casgevy is given one-time (per lifetime) as a single dose, which contains a minimum of 3 x 10^6 cluster of differentiation 34+ (CD34+) cells/kg of body weight. Casgevy is given as an intravenous (IV) infusion. The manufacturing time (which includes quality control) for Casgevy can take up to 6 months. However, the entire process can take 8 months or longer as patients need to undergo mobilization and apheresis procedures and myeloablative conditioning prior to Casgevy infusion.

Casgevy is prepared from the patient's own hematopoietic stem cells, which are obtained via apheresis procedure(s).[1,2] The CD34+ cells collected from the patient are modified *ex-vivo* by highly specific clustered, regularly interspaced, short palindromic repeats (CRISPR) and CRISPR-associated protein 9 nucleases (CRISPR/Cas9)-mediated gene editing. CRISPR/Cas9 specifically edits the B-cell lymphoma/leukemia 11A (BCL11A) gene. After Casgevy infusion, the edited CD34+ cells engraft in the bone marrow and differentiate to erythroid lineage cells with reduced BCL11A expression. Downregulation of BCL11A expression in the erythroid progenitors of the bone marrow results in reduced BCL11A protein levels, which leads to an increase in γ-globin expression and increased fetal hemoglobin (HbF) production. In patients with TDT, γ-globin production improves the α-globin to non α-globin imbalance, thereby reducing ineffective erythropoiesis and hemolysis and increasing total hemoglobin (Hb) levels, which eliminates the dependence on regular red blood cell (RBC) transfusions. In patients with sickle cell disease, increased HbF levels (≥ 20%) are protective against disease complications, including preventing VOCs.[2]

Disease Overview

Sickle Cell Disease

Sickle cell disease is a group of inherited RBC disorders characterized by the presence of a mutated Hb subunit beta gene.[3-5] Healthy RBCs are round and contain Hb. In contrast, in a patient with sickle cell disease, RBCs are sickle-shaped and die early, resulting in a constant shortage of RBCs. Furthermore, the sickle-shaped RBCs aggregate in the bloodstream, causing vaso-occlusion, which deprive downstream tissues of nutrients and oxygen, resulting in tissue ischemia, organ damage, and hemolysis (which leads to anemia). In the US, approximately 100,000 persons have the condition and it is estimated 20,000 patients have severe sickle cell disease.[2,3]

Patients with severe sickle cell disease have one of the following genotypes: β^S/β^S, β^S/β^0, β^S/β^+.[2-5] These patients have recurrent VOCs/vaso-occlusive events, while receiving appropriate supportive care (e.g., pain management, hydroxyurea). Management of sickle cell disease focuses on preventing and treating pain episodes and other complications; symptomatic treatment includes use of analgesics, fluids (hydration),

oxygen supplementation, and blood transfusion. Allogeneic hematopoietic stem cell transplantation (HSCT), a potentially curative therapy, requires a stem cell donor, typically a human leukocyte antigen (HLA)-matched donor; less than 20% of patients with sickle cell disease have a suitable donor.[2] Pharmacologic treatments for sickle cell disease include Adakveo® (crizanlizumab-tmca IV infusion), Endari® (L-glutamine oral powder), hydroxyurea, and Oxbryta® (voxelotor tablets and tablets for oral suspension).[6-10]

Transfusion-Dependent Beta-Thalassemia

The condition of beta-thalassemia is a group of recessively inherited blood disorders caused by beta-globin gene mutations that either reflect a reduced (β^+) or relative lack (β^0) of production of functional beta-globin.[11] The attenuated or lack of Hb results in chronic anemia of varying degrees of severity and insufficient delivery of oxygen to the body. Those with severe anemia may require lifelong RBC transfusions and regular iron chelation to prevent iron overload. The extremely low Hb levels can lead to many types of symptoms and health-related issues (e.g., dizziness, weakness, fatigue, increased cardiac effort, tachycardia, poor growth) or ineffective erythropoiesis (e.g., bone changes, massive splenomegaly). An estimated 3,000 persons in the US have beta-thalassemia and slightly less than one-half of the patients are dependent on RBC transfusions.

Clinical Efficacy

Sickle Cell Disease

Casgevy is being evaluated in an ongoing, single-dose, multicenter study involving adolescents and adults with sickle cell disease.[1,2] Eligible patients underwent mobilization and apheresis procedures to collect CD34+ stem cells for Casgevy manufacturing, followed by myeloablative conditioning with busulfan and infusion of Casgevy. All of the enrolled patients had one of the following genotypes: β^S/β^S, β^S/β^0, or β^S/β^+. In addition, all patients had severe sickle cell disease, as defined by the occurrence of at least two of the following VOC events per year during the 2-year period before screening, while receiving appropriate supportive care: acute pain that required a visit to a medical facility and administration of pain medications (opioids or IV nonsteroidal anti-inflammatory drugs) or RBC transfusions; acute chest syndrome; priapism lasting more than 2 hours and requiring a visit to a medical facility; or splenic sequestration. Key exclusion criteria were patients with the following: clinically significant and active bacterial, viral, fungal, or parasitic infection; advanced liver disease; history or presence of Moyamoya disease; and prior or current malignancy or myeloproliferative disorder or significant immunodeficiency disorder. The primary efficacy set (PES) [n = 31] was composed of patients who received Casgevy infusion and were followed for at least 16 months after infusion.[1] At the interim analysis (June 2023 cut-off date), the median age of patients in the PES was 21 years; 23% of patients were adolescents (≥ 12 and < 18 years of age). At baseline, the annualized (median) rate of severe VOCs during the previous 2 years was 3.5 and the annualized (median) rate of hospitalizations due to severe VOCs during the previous 2 years was 2.0. All patients received plerixafor for mobilization and busulfan for myeloablative conditioning. Casgevy was administered as an IV infusion. The primary efficacy endpoint was the proportion of patients who did not experience a severe VOC for at least 12 consecutive months within the first 24 months after Casgevy infusion (VF12 responders) and the key secondary endpoint was the proportion of patients who did not require hospitalization due to severe VOCs for at least 12 consecutive months within the first 24 months after Casgevy infusion (HF12 responders). Evaluation of both endpoints began 60 days after the last RBC transfusion for post-transplant support or sickle cell disease support. The VF12 response rate was 93.5% (n = 29/31) and all 30 patients evaluable for HF12 response achieved this endpoint.

Transfusion-Dependent Beta-Thalassemia

Casgevy is being studied in an ongoing, open-label, multicenter, single-arm study involving adolescents and adults with TDT.[1] Eligible patients underwent mobilization and apheresis procedures to collect CD34+ stem cells for Casgevy manufacturing, followed by myeloablative conditioning and Casgevy infusion. Patients were followed for 24 months after Casgevy infusion. All of the enrolled patients had a history of requiring transfusions of 100 mL/kg/year or more of packed RBCs in the 2 years prior to enrollment or requiring at least 10 units/year of packed RBCs in the 2 years prior to enrollment. In addition, patients had one of the following genotypes for beta-thalassemia: β^0/β^0-like (including β0/β+[IVS-I-110] and β+[IVS-I-110]/β+[IVS-I-110]) and non-β^0/β^0-like. The PES [n = 35] was composed of patients who received Casgevy infusion and had adequate follow-up for evaluation of the primary efficacy endpoint. At the interim analysis (conducted based on January 2023 data cut-off), the median age of the patients was 20 years; 31.4% of the patients were adolescents (≥ 12 and < 18 years of age). At baseline, the annualized (median) RBC transfusion volume was 205 mL/kg and the annualized (median) number of RBC transfusion episodes was 17. All of the patients received a granulocyte-colony stimulating factor (G-CSF) and plerixafor to mobilize stem cells for apheresis and busulfan for myeloablative conditioning. Casgevy (median dose of 7.5×10^6 cells/kg) was administered as an IV infusion. At the interim analysis, the median (minimum, maximum) duration of follow-up was 23.8 (16.1, 48.1) months after Casgevy infusion. The primary efficacy endpoint was the proportion of patients achieving transfusion independence for at least 12 consecutive months (TI12), which was defined as maintaining weighted average Hb ≥ 9 g/dL without RBC transfusions for at least 12 consecutive months, within the first 24 months after Casgevy infusion. Evaluation of this endpoint started 60 days after the last RBC transfusion for post-transplant support or TDT disease management. In total, 32 of 35 patients achieved TI12; the responder rate was 91.4% (98.3% one-sided confidence interval [CI]: 75.7%, 100%). All of the patients who achieved TI12 remained transfusion-independent, with a median duration of 20.8 months and normal mean weighted average total Hb levels of 13.1 g/dL. The median time to last RBC transfusion for patients who achieved TI12 was 30 days after Casgevy infusion. The three patients who did not achieve TI12 had reductions in annualized RBC transfusion volume requirements of 79.8%, 83.9%, and 97.9%, respectively, compared to baseline requirements. In addition, the three patients had reductions in annualized transfusion frequency of 78.6%, 67.4%, and 94.6%, respectively, compared to baseline requirements.

Guidelines

Sickle Cell Disease

Sickle cell disease guidelines have not incorporated gene therapies following their FDA approval. The American Society of Hematology (ASH) released evidence-based recommendations for stem cell transplantation for patients with sickle cell disease in 2021.[12] ASH notes that it is unclear how gene therapies will affect sickle cell disease outcomes, including organ complications and if broader access to curative therapy will alter the trajectory of sickle cell disease outcomes. ASH notes that while success rates after allogeneic HSCT are increasing, survival rates in patients receiving disease-modifying medications (e.g., hydroxyurea, L-glutamine, Adakveo, Oxbryta) and supportive care are also improving. More than 90% of patients who have undergone HSCT (predominantly using HLA-identical family donors) have been cured of sickle cell disease, as reported in short-term follow-up. Allogeneic HSCT is an established therapeutic option for patients with sickle cell disease with a clinical indication and an HLA-identical family donor. However, for the majority of patients, there are no suitable donors.

Transfusion-Dependent Beta-Thalassemia

Guidelines have not addressed Casgevy. In 2021, the Thalassaemia International Federation published guidelines for the management of TDT.[13]

- **Chelation therapy** was cited as an effective treatment modality in improving survival, decreasing the risk of heart failure, and decreasing morbidities from transfusion-induced iron overload. The

optimal chelation regimen should be individualized and will vary among patients and their clinical status.

- **Allogeneic hematopoietic stem cell transplant (HSCT)** should be offered to patients with beta-thalassemia at an early age, before complications due to iron overload have developed if an HLA-identical sibling is available. In some clinical circumstances, a matched unrelated donor can be adequate.
- **Reblozyl®** (luspatercept-aamt subcutaneous injection), an erythroid maturation agent, can be considered for patients ≥ 18 years of age who require regular RBC transfusions.
- **Zynteglo®** (betibeglogene autotemcel intravenous infusion), when available, may be an option for selected patients. Examples include young patients (12 to 17 years of age) with a β^+ genotype who do not have an HLA-compatible sibling donor. Also, Zynteglo can be considered in patients 17 to 55 years of age with a β+ genotype who do not have severe comorbidities and are at risk or ineligible to undergo allogeneic HSCT but can otherwise undergo an autologous gene therapy procedure with an acceptable risk.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Casgevy. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Casgevy as well as the specialized training required for administration of Casgevy, approval requires Casgevy to be prescribed by a physician who specializes in the condition being treated. All approvals are provided for one-time (per lifetime) as a single dose. The approval duration is 1 year to allow for an adequate timeframe to prepare and administer one dose of therapy. If claims history is available, verification is required for certain criteria as noted by **[verification in claims history required]**. For the dosing criteria, verification of the appropriate weight-based dosing is required by a Medical Director as noted by **[verification required]**. In the criteria for Casgevy, as appropriate, the symbol (†) is noted next to the specified gender. In this context, the specified gender is defined as follows: females/males are defined as individuals with the biological traits of a woman/man, regardless of the individual's gender identity or gender expression.

All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. Some clients have elected Embarc Benefit Protection for Casgevy for the treatment of sickle cell disease; treatment of beta-thalassemia is not part of the Embarc Benefit Protection program. For these clients, the Medical Director will coordinate with eviCore to ensure the Embarc Benefit Protection portion of the review (for sickle cell disease) has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

Documentation: Documentation is required for use of Casgevy as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory results, medical test results, claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Casgevy is recommended in those who meet ONE of the following criteria:

FDA-Approved Indications

1. **Sickle Cell Disease.** Approve a one-time (per lifetime) single dose if the patient meets ALL of the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, and O):
   - **A)** Patient is ≥ 12 years of age; AND
   - **B)** Patient has not received a gene therapy for sickle cell disease in the past **[verification in claims history required]**; AND
     Note: If no claim for Casgevy or Lyfgenia (lovotibeglogene autotemcel intravenous infusion) is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Casgevy or Lyfgenia.
   - **C)** According to the prescribing physician, a hematopoietic stem cell transplantation is appropriate for the patient; AND
   - **D)** Patient meets ONE of the following (i or ii):
     - **i.** Patient does not have a Human Leukocyte Antigen (HLA)-matched donor; OR
     - **ii.** Patient has an HLA-matched donor, but the individual is not able or is not willing to donate; AND
   - **E)** Genetic testing **[documentation required]** indicates the patient has ONE of the following sickle cell disease genotypes (i, ii, or iii):
     - **i.** β^S/β^S genotype; OR
     - **ii.** β^S/β^0 genotype; OR
     - **iii.** β^S/β^+ genotype; AND

     Note: Other genotypes will be reviewed by the Medical Director on a case-by-case basis.
   - **F)** Patient has tried at least ONE pharmacologic treatment for sickle cell disease **[documentation required]**; AND
     Note: Examples of pharmacologic treatment for sickle cell disease include hydroxyurea, L-glutamine, Adakveo (crizanlizumab-tmca intravenous infusion), and Oxbryta (voxelotor tablets and tablets for oral suspension).
   - **G)** While receiving appropriate standard treatment for sickle cell disease, patient had at least four severe vaso-occlusive crises or events in the previous 2 years, as defined by the following (i, ii, iii, iv, or v):
     - **i.** An episode of acute pain that resulted in a visit to a medical facility which required administration of at least ONE of the following (a or b) **[documentation required]**:
       - **a)** Intravenous opioid; OR
       - **b)** Intravenous nonsteroidal anti-inflammatory drug; OR
     - **ii.** Acute chest syndrome **[documentation required]**; OR
       Note: Acute chest syndrome is defined by the presence of a new pulmonary infiltrate associated with pneumonia-like symptoms (e.g., chest pain, fever [> 99.5°F], tachypnea, wheezing or cough, or findings upon lung auscultation).
     - **iii.** Acute hepatic sequestration **[documentation required]**; OR
       Note: Acute hepatic sequestration is defined by a sudden increase in liver size associated with pain in the right upper quadrant, abnormal results of liver function test not due to biliary tract disease, and the reduction of hemoglobin concentration by ≥ 2 g/dL below the baseline value.
     - **iv.** Acute splenic sequestration **[documentation required]**; OR
       Note: Acute splenic sequestration is defined by an enlarged spleen, left upper quadrant pain, and an acute decrease in hemoglobin concentration of ≥ 2 g/dL below the baseline value.

v. Acute priapism lasting > 2 hours and requiring a visit to a medical facility **[documentation required]**; AND

H) Patient does **not** have the following (i, ii, iii, and iv):
- **i.** Clinically significant and active bacterial, viral, fungal, or parasitic infection; AND
- **ii.** Advanced liver disease **[documentation required]**; AND
  Note: Examples of advanced liver disease include alanine transaminase > 3 times upper limit of normal; direct bilirubin value > 2.5 times upper limit of normal; baseline prothrombin time (international normalized ratio [INR]) > 1.5 times upper limit of normal; cirrhosis; bridging fibrosis; or active hepatitis.
- **iii.** Severe cerebral vasculopathy as defined by history of untreated Moyamoya disease or presence of Moyamoya disease that puts the patient at risk of bleeding, per the prescribing physician; AND
- **iv.** Prior or current malignancy or myeloproliferative disorder or significant immunodeficiency disorder; AND

I) According to the prescribing physician, patient will have been discontinued from the following medications (for the duration noted) [i and ii]:
- **i.** Disease-modifying therapies for sickle cell disease for at least 2 months before the planned start of mobilization and conditioning; AND
  Note: Examples of disease-modifying therapies for sickle cell disease include hydroxyurea, Adakveo, L-glutamine, and Oxbryta.
- **ii.** Iron chelation therapy for at least 7 days prior to myeloablative conditioning; AND
  Note: Examples of iron chelators used for this condition include deferoxamine injection, deferiprone tablets or solution, and deferasirox tablets.

J) According to the prescribing physician, patient meets ALL of the following (i, ii, iii, and iv):
- **i.** Patient will undergo mobilization, apheresis, and myeloablative conditioning; AND
- **ii.** A hematopoietic stem cell mobilizer will be utilized for mobilization; AND
  Note: Mozobil (plerixafor subcutaneous injection) is an example of a hematopoietic stem cell mobilizer.
- **iii.** Busulfan will be used for myeloablative conditioning; AND
- **iv.** Sickle hemoglobin level will be < 30% of total hemoglobin with total hemoglobin concentration ≤ 11 g/dL at BOTH of the following timepoints (a and b):
  - **a)** Prior to planned start of mobilization; AND
  - **b)** Until initiation of myeloablative conditioning; AND

K) Prior to collection of cells for manufacturing, cellular screening is negative for ALL of the following (i, ii, iii, and iv):
- **i.** Human immunodeficiency virus-1 and -2 **[documentation required]**; AND
- **ii.** Hepatitis B virus **[documentation required]**; AND
  Note: A patient who has been vaccinated against hepatitis B virus (HBV) [HBV surface antibody-positive] who is negative for other markers of prior HBV infection (e.g., negative for HBV core antibody) is eligible; a patient with past exposure to HBV is also eligible as long as patient is negative for HBV DNA.
- **iii.** Hepatitis C virus **[documentation required]**; AND
- **iv.** Human T-lymphotrophic virus-1 and -2 **[documentation required]**; AND

L) According to the prescribing physician, patient meets ONE of the following (i or ii):
- **i.** A female† of reproductive potential meets BOTH of the following (a and b):
  - **a)** A negative serum pregnancy test will be confirmed prior to the start of each mobilization cycle and re-confirmed prior to myeloablative conditioning; AND
  - **b)** Patient will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Casgevy; OR

ii. A male† of reproductive potential will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Casgevy; AND

M) The medication is prescribed by a hematologist or a stem cell transplant physician; AND

N) Current patient body weight has been obtained within 30 days **[documentation required]**; AND

O) If criteria A through N are met, approve one dose of Casgevy by intravenous infusion to provide a one-time (per lifetime) single dose, which contains a minimum of 3 x 10^6 CD34+ cells/kg of body weight **[verification required]**.
Note: A single dose of Casgevy is composed of one or more vial(s).

† Refer to the Policy Statement.

Dosing. The recommended dose of Casgevy is a one-time (per lifetime) single intravenous infusion of 3 x 10^6 CD34+ cells per kg based on current body weight in kg (within the past 30 days).

2. Transfusion-Dependent Beta-Thalassemia. Approve a one-time (per lifetime) single dose if the patient meets ALL of the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, and P):

A) Patient is ≥ 12 years and < 51 years of age; AND

B) Patient has not received a gene therapy for beta-thalassemia in the past **[verification in claims history required]**; AND
Note: If no claim for Casgevy or Zynteglo (betibeglogene autotemcel intravenous infusion) is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Casgevy or Zynteglo.

C) According to the prescribing physician, a hematopoietic stem cell transplantation is appropriate for the patient; AND

D) Patient meets ONE of the following (i or ii):
i. Patient does not have a Human Leukocyte Antigen (HLA)-matched donor; OR
ii. Patient has a HLA-matched donor, but the individual is not able or is not willing to donate; AND

E) Patient has ONE of the following genotypes as confirmed by genetic testing (i or ii):
i. Non-β^0/β^0 genotype **[documentation required]**; OR
Note: Examples include β^0/β^+, β^E/β^0, and β^+/β^+.
ii. β^0/β^0 genotypes **[documentation required]**; AND
Note: Other examples include $\beta^0/\beta^{+(IVS\text{-}I\text{-}110)}$ and $\beta^{+(IVS\text{-}I\text{-}110)}/\beta^{+(IVS\text{-}I\text{-}110)}$.

F) Patient is transfusion-dependent, as defined by meeting ONE of the following (i or ii):
i. Receipt of transfusions of ≥ 100 mL per kg of body weight of packed red blood cells per year in the previous 2 years **[documentation required]**; OR
ii. Receipt of transfusions of ≥ 10 units of packed red blood cells per year in the previous 2 years **[documentation required]**; AND

G) Patient meets BOTH of the following (i and ii):
i. Patient has been evaluated for the presence of severe iron overload **[documentation required]**; AND
ii. Patient does not have evidence of severe iron overload; AND
Note: Examples include abnormal myocardial iron results (a T2*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec); high liver iron concentration (≥ 15.5 mg/g); liver biopsy results suggest abnormalities; or clinical evidence of organ damage (e.g., endocrine comorbidities).

H) Patient does not currently have an active bacterial, viral, fungal, or parasitic infection; AND

I) Patient does not have the following (i and ii):

i. Prior or current malignancy, myeloproliferative disorder, or significant immunodeficiency disorder; AND
Note: This does not include adequately treated cone biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin.

ii. Advanced liver disease **[documentation required]**; AND
Note: Examples include alanine transaminase or aspartate transaminase greater than three times upper limit of normal, direct bilirubin value greater than three times upper limit of normal; active hepatitis, extensive bridging fibrosis, or cirrhosis.

J) According to the prescribing physician, patient will have been discontinued from iron chelation therapy for at least 7 days prior to myeloablative conditioning; AND
Note: Examples of iron chelators used for this condition include deferoxamine injection, deferiprone tablets or solution, and deferasirox tablets.

K) According to the prescribing physician, patient meets ALL of the following (i, ii, iii, and iv):

i. Patient will undergo mobilization, apheresis, and myeloablative conditioning; AND

ii. A granulocyte-colony stimulating factor product and a hematopoietic stem cell mobilizer will be utilized for mobilization; AND
Note: Filgrastim products are examples of a granulocyte-colony stimulating factor therapy and Mozobil (plerixafor subcutaneous injection) is an example of a hematopoietic stem cell mobilizer.

iii. Busulfan will be used for myeloablative conditioning; AND

iv. Total hemoglobin level is ≥ 11 g/dL at the following timepoints (a and b):

a) Prior to mobilization; AND

b) Prior to myeloablative conditioning; AND

L) Prior to collection of cells for manufacturing, cellular screening is negative for ALL of the following (i, ii, iii, and iv):

i. Human immunodeficiency virus-1 and -2 **[documentation required]**; AND

ii. Hepatitis B virus **[documentation required]**; AND

iii. Hepatitis C virus **[documentation required]**; AND

iv. Human T-lymphotropic virus-1 and -2 **[documentation required]**; AND

M) According to the prescribing physician, patient meets ONE of the following (i or ii):

i. A female† of reproductive potential meets BOTH of the following (a and b):

a) A negative serum pregnancy test will be confirmed prior to the start of each mobilization cycle and re-confirmed prior to myeloablative conditioning; AND

b) Patient will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Casgevy; OR

ii. A male† of reproductive potential will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Casgevy; AND

N) The medication is prescribed by a hematologist or a stem cell transplant physician; AND

O) Current patient body weight has been obtained within 30 days **[documentation required]**; AND

P) If criteria A through O are met, approve one dose of Casgevy by intravenous infusion to provide a one-time (per lifetime) single dose, which contains a minimum of 3 x 10^6 CD34+ cells/kg of body weight **[verification required]**.
Note: A single dose of Casgevy is composed of one or more vial(s).

† Refer to the Policy Statement

Dosing. The recommended dose of Casgevy is a one-time (per lifetime) single intravenous infusion of 3 x 10^6 CD34+ cells per kg based on current body weight in kg (within the past 30 days).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Casgevy is not recommended in the following situations:

1. **Prior Hematopoietic Stem Cell Transplantation.**
   Note: Prescribing physician must confirm that the patient has not received a prior hematopoietic stem cell transplantation.
   Casgevy has not been studied in a patient who has received a prior allogeneic or autologous hematopoietic stem cell transplant. Treatment with Casgevy is not recommended.

2. **Prior Receipt of Gene Therapy.** Casgevy has not been studied in a patient who has received prior gene therapy such as Lyfgenia® (lovotibeglogene autotemcel intravenous infusion) and Zynteglo® (betibeglogene autotemcel intravenous infusion). Treatment with Casgevy is not recommended.

3. **Concurrent Use with Reblozyl® (luspatercept-aamt subcutaneous injection)**. Reblozyl was not utilized with Casgevy in the pivotal trial assessing the efficacy of Casgevy in patients with transfusion-dependent beta-thalassemia.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/31/2024
Selected Revision	**Policy Statement:** The statement regarding verification in claims history for certain criteria was revised to add the qualifier "if claims history is available". The revised statement reads: If claims history is available, verification is required for certain criteria as noted by **[verification in claims history required]**. **Sickle Cell Disease:** **1.** The Note regarding the requirement for no previous gene therapy for sickle cell disease was revised to add the qualifier "(or if claims history is not available)" and to remove "Verify through claims history that the patient has not previously received Casgevy or Lyfgenia (lovotibeglogene autotemcel intravenous infusion)". The revised Note reads: If no claim for Casgevy or Lyfgenia (lovotibeglogene autotemcel intravenous infusion) is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Casgevy or Lyfgenia. **2.** The criterion regarding cellular screening was revised such that cellular screening is negative for human immunodeficiency virus (HIV)-1 and -2 and negative for Human T-lymphotrophic virus-1 and -2; previously, it was HIV-1 or -2 and Human T-lymphotrophic virus-1 or -2. **3.** In the criterion regarding a male* of reproductive potential, the additional phrase in parenthesis, "(i.e., capable of fathering a child)" was removed (not needed). **4.** The criterion regarding current patient weight was revised to remove the qualifier "before intended receipt of Casgevy". The revised criterion reads: Current patient body weight has been obtained within 30 days **[documentation required]**. **Transfusion-Dependent Beta-Thalassemia:** This condition and criteria for approval were added to the policy. **Conditions Not Recommended for Approval:** For the condition "Prior Receipt of Gene Therapy", Zynteglo (betibeglogene autotemcel intravenous infusion) was added as an example of a gene therapy. Concurrent Use with Reblozyl (luspartercept-aamt subcutaneous injection): This condition was added to the policy.	03/20/2024

EXPRESS SCRIPTS®

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Gene Therapy – Lyfgenia UM Medical Policy
- Lyfgenia® (lovotibeglogene autotemcel intravenous infusion – bluebird bio)

REVIEW DATE: 01/31/2024; selected revision 03/20/2024

OVERVIEW

Lyfgenia, an autologous hematopoietic stem cell-based gene therapy, is indicated for the treatment of **sickle cell disease** in patients ≥ 12 years of age with a history of vaso-occlusive events (VOEs).[1] Limitation of Use. Following treatment with Lyfgenia, patients with α-thalassemia trait (-α3.7/-α3.7) may experience anemia with erythroid dysplasia that may require chronic red blood cell (RBC) transfusions. Lyfgenia has not been studied in patients with more than two α-globin gene deletions.

Lyfgenia is given as a single dose (once per lifetime), which contains a minimum of 3 x 10^6 cluster of differentiation 34+ (CD34+) cells/kg of body weight. Lyfgenia is given as an intravenous (IV) infusion. The manufacturing time for Lyfgenia takes between 10 to 15 weeks. However, the entire process can take 6 months or longer as patients need to undergo mobilization and apheresis procedures and myeloablative conditioning prior to Lyfgenia infusion.

Lyfgenia is prepared with the patient's own hematopoietic stem cells, which are collected via apheresis procedure(s).[1,2] The CD34+ cells collected from the patient are transduced *ex vivo* with BB305 lentiviral vector (BB305 LVV). The BB305 LVV encodes a modified β-globin gene, which ultimately results in the production of HbA^{T87Q}, a modified adult hemoglobin (HbA). HbA^{T87Q} maintains 99.9% identity to HbA and has a similar oxygen-binding affinity as that of HbA; the difference is that HbA^{T87Q} is designed to inhibit polymerization of the sickle hemoglobin.

Disease Overview

Sickle cell disease is a group of inherited RBC disorders characterized by the presence of a mutated hemoglobin (Hb) subunit beta gene.[3-5] Healthy RBCs are round and contain Hb. In contrast, in a patient with sickle cell disease, RBCs are sickle-shaped and die early, resulting in a constant shortage of RBCs. Furthermore, the sickle-shaped RBCs aggregate in the bloodstream, causing vaso-occlusion, which deprive downstream tissues of nutrients and oxygen, resulting in tissue ischemia, organ damage, and hemolysis (which leads to anemia). In the US, approximately 100,000 persons have the condition and it is estimated 20,000 patients have severe sickle cell disease.[3,6]

Patients with severe sickle cell disease have one of the following genotypes: β^S/β^S, β^S/β^0, β^S/β^+.[3-5] These patients have recurrent vaso-occlusive crises/VOEs, while receiving appropriate supportive care (e.g., pain management, hydroxyurea). Management of sickle cell disease focuses on preventing and treating pain episodes and other complications; symptomatic treatment includes use of analgesics, fluids (hydration), oxygen supplementation, and blood transfusion. Allogeneic hematopoietic stem cell transplantation (HSCT) requires a stem cell donor, typically a human leukocyte antigen (HLA)-matched donor; less than 20% of patients with sickle cell disease have a suitable donor.[6] Pharmacologic treatments for sickle cell disease include Adakveo® (crizanlizumab-tmca IV infusion), Endari® (L-glutamine oral powder), hydroxyurea, and Oxbryta® (voxelotor tablets and tablets for suspension).[7-11]

Clinical Efficacy

The efficacy of Lyfgenia was studied in a single-arm, 24-month, open-label, multicenter Phase I/II study involving adolescents and adults with sickle cell disease.[1,2] In total, there were 36 patients who underwent apheresis after mobilization with plerixafor and received myeloablative conditioning with busulfan and Lyfgenia infusion.[1] Of the 36 patients, 32 patients met the criteria for the "transplant population for VOE efficacy outcomes", which included patients who met the VOE requirement; this population was used to analyze the efficacy endpoints. Patients were eligible to enroll if they had one of the following sickle cell disease genotypes: β^S/β^S, β^S/β^0, or β^S/β^+. However, all patients had the β^S/β^S genotype. In addition, the patients had at least four (protocol-defined) severe VOEs in the 24 months before enrollment and had to have failed hydroxyurea treatment or have intolerance to hydroxyurea. A VOE was defined as any of the following events requiring evaluation at a medical facility: an episode of acute pain with no medically determined cause other than vaso-occlusion and lasting > 2 hours; acute chest syndrome; acute hepatic sequestration; and acute splenic sequestration. Severe VOEs were defined as either a VOE requiring a hospitalization or multiple visits to an emergency department/urgent care over 72 hours and requiring IV medications at each visit OR priapism requiring any level of medical attention. Key exclusion criteria were patients with the following: clinically significant and active bacterial, viral, fungal, or parasitic infection; advanced liver disease; history or presence of Moyamoya disease; and prior or current malignancy or myeloproliferative disorder or significant immunodeficiency disorder. The median age of the patients was 25 years; 25% of the patients were adolescents (≥ 12 years to < 18 years of age). The primary efficacy endpoint was complete resolution of severe VOEs; the investigators also reported complete resolution of VOEs. Both outcomes were assessed between 6 and 18 months after Lyfgenia infusion. In total, 94% of patients (n = 30/32) had complete resolution of severe VOEs and 88% of patients (n = 28/32) had complete resolution of VOEs.

Guidelines

Sickle cell disease guidelines have not incorporated gene therapies following their FDA approval. The American Society of Hematology (ASH) released evidence-based recommendations for stem cell transplantation for patients with sickle cell disease in 2021.[12] ASH notes that it is unclear how gene therapies will affect sickle cell disease outcomes, including organ complications and if broader access to curative therapy will alter the trajectory of sickle cell disease outcomes. ASH notes that while success rates after allogeneic HSCT are increasing, survival rates in patients receiving disease-modifying medications (e.g., hydroxyurea, L-glutamine, Adakveo, Oxbryta) and supportive care are also improving. More than 90% of patients who have undergone HSCT (predominantly using HLA-identical family donors) have been cured of sickle cell disease, as reported in short-term follow-up. Allogeneic HSCT is an established therapeutic option for patients with sickle cell disease with a clinical indication and an HLA-identical family donor. However, for the majority of patients, there are no suitable donors.

Safety

Lyfgenia has a Boxed Warning regarding hematologic malignancy.[1] At the time of initial product approval, two patients treated with an earlier version of Lyfgenia using a different manufacturing process and transplant procedure developed acute myeloid leukemia and one patient with an α-thalassemia trait was diagnosed with myelodysplastic syndrome. Patients should be monitored for evidence of malignancy through complete blood counts at least every 6 months and through integration site analysis at Months 6, 12, and as warranted.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Lyfgenia. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lyfgenia as well as the specialized training required for administration of Lyfgenia, approval requires Lyfgenia to be prescribed by a physician who specializes in the condition being treated. All approvals are provided for one-time (per lifetime) as a single dose. The approval duration is 1 year to allow for an adequate time frame to prepare and administer one dose of therapy. If claims history is available, verification is required for certain criteria as noted by **[verification in claims history required]**. For the dosing criteria, verification of the appropriate weight-based dosing is required by a Medical Director as noted by **[verification required]**. In the criteria for Lyfgenia, as appropriate, the symbol (†) is noted next to the specified gender. In this context, the specified gender is defined as follows: females/males are defined as individuals with the biological traits of a woman/man, regardless of the individual's gender identity or gender expression.

All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with eviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

Documentation: Documentation is required for use of Lyfgenia as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory results, medical test results, claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lyfgenia is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Sickle Cell Disease.** Approve a one-time (per lifetime) single dose if the patient meets ALL of the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, and O):
   - **A)** Patient is ≥ 12 years of age; AND
   - **B)** Patient has not received a gene therapy for sickle cell disease in the past **[verification in claims history required]**; AND
     Note: If no claim for Lyfgenia or Casgevy (exagamglogene autotemcel intravenous infusion) is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Lyfgenia or Casgevy.
   - **C)** According to the prescribing physician, a hematopoietic stem cell transplantation is appropriate for the patient; AND
   - **D)** Patient meets ONE of the following (i or ii):
     - **i.** Patient does not have a Human Leukocyte Antigen (HLA)-matched donor; OR
     - **ii.** Patient has an HLA-matched donor, but the individual is not able or is not willing to donate; AND
   - **E)** Genetic testing **[documentation required]** indicates the patient has ONE of the following sickle cell disease genotypes (i, ii, or iii):
     - **i.** β^S/β^S genotype; OR

ii. β^S/β^0 genotype; OR
iii. β^S/β^+ genotype; AND
Note: Other genotypes will be reviewed by the Medical Director on a case-by-case basis.

F) Patient has tried at least ONE pharmacologic treatment for sickle cell disease **[documentation required]**; AND
Note: Examples of pharmacologic treatment for sickle cell disease include hydroxyurea, L-glutamine, Adakveo (crizanlizumab-tmca intravenous injection), and Oxbryta (voxelotor tablets and tablets for oral suspension).

G) While receiving appropriate standard treatment for sickle cell disease, patient had at least four severe vaso-occlusive crises or events in the previous 2 years, as defined by the following (i, ii, iii, iv, or v):
i. An episode of acute pain that resulted in a visit to a medical facility which required administration of at least ONE of the following (a or b) **[documentation required]**:
a) Intravenous opioid; OR
b) Intravenous nonsteroidal anti-inflammatory drug; OR
ii. Acute chest syndrome **[documentation required]**; OR
Note: Acute chest syndrome is defined by the presence of a new pulmonary infiltrate associated with pneumonia-like symptoms (e.g., chest pain, fever [> 99.5°F], tachypnea, wheezing or cough, or findings upon lung auscultation).
iii. Acute hepatic sequestration **[documentation required]**; OR
Note: Acute hepatic sequestration is defined by a sudden increase in liver size associated with pain in the right upper quadrant, abnormal results of liver function test not due to biliary tract disease, and the reduction of hemoglobin concentration by ≥ 2 g/dL below the baseline value.
iv. Acute splenic sequestration **[documentation required]**; OR
Note: Acute splenic sequestration is defined by an enlarged spleen, left upper quadrant pain, and an acute decrease in hemoglobin concentration of ≥ 2 g/dL below the baseline value.
v. Acute priapism lasting > 2 hours and requiring a visit to a medical facility **[documentation required]**; AND

H) Patient does **not** have the following (i, ii, iii, iv, and v):
i. More than two α-globin gene deletions **[documentation required]**; AND
ii. Clinically significant and active bacterial, viral, fungal, or parasitic infection; AND
iii. Advanced liver disease **[documentation required]**; AND
Note: Examples of advanced liver disease include alanine transaminase > 3 times upper limit of normal; direct bilirubin value > 2.5 times upper limit of normal; baseline prothrombin time (international normalized ratio [INR]) > 1.5 times upper limit of normal; cirrhosis; bridging fibrosis; or active hepatitis.
iv. Severe cerebral vasculopathy as defined by history of untreated Moyamoya disease or presence of Moyamoya disease that puts the patient at risk of bleeding, per the prescribing physician; AND
v. Prior or current malignancy, myeloproliferative disorder, or significant immunodeficiency disorder; AND

I) According to the prescribing physician, patient will have been discontinued from the following medications (for the duration noted) prior to mobilization (i, ii, iii, and iv):
i. Disease-modifying therapies for sickle cell disease for at least 2 months; AND
Note: Examples of disease-modifying therapies for sickle cell disease include hydroxyurea, Adakveo, L-glutamine, and Oxbryta.
ii. Erythropoietin for at least 2 months; AND
iii. Iron chelation therapy for at least 7 days; AND
Note: Examples of iron chelators used for this condition include deferoxamine injection, deferiprone tablets or solution, and deferasirox tablets.

iv. Anti-retrovirals (prophylactic for human immunodeficiency virus [HIV]) for at least 1 month; AND
Note: Examples of anti-retrovirals for HIV include abacavir, emtricitabine, lamivudine, and zidovudine.

J) According to the prescribing physician, patient meets ALL of the following (i, ii, iii, and iv):
- **i.** Patient will undergo mobilization, apheresis, and myeloablative conditioning; AND
- **ii.** A hematopoietic stem cell mobilizer will be utilized for mobilization; AND
  Note: Mozobil (plerixafor subcutaneous injection) is an example of a hematopoietic stem cell mobilizer.
- **iii.** Busulfan will be used for myeloablative conditioning; AND
- **iv.** Sickle hemoglobin level will be < 30% of total hemoglobin with total hemoglobin concentration ≤ 11 g/dL at BOTH of the following timepoints (a and b):
  - **a)** Prior to planned start of mobilization; AND
  - **b)** Until initiation of myeloablative conditioning; AND

K) Prior to collection of cells for manufacturing, cellular screening is negative for ALL of the following (i, ii, iii, and iv):
- **i.** Human immunodeficiency virus-1 and -2 **[documentation required]**; AND
- **ii.** Hepatitis B virus **[documentation required]**; AND
  Note: A patient who has been vaccinated against hepatitis B virus (HBV) [HBV surface antibody-positive] who is negative for other markers of prior HBV infection (e.g., negative for HBV core antibody) is eligible; a patient with past exposure to HBV is also eligible as long as patient is negative for HBV DNA.
- **iii.** Hepatitis C virus **[documentation required]**; AND
- **iv.** Human T-lymphotrophic virus-1 and -2 **[documentation required]**; AND

L) According to the prescribing physician, patient meets ONE of the following (i or ii):
- **i.** A female† of reproductive potential meets BOTH of the following (a and b):
  - **a)** A negative serum pregnancy test will be confirmed prior to the start of each mobilization cycle and re-confirmed prior to myeloablative conditioning; AND
  - **b)** Patient will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Lyfgenia; OR
- **ii.** A male† of reproductive potential will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Lyfgenia; AND

M) The medication is prescribed by a hematologist or a stem cell transplant physician; AND

N) Current patient body weight has been obtained within 30 days **[documentation required]**; AND

O) If criteria A through N are met, approve one dose of Lyfgenia by intravenous infusion to provide a one-time (per lifetime) single dose, which contains a minimum of 3 x 10^6 CD34+ cells/kg of body weight **[verification required]**.
Note: A single dose of Lyfgenia is composed of one or more infusion bag(s).

† Refer to the Policy Statement.

Dosing. The recommended dose of Lyfgenia is a one-time (per lifetime) single intravenous infusion of 3 x 10^6 CD34+ cells per kg based on current body weight in kg (within the past 30 days).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lyfgenia is not recommended in the following situations:

1. **Prior Hematopoietic Stem Cell Transplantation.**
   Note: Prescribing physician must confirm that the patient has not received a prior hematopoietic stem cell transplantation.
   Lyfgenia has not been studied in a patient who has received a prior allogeneic or autologous hematopoietic stem cell transplant. Treatment with Lyfgenia is not recommended.

2. **Prior Receipt of Gene Therapy.** Lyfgenia has not been studied in a patient who has received prior gene therapy such as Casgevy™ (exagamglogene autotemcel intravenous infusion). Treatment with Lyfgenia is not recommended.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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12. Kanter J, Liem RI, Bernaudin F, et al. American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation. *Blood Adv*. 2021;5:3668-3689.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/31/2024
Selected Revision	**Policy Statement:** The statement regarding verification in claims history for certain criteria was revised to add the qualifier "if claims history is available". The revised statement reads: If claims history is available, verification is required for certain criteria as noted by **[verification in claims history required]**. **Sickle Cell Disease:** **1.** The Note regarding the requirement for no previous gene therapy for sickle cell disease was revised to add the qualifier "(or if claims history is not available)" and to remove "Verify through claims history that the patient has not previously received Lyfgenia or Casgevy (exagamglogene autotemcel intravenous infusion)". The revised Note reads: If no claim for Lyfgenia or Casgevy (exagamglogene autotemcel intravenous infusion) is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Lyfgenia or Casgevy. **2.** The criterion regarding cellular screening was revised such that cellular screening is negative for human immunodeficiency virus (HIV)-1 and -2 and negative for Human T-lymphotrophic virus-1 and -2; previously, it was HIV-1 or -2 and human T-lymphotrophic virus-1 or -2. **3.** In the criterion regarding a male* of reproductive potential, the additional phrase in parenthesis, "(i.e., capable of fathering a child)" was removed (not needed). **4.** The criterion regarding current patient weight was revised to remove the qualifier "before intended receipt of Lyfgenia". The revised criterion reads: Current patient body weight has been obtained within 30 days **[documentation required]**.	03/20/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Gene Therapy – Zynteglo Utilization Management Medical Policy
- Zynteglo™ (betibeglogene autotemcel intravenous infusion – Bluebird Bio)

REVIEW DATE: 03/20/2024

OVERVIEW

Zyntelgo, an autologous hematopoietic stem cell-based gene therapy, is indicated for the treatment of beta-thalassemia in adult and pediatric patients who require regular red blood cell (RBC) transfusions.[1] The efficacy and safety of Zynteglo in children < 4 years of age have not been established; no data are available in this population. Casgevy™ (exagamglogene autotemcel intravenous infusion), an autologous hematopoietic stem cell-based gene therapy, is indicated for the treatment of transfusion-dependent beta-thalassemia in patients ≥ 12 years of age.[5] Casgevy is also indicated for the treatment of sickle cell disease in patients ≥ 12 years of age with recurrent vaso-occlusive crises. This therapy is also given as a one-time (per lifetime) single dose.

Zynteglo is given as a one-time (per lifetime) single dose which contains a minimum of 5.0 x 10^6 CD34+ cells/kg of body weight. Zynteglo is given as an intravenous infusion. The median dose of Zynteglo in the pivotal trials was 9.4 x 10^6 CD34+ cells/kg. The manufacturing time (which includes quality control) can take up to 6 months. Patients need to undergo mobilization and apheresis procedures, as well as myeloablative conditioning prior to Zynteglo infusion.

Zynteglo is prepared from the patient's own hematopoietic stem cells, which are obtained via apheresis procedure(s). Zynteglo is a $\beta^{A\text{-}T87Q}$-globin gene therapy comprised of autologous CD34+ cells, containing hematopoietic stem cells transduced with BB305 lentiviral vector (LVV) encoding $\beta^{A\text{-}T87Q}$-globin. Zynteglo adds functional copies of a modified form of the β-globin gene ($\beta^{A\text{-}T87Q}$-globin gene) into individual hematopoietic stem cells.

Disease Overview

The condition of beta-thalassemia is a group of recessively inherited blood disorders caused by β-globin gene mutations that either reflect a reduced (β^+) or relative lack (β^0) of production of functional β-globin.[2] The attenuated or lack of hemoglobin (Hb) results in chronic anemia of varying degrees of severity and insufficient delivery of oxygen to the body. Those with severe anemia may require lifelong RBC transfusions and regular iron chelation to prevent iron overload. The extremely low Hb levels can lead to many types of symptoms and health-related issues (e.g., dizziness, weakness, fatigue, increased cardiac effort, tachycardia, poor growth) or ineffective erythropoiesis (e.g., bone changes, massive splenomegaly). An estimated 3,000 patients in the US have beta-thalassemia and slightly less than one-half of the patients are dependent on RBC transfusions.

Clinical Efficacy

The efficacy of Zynteglo was evaluated in two ongoing, open-label, 2-year, single-arm, Phase III trials that involved patients ≤ 50 years of age with transfusion-dependent beta-thalassemia (NORTHSTAR-2 and NORTHSTAR-3) who received one dose of Zynteglo.[1,3] All patients underwent mobilization of stem cells (with granulocyte colony-stimulating factor and Mozobil® [plerixafor subcutaneous injection]) and pre-treatment myeloablative conditioning with busulfan prior to treatment with Zynteglo. NORTHSTAR-2 (n = 23) involved patients who had a non-β^0/β^0 genotype. NORTHSTAR-3 (n = 18) involved patients who had a β^0/β^0 or non-β^0/β^0 genotype. In NORTHSTAR-2, 91% of patients obtained transfusion independence,

the primary endpoint. Among the patients who obtained transfusion independence, the median weighted average Hb during transfusion independence was 11.8 g/dL.[1] In NORTHSTAR-3, transfusion independence was achieved by 86% of patients. Among the patients who obtained transfusion independence, the median weighted average Hb during transfusion independence was 10.2 g/dL. The median time for the last RBC transfusion prior to transfusion independence after administration of Zynteglo was slightly under 1 month in both trials. In total, 29 patients from NORTHSTAR-2 and NORTHSTAR-3 enrolled in a long-term extension. Data suggest durable results regarding transfusion independence as these two studies have had follow up for over 24 months.

Guidelines

Guidelines have not addressed Zynteglo or Casgevy post approval in the US. In 2021, the Thalassaemia International Federation published guidelines for the management of transfusion-dependent thalassemia.[4]

- **Chelation therapy** was cited as an effective treatment modality in improving survival, decreasing the risk of heart failure, and decreasing morbidities from transfusion-induced iron overload. The optimal chelation regimen should be individualized and will vary among patients and their clinical status.
- **Allogeneic hematopoietic stem cell transplant (HSCT)** should be offered to patients with beta-thalassemia at an early age, before complications due to iron overload have developed if a human leukocyte antigen (HLA) identical sibling is available. In some clinical circumstances, a matched unrelated donor can be adequate.
- **Reblozyl®** (luspatercept-aamt subcutaneous injection), an erythroid maturation agent, can be considered for patients ≥ 18 years of age who require regular RBC transfusions.
- **Zynteglo**, when available, may be an option for selected patients. Examples include young patients (12 to 17 years of age) with a β^+ genotype who do not have an HLA-compatible sibling donor. Also, Zynteglo can be considered in patients 17 to 55 years of age with a β+ genotype who do not have severe comorbidities and are at risk or ineligible to undergo allogeneic HSCT but can otherwise undergo an autologous gene therapy procedure with an acceptable risk.

POLICY STATEMENT

Prior Authorization is recommended for benefit coverage of Zynteglo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zynteglo as well as the specialized training required for administration of Zynteglo, approval requires Zynteglo to be prescribed by a physician who specializes in the condition being treated. All approvals are provided for one-time (per lifetime) as a single dose. The approval duration is 1 year to allow for an adequate time frame to prepare and administer one dose of therapy. If claims history is available, verification is required for certain criteria as noted by **[verification in claims history required]**. For the dosing criteria, verification of the appropriate weight-based dosing is required by the Medical Director as noted by **[verification required]**. In the criteria for Zynteglo, as appropriate, the symbol (†) is noted next to the specified gender. In this context, the specified gender is defined as follows: females/males are defined as individuals with the biological traits of a woman/man, regardless of the individual's gender identity or gender expression.

All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with eviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

Documentation: Documentation is required for use of Zynteglo where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory results, medical test results, claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zynteglo is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Transfusion-Dependent Beta Thalassemia.** Approve for a one-time (per lifetime) single dose if the patient meets ALL of the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, and P):
   - **A)** Patient is ≥ 4 years to < 51 years of age; AND
   - **B)** Patient has not received a gene therapy for beta-thalassemia in the past **[verification in claims history required]**; AND
     Note: If no claim for Zynteglo or Casgevy (exagamglogene autotemcel intravenous infusion) is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Zynteglo or Casgevy.
   - **C)** According to the prescribing physician, a hematopoietic stem cell transplantation is appropriate for the patient; AND
   - **D)** Patient meets ONE of the following (i or ii):
     - **i.** Patient does not have a Human Leukocyte Antigen (HLA)-matched donor; OR
     - **ii.** Patient has an HLA-matched donor, but the individual is not able or is not willing to donate; AND
   - **E)** Patient has ONE of the following genotypes as confirmed by genetic testing (i or ii):
     - **i.** Non-β^0/β^0 genotype **[documentation required]**; OR
       Note: Examples include β^0/β^+, β^E/β^0, and β^+/β^+.
     - **ii.** β^0/β^0 genotypes **[documentation required]**; AND
       Note: Other examples include $\beta^0/\beta^{+(IVS\text{-}I\text{-}110)}$ and $\beta^{+(IVS\text{-}I\text{-}110)}/\beta^{+(IVS\text{-}I\text{-}110)}$.
   - **F)** Patient is transfusion-dependent, as defined by meeting ONE of the following (i or ii):
     - **i.** Receipt of transfusions of ≥ 100 mL per kg of body weight of packed red cells per year in the previous 2 years **[documentation required]**; OR
     - **ii.** Receipt of transfusions eight or more times per year in the previous 2 years **[documentation required]**; AND
   - **G)** Patient meets BOTH of the following (i and ii):
     - **i.** Patient has been evaluated for the presence of severe iron overload **[documentation required]**; AND
     - **ii.** Patient does not have evidence of severe iron overload; AND
       Note: Examples include abnormal myocardial iron results (a T2*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec), high liver iron concentration (≥ 15.5 mg/g), liver biopsy results suggest abnormalities, or clinical evidence of organ damage (e.g., endocrine comorbidities).
   - **H)** Patient does not currently have an active bacterial, viral, fungal, or parasitic infection; AND
   - **I)** Patient does not have any of the following (i and ii):
     - **i.** Prior or current malignancy, myeloproliferative disorder, or significant immunodeficiency disorder; AND

Note: This does not include adequately treated cone biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin.

ii. Advanced liver disease **[documentation required]**; AND
Note: Examples include alanine transaminase or aspartate transaminase greater than three times upper limit of normal, direct bilirubin value greater than three times upper limit of normal, active hepatitis, extensive bridging fibrosis, or cirrhosis.

J) According to the prescribing physician, patient will have been discontinued from iron chelation therapy for at least 7 days prior to myeloablative conditioning; AND
Note: Examples of iron chelators used for this condition include deferoxamine injection, deferiprone tablets or solution, and deferasirox tablets.

K) According to the prescribing physician, patient meets ALL of the following (i, ii, iii, and iv):
- **i.** Patient will undergo mobilization, apheresis, and myeloablative conditioning; AND
- **ii.** A granulocyte-colony stimulating factor product and a hematopoietic stem cell mobilizer will be utilized for mobilization; AND
  Note: Filgrastim products are examples of a granulocyte-colony stimulating factor therapy and Mozobil (plerixafor subcutaneous injection) is an example of a hematopoietic stem cell mobilizer.
- **iii.** Busulfan will be used for myeloablative conditioning; AND
- **iv.** Total hemoglobin level is ≥ 11.0 g/dL at BOTH of the following timepoints (a and b):
  - **a)** Prior to mobilization; AND
  - **b)** Prior to myeloablative conditioning; AND

L) Prior to collection of cells for manufacturing, cellular screening is negative for ALL the following (i, ii, iii, and iv):
- **i.** Human immunodeficiency virus-1 and -2 **[documentation required]**; AND
- **ii.** Hepatitis B virus **[documentation required]**; AND
- **iii.** Hepatitis C virus **[documentation required]**; AND
- **iv.** Human T-lymphotropic virus-1 and -2 **[documentation required]**; AND

M) According to the prescribing physician, patient meets ONE of the following (i or ii):
- **i.** A female† of reproductive potential meets BOTH of the following (a and b):
  - **a)** A negative serum pregnancy test will be confirmed prior to the start of mobilization and re-confirmed prior to myeloablative conditioning; AND
  - **b)** Patient will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Zynteglo; OR
- **ii.** A male† of reproductive potential will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Zynteglo; AND

N) The medication is prescribed by a hematologist or a stem cell transplant specialist physician; AND

O) Current patient body weight has been obtained within 30 days **[documentation required]**; AND

P) If criteria A through O are met, approve one dose of Zynteglo by intravenous infusion to provide a one-time (per lifetime) single dose which contains a minimum of 5.0 x 10^6 CD34+ cells/kg of body weight **[verification required]**.

† Refer to the Policy Statement.

Dosing. The recommended dose of Zynteglo is one dose by intravenous infusion to provide a one-time (per lifetime) single dose which contains a minimum of 5.0 x 10^6 CD34+ cells/kg of body weight.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zynteglo is not recommended in the following situations:

1. **Prior Hematopoietic Stem Cell Transplantation**.
   Note: Prescribing physician must confirm that the patient has not received a prior hematopoietic stem cell transplantation.
   Zynteglo has not been studied in a patient who has received a prior allogeneic or autologous hematopoietic stem cell transplant. Treatment with Zynteglo is not recommended.

2. **Prior Receipt of Gene Therapy**. Prior receipt of gene therapy was a reason for patient exclusion in the two pivotal trials.

3. **Concurrent Use with Reblozyl** (luspatercept-aamt subcutaneous injection). Reblozyl was not utilized with Zynteglo in the pivotal trials assessing Zynteglo in patients with transfusion-dependent beta-thalassemia.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Zynteglo™ intravenous infusion [prescribing information]. Somerville, MA: Bluebird Bio; August 2022.
2. Taher AT, Musallam KM, Cappellini MD, et al. β-thalassemias. *N Engl J Med*. 2021;384;727-743.
3. Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene autotemcel gene therapy for non-β^0/β^0 genotype β-thalassemia. *N Engl J Med*. 2022;386:417-427.
4. Farmakis D, Porter J, Taher A, et al, for the 2021 TIF Guidelines Taskforce. 2021 Thalassaemia International Federation guidelines for the management of transfusion-dependent thalassemia. *Hemasphere*. 2022;6:8(e732).
5. Casgevy™ intravenous infusion [prescribing information]. Waltham, MA: Vertex; January 2024.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	In the Policy Statement [attestation required by physician] was removed from this policy. It was added that for certain criteria, verification is required as noted by [verification in claims history required]. In addition, the following changes were made: **1. Beta Thalassemia:** The phrase "as determined by the prescribing physician" was removed from the requirement regarding that the patient is without an active infection (bacterial, viral, fungal, or parasitic). The phrase "plans to" was changed to "will" to be more directive in the requirement that the patient undergoes mobilization, apheresis, and myeloablative conditioning. Regarding the requirement that Mozobil will be utilized for mobilization, this was changed to the more broad term "hematopoietic stem cell mobilizer" and Mozobil was added to the Note stating that it is an example of a hematopoietic stem cell mobilizer. In the requirement that use of iron chelators will be avoided for 6 months after infusion of Zynteglo, the [attestation required by physician] was removed. The word "recent" was replaced with the phrase "within 30 days before intended receipt of Zynteglo" regarding meeting thresholds for white blood cell count and platelet count. Regarding the requirement that the patient does not have evidence of severe iron overload, the [attestation required by physician] was removed. It was added that the patient has not received Zynteglo in the past, with [verification in claims history required]. Dosing was added in an additional section with the other standard requirements for alignment with similar policies; dosing requirements were always present with Zynteglo for this policy. **2. Conditions Not Recommended for Approval:** The [attestation required by physician] was removed from the exclusion regarding prior hematopoietic stem cell transplantation. A Note was added that the prescribing physician must confirm that the patient has not received a prior hematopoietic stem cell transplantation.	11/01/2023

HISTORY (CONTINUED)

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	In the **Policy Statement**, wording was revised to emphasize that approval for Zynteglo is one-time (per lifetime) as a single dose. The approval duration was changed from 6 months to 1 year to allow an adequate timeframe to prepare and administer Zynteglo. The requirement of verification in claims history was revised to add the qualifier "if claims history is available". The revised statement is as follows: If claims history is available, verification is required for certain criteria as noted by **[verification in claims history required]**. A sentence was added that for the Dosing criteria, verification of appropriate weight-based dosing is required by the Medical Director as noted by **[verification required]**. The following changes were made for **Transfusion-Dependent Beta-Thalassemia** (previously listed as "Beta Thalassemia"): **1.** The required patient upper age threshold was clarified to be < 51 years (previously listed as ≤ 50 years). **2.** Regarding use of Zynteglo in the past, the criterion was changed due to the recent approval of Casgevy for this indication. It now states that the patient has not received "a gene therapy for beta-thalassemia" in the past instead of requiring that the patient has not received Zynteglo in the past. It was added that there should not be claims present for Casgevy and that if claims history is not available, the prescribing physician confirms that the patient has not previously received Casgevy (previously, this only addressed Zynteglo). In the Note, the following statement was deleted: verify through claims history that the patient has not previously received Zynteglo. **3.** The reference to matched family donor was changed to remove "family". **4.** Regarding the confirmation that the patient has a specific genotype, the phrase "by DNA analysis" was changed to "by genetic testing". **5.** In the requirements that define a patient as transfusion-dependent, the phrases "preceding enrollment" and "before enrollment" were removed. **6.** The requirement was removed that the patient has received or is planning to receive prophylaxis for hepatic veno-occlusive disease/hepatic sinusoidal obstruction syndrome before myeloablative conditioning with busulfan. **7.** The requirement was removed that the patient who is ≥ 16 years of age has a Karnofsky performance status score of ≥ 80, as well as the requirement that a patient < 16 years of age has a Lansky performance status score of ≥ 80. **8.** The requirements were removed that within 30 days before intended receipt of Zynteglo that the patient has a white blood cell count ≥ 3 x 10^9/L and has a platelet count ≥ 100 x 10^9/L. **9.** A requirement was added that the patient does not have significant immunodeficiency disorder. **10.** Documentation requirements were added to the requirement previously in the policy that the patient does not have advanced liver disease. Also, the examples of liver disease provided in the Note were revised. **11.** The requirements were removed that the patient does not have the presence of any the following: familial cancer syndrome or a history of such in their immediate family; an estimated glomerular filtration rate < 70 mL/min/1.73 m^2; an uncorrected bleeding disorder; and a diffusion capacity of carbon monoxide < 50% of predicted. **12.** Regarding iron chelation therapy, the phrase "according to the prescribing physician" was added in reference to the requirement that the patient has been discontinued from this therapy for at least 7 days prior to myeloablative conditioning. Also, the requirement was removed that use of iron chelators will be avoided for 6 months after infusion of Zynteglo. **13.** The phrase "according to the prescribing physician" was added regarding the following: that the patient will undergo mobilization, apheresis, and myeloablative conditioning; that for mobilization, a granulocyte-colony stimulating factor product and a hematopoietic stem cell mobilizer will be utilized; and that busulfan will be used for myeloablative conditioning. **14.** The word "total" was added in reference to the requirement that the hemoglobin level is ≥ 11.0 g/dL. The wording "prescribing physician confirms" was changed to "according to the prescribing physician". **15.** A requirement was added that the patient is negative for both hepatitis B virus and hepatitis C virus.	03/20/2024

HISTORY (CONTINUED)

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**16.** The requirement was removed that a negative serum pregnancy test be confirmed before Zynteglo administration. **17.** Dosing was clarified with emphasis that Zynteglo is given as a "one-time (per lifetime) single dose." Also, **[documentation required]** was replaced with **[verification required]**.	03/20/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Reblozyl Utilization Management Medical Policy
- Reblozyl® (luspatercept-aamt subcutaneous injection – Celgene/Bristol Myers Squibb)

REVIEW DATE: 12/20/2023; selected revision 04/24/2024

OVERVIEW

Reblozyl, an erythroid maturation agent, is indicated for the following conditions:[1]

- **Beta-thalassemia**, for the treatment of adults with anemia who require regular red blood cell (RBC) transfusions.
- **Myelodysplastic syndromes (MDS)**, very low to intermediate-risk, for the treatment of adults who may require regular RBC transfusions with anemia without previous erythropoiesis-stimulating agent (ESA) use (ESA-naïve).
- **MDS with ring sideroblasts**, very low- to intermediate-risk disease, or with **myelodysplastic/myeloproliferative neoplasm** (MDS/MPN) with ring sideroblasts and thrombocytosis for the treatment of anemic adults who have failed an ESA and require two or more RBC units over 8 weeks.

Clinical Efficacy

Beta-Thalassemia

In the BELIEVE trial, all patients required regular RBC transfusions at baseline, defined as at least six units of packed RBCs in the preceding 24 weeks, with no transfusion-free intervals > 35 days in that timeframe.[1,2] A response to Reblozyl was defined as a 33% reduction in transfusion requirement from pretreatment baseline and a reduction in transfusion requirements of at least two RBC units during Weeks 13 through 24 compared with pretreatment baseline. The percentage of patients who had a reduction in the transfusion burden of at least 33% from baseline during Weeks 13 through 24 plus a reduction of at least two RBC units over this 12-week interval was greater for patients given Reblozyl (21.4%) vs. patients given placebo (4.5%) [$P < 0.001$].

MDS or MDS/MPN

In the MEDALIST trial, patients were required to have ring sideroblasts according to World Health Organization criteria (i.e., ≥ 15% or ≥ 5% if *SF3B1* mutation was present).[1,3] Patients with deletion 5q [del(5q)] were excluded from enrollment. All patients were required to have disease refractory or unlikely to respond to ESAs (unless endogenous erythropoietin level was elevated), and the median pretransfusion hemoglobin level was 7.6 g/dL (range 5 to 10 g/dL). Patients had to require RBC transfusions (two or more RBC units over 8 weeks). During the initial 24 weeks of the trial, 58% of patients had transfusion independence for 8 weeks or longer compared with 13% of patients in the placebo group.[1] In the pivotal MEDALIST trial publication, which primarily involved patients with MDS, improvements in hemoglobin from baseline were sustained through at least Week 25. It is notable that the MDS disease course may evolve over time and potentially lead to loss of response of previously effective agents; thus, close follow-up is appropriate to verify that therapeutic response is maintained.

COMMANDS was an open-label trial that compared Reblozyl with epoetin alfa in patients with very low, low, or intermediate risk MDS or with MDS/MPN with ring sideroblasts and thrombocytosis.[1,4] Patients were required to have had two to six RBC units in 8 weeks and erythropoietin levels < 500 U/L at screening. The primary endpoint was RBC transfusion independence for at least 12 weeks with a concurrent mean

hemoglobin increase of at least 1.5 g/dL during Weeks 1 to 24 which was met by 58.5% of patients in the Reblozyl group vs. 31.2% of patients in the epoetin alfa group.

Dosing Information

For all indications, the starting dose is 1 mg/kg given subcutaneously once every 3 weeks.[1] Assess and review hemoglobin levels and transfusion record prior to each dose. Discontinue if a patient does not experience a decrease in transfusion burden after 9 weeks of treatment (administration of three doses) at the maximum dose level. For beta-thalassemia, the maximum recommended dose is 1.25 mg/kg given once every 3 weeks. For MDS and MDS/MPN, the maximum dose is 1.75 mg/kg given once every 3 weeks.

Guidelines

The Thalassaemia International Federation published guidelines for the management of transfusion-dependent thalassemia (2021).[5]

- **Chelation therapy** was cited as an effective treatment modality in improving survival, decreasing the risk of heart failure, and decreasing morbidities from transfusional-induced iron overload. The optimal chelation regimen should be individualized and will vary among patients and their clinical status.
- **Allogeneic hematopoietic stem cell transplant (HSCT)** should be offered to patients with beta-thalassemia at an early age, before complications due to iron overload have developed if a human leukocyte antigen (HLA) identical sibling is available. In some clinical circumstances, a matched unrelated donor can be adequate.
- **Reblozyl** can be considered for patients ≥ 18 years of age who require regular RBC transfusions.
- **Zynteglo™** (betibeglogene autotemcel intravenous infusion), a gene therapy, may be an option for selected patients when available. Examples include young patients (12 to 17 years of age) with a β^+ genotype who do not have an HLA-compatible sibling donor. Also, Zynteglo can be considered in patients 17 to 55 years of age with a β^+ genotype who do not have severe comorbidities and are at risk or ineligible to undergo allogeneic HSCT but can otherwise undergo an autologous gene therapy procedure with an acceptable risk.

The National Comprehensive Cancer Network guidelines for MDS (version 3.2023 – November 10, 2023) recommend Reblozyl in the following situations:[6]

- **MDS:** Treatment with Reblozyl is supported for lower-risk disease associated with symptomatic anemia with no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts ≥ 15% (or ring sideroblasts ≥ 5% with an *SF3B1* mutation) as a single agent (category 1). Treatment with Reblozyl is supported for lower-risk disease associated with symptomatic anemia with no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts < 15% (or ring sideroblasts < 5% with an *SF3B1* mutation) and serum erythropoietin levels ≤ 500 mU/L as a single agent or following no response to an ESA (despite adequate iron stores) [category 2A].
- **MDS/MPN:** Treatment with Reblozyl can be considered for MDS/MPN with an *SF3B1* mutation and thrombocytosis as a single agent (category 2B). Reblozyl can also be used for wild-type *SF3B1* if the patient has thrombocytosis and ring sideroblasts ≥ 15% [category 2B].

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Reblozyl. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is

authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Reblozyl as well as the monitoring required for adverse events and long-term efficacy, approval requires Reblozyl to be prescribed by or in consultation with a physician who specializes in the condition being treated.

*Indications and/or approval conditions noted with **[eviCore]** are managed by eviCore healthcare for those clients who use eviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to eviCore at www.eviCore.com.*

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Reblozyl is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Transfusion Dependent Beta-Thalassemia.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 4 months if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** According to the prescriber, the patient requires regular red blood cell transfusions as defined by meeting BOTH of the following (a and b):
       - **a)** Patient has received at least 6 units of packed red blood cells within the preceding 24 weeks; AND
       - **b)** Patient has not had any transfusion-free period > 35 days within the preceding 24 weeks; AND
     - **iii.** Patient has not received a gene therapy for transfusion dependent beta-thalassemia in the past; AND
       Note: Examples include Zynteglo (betibeglogene autotemcel intravenous infusion) and Casgevy (exagamglogene autotemcel intravenous infusion).
     - **iv.** The medication is being prescribed by or in consultation with a hematologist.
   - **B)** Patient is Currently Receiving Reblozyl. Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):
     - **i.** According to the prescriber, the patient has experienced a clinically meaningful decrease in transfusion burden as defined by a decrease of at least 2 units in red blood cell transfusion burden over the past 6 months compared with the pretreatment baseline (prior to the initiation of Reblozyl); AND
     - **ii.** Patient has not received a gene therapy for transfusion dependent beta-thalassemia in the past.
       Note: Examples include Zynteglo (betibeglogene autotemcel intravenous infusion) and Casgevy (exagamglogene autotemcel intravenous infusion).

   Dosing. Approve up to 1.25 mg/kg by subcutaneous injection administered not more frequently than once every 3 weeks.

2. **Myelodysplastic Syndrome.** ***[eviCore]*** Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, vii, and viii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** According to the prescriber, the patient has myelodysplastic syndromes and meets ONE of the following (a or b):
  - **a)** Ring sideroblast positivity; OR
    Note: This is defined as ring sideroblasts ≥ 15% or ring sideroblasts ≥ 5% with an *SF3B1* mutation.
  - **b)** Serum erythropoietin level is ≤ 500 mU/mL; AND
- **iii.** Patient has very low- to intermediate-risk myelodysplastic syndromes, as determined by the prescriber; AND
  Note: This is determined using the International Prognostic Scoring System (IPSS).
- **iv.** Patient does not have a confirmed mutation with deletion 5q [del(5q)]; AND
- **v.** Patient currently requires blood transfusions, defined as at least two red blood cell units over the previous 8 weeks; AND
- **vi.** Pretreatment hemoglobin level is < 10.0 g/dL; AND
- **vii.** Reblozyl will not be used in combination with an erythropoiesis stimulating agent; AND
- **viii.** The medication is being prescribed by or in consultation with an oncologist or hematologist.

B) Patient is Currently Receiving Reblozyl. Approve for 6 months if, according to the prescriber, the patient has experienced a clinically meaningful decrease in transfusion burden or the hemoglobin level has increased by ≥ 1.5 g/dL compared with the pretreatment baseline.

Dosing. Approve up to 1.75 mg/kg by subcutaneous injection administered not more frequently than once every 3 weeks.

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3. Myelodysplastic/Myeloproliferative Neoplasm. *[eviCore]* Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, vii, and viii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** According to the prescriber, the patient has myelodysplastic/myeloproliferative neoplasm and meets BOTH of the following (a and b):
  - **a)** Ring sideroblast positivity; AND
    Note: This is defined as ring sideroblasts ≥ 15% or ring sideroblasts ≥ 5% with an *SF3B1* mutation.
  - **b)** Thrombocytosis defined as platelet count ≥ 450 x 10^9/L; AND
- **iii.** Patient has very low- to intermediate-risk disease, as determined by the prescriber; AND
  Note: This is determined using the International Prognostic Scoring System (IPSS).
- **iv.** Patient does not have a confirmed mutation with deletion 5q [del(5q)]; AND
- **v.** Patient currently requires blood transfusions, defined as at least two red blood cell units over the previous 8 weeks; AND
- **vi.** Pretreatment hemoglobin level is < 10.0 g/dL; AND
- **vii.** Reblozyl will not be used in combination with an erythropoiesis stimulating agent; AND
- **viii.** The medication is being prescribed by or in consultation with an oncologist or hematologist.

B) Patient is Currently Receiving Reblozyl. Approve for 1 year if, according to the prescriber, the patient has experienced a clinically meaningful decrease in transfusion burden or the hemoglobin level has increased by ≥ 1.5 g/dL compared with the pretreatment baseline.

Dosing. Approve up to 1.75 mg/kg by subcutaneous injection administered not more frequently than once every 3 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Reblozyl is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Reblozyl® subcutaneous injection [prescribing information]. Summit; NJ: Celgene/Bristol-Myers Squibb; August 2023.
2. Cappellini MD, Viprakasit V, Taher AT, et al; BELIEVE Investigators. A Phase 3 Trial of luspatercept in patients with transfusion-dependent β-thalassemia. *N Engl J Med*. 2020;382(13):1219-1231.
3. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes. *N Engl J Med*. 2020;382(2):140-151.
4. Platzbecker U, Della Porta MG, Santini V, et al. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naïve, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomized controlled trial. *Lancet*. 2023;402:373-385.
5. Farmakis D, Porter J, Taher A, et al, for the 2021 TIF Guidelines Taskforce. 2021 Thalassaemia International Federation guidelines for the management of transfusion-dependent thalassemia. *Hemasphere*. 2022;6:8(e732).
6. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 3.2023 – November 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 13, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	01/04/2023
Selected Revision	**Beta Thalassemia:** In initial therapy criteria, regarding the requirement for regular red blood cell transfusions, this was further defined to mean that the patient has received at least 6 units of packed red blood cells within the preceding 24 weeks, and the patient has not had any transfusion-free period > 35 days within the preceding 24 weeks. The Note which previously stated that this includes patients who are transfusion-dependent was removed (no longer needed). In continuation criteria, a clinically meaningful decrease in transfusion burden was defined by as decreased in at least 2 units in red blood cell transfusion burden over the past 6 months compared with the pretreatment baseline (prior to the initiation of Reblozyl). **Myelodysplastic Syndrome:** In the initial therapy criteria, the requirement for myelodysplastic syndromes "with ring sideroblasts" was revised to state that the ring sideroblasts must be ≥ 15%, or ring sideroblasts must be ≥ 5% with an *SF3B1* mutation. In continuation criteria, the approval duration was decreased from 1 year to 6 months. Additionally, a clinically meaningful decrease in transfusion burden was defined by meeting one of the following: 1) if the patient had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of ≥ 4 units per 8 weeks, the red blood cell transfusion burden has decreased by ≥ 4 units per 8 weeks from pretreatment baseline; OR 2) if the patient had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of < 4 units per 8 weeks, hemoglobin has increased by at least 1.5 g/dL compared with the pretreatment baseline. **Myelodysplastic/Myeloproliferative Neoplasm:** In the initial therapy criteria, the requirement for myelodysplastic/myeloproliferative neoplasm "with ring sideroblasts" was revised to state that the ring sideroblasts must be ≥ 15%, or ring sideroblasts must be ≥ 5% with an *SF3B1* mutation. Additionally, the requirement for "thrombocytosis-associated anemia" was reworded to "thrombocytosis defined as platelet count ≥ 450 x 10^9/L". In continuation criteria, a clinically meaningful decrease in transfusion burden was defined by meeting one of the following: 1) if the patient had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of ≥ 4 units per 8 weeks, the red blood cell transfusion burden has decreased by ≥ 4 units per 8 weeks from pretreatment baseline; OR 2) if the patient had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of < 4 units per 8 weeks, hemoglobin has increased by at least 1.5 g/dL compared with the pretreatment baseline.	01/11/2023

HISTORY (CONTINUED)

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Myelodysplastic Syndrome:** In the initial therapy criteria, the requirement that a patient has ring sideroblasts ≥ 15% or ring sideroblasts ≥ 5% with an *SF3B1* mutation was changed to either the patient has ring sideroblast positivity (with the definition in a Note) or has serum erythropoietin levels ≤ 500 mU/mL. The requirement was removed that the patient has tried an erythropoiesis-stimulating agent for at least 6 weeks (unless intolerant) or that the serum erythropoietin level is greater than 500 mU/mL. In the criteria in which the patient is currently receiving Reblozyl, the following requirements that defined that the patient has experienced a clinically meaningful decrease in transfusion burden were removed: 1) for a patient that had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of ≥ 4 units per 8 weeks, that red blood cell transfusion burden has decreased by ≥ 4 units per 8 weeks from the pretreatment baseline; OR 2) for a patient that had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of < 4 units per 8 weeks, that the hemoglobin levels has increased by ≥ 1.5 g/dL compared with the pretreatment baseline. A patient is still required to have experienced a clinically meaningful decrease in transfusion burden per the prescriber (without the definitions above) and the phrase "or hemoglobin has increased by 1.5 g/dL compared with the pretreatment baseline" was added. **Myelodysplastic/Myeloproliferative Neoplasm:** In the initial therapy criteria, the requirement that a patient has ring sideroblasts ≥ 15% or ring sideroblasts ≥ 5% with an *SF3B1* mutation was changed to just state that the patient has ring sideroblast positivity (with the definition in a Note). The requirement was removed that the patient has tried an erythropoiesis-stimulating agent for at least 6 weeks (unless intolerant) or that the serum erythropoietin level is greater than 500 mU/mL. In the criteria in which the patient is currently receiving Reblozyl, the following requirements that defined that the patient has experienced a clinically meaningful decrease in transfusion burden were removed: 1) for a patient that had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of ≥ 4 units per 8 weeks, that red blood cell transfusion burden has decreased by ≥ 4 units per 8 weeks from the pretreatment baseline; OR 2) for a patient that had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of < 4 units per 8 weeks, that the hemoglobin has increased by ≥ 1.5 g/dL compared with the pretreatment baseline. A patient is still required to have experienced a clinically meaningful decrease in transfusion burden per the prescriber (without the definitions above) and the phrase "or hemoglobin has increased by 1.5 g/dL compared with the pretreatment baseline" was added.	12/20/2023
Selected Revision	**Transfusion Dependent Beta-Thalassemia:** The name of the indication of use was changed to as listed (previously it was cited as beta-thalassemia). The criterion that the patient has not received Zynteglo in the past was changed to state that the patient has not received a gene therapy for transfusion-dependent beta-thalassemia in the past. A Note was added that examples are Zynteglo and Casgevy.	04/24/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Ryplazim Utilization Management Medical Policy
- Ryplazim® (plasminogen, human-tvmh intravenous infusion – Prometic/Kedrion)

REVIEW DATE: 01/03/2024

OVERVIEW

Ryplazim, a plasma-derived human plasminogen, is indicated for the treatment of **plasminogen deficiency type 1 (hypoplasminogenemia)**.[1]

Disease Overview

Congenital plasminogen deficiency is an ultra-rare, autosomal recessive disease affecting approximately 500 patients in the US (estimated prevalence of 1.6 per million individuals).[2] Female predominance has been reported. The median age of first clinical manifestations has been reported as approximately 10 months in one case series.[3] Type 1 deficiency is considered "true" plasminogen deficiency and results in decreased plasminogen antigen and activity levels. Type 2 deficiency is referred to as dysplasminogenemia; plasminogen antigen levels are normal, but functional activity is reduced. Type 2 deficiency is asymptomatic and not clinically relevant. By contrast, type 1 deficiency may present with multisystem disease characterized by fibrin-rich ("woody") pseudomembranes on mucous membranes.[2] Treatment of congenital plasminogen deficiency should be coordinated by a hematologist who is knowledgeable about the disorder.[4]

Clinical Efficacy

Clinical efficacy of Ryplazim was evaluated in one Phase II/III pivotal study in patients with plasminogen deficiency type 1 (n = 15).[1,5] All patients had a baseline plasminogen activity level between < 5% and 45% of normal, as well as biallelic mutations in the *PLG* (plasminogen) gene.[1] The primary clinical efficacy endpoint was overall clinical success. Overall clinical success was defined as 50% of patients with visible or other measurable lesions achieving at least a 50% improvement in lesion number/size or functionality impact from baseline. Patients were not required to have active lesions at baseline; however, they were required to have a history of lesions and symptoms consistent with a diagnosis of congenital plasminogen deficiency. Among the 15 patients in the study, a total of 32 external lesions and 12 internal lesions were evaluated. The majority of lesions were resolved by Week 48; no patients experienced new or recurrent lesions.

Dosing Information

Ryplazim dosing frequency is adjusted based on trough plasminogen activity level; the most frequent recommended dosing interval is once every other day. It is recommended to continue dosing for 12 weeks while treating active lesions and then assess for clinical response. If lesions do not resolve by 12 weeks, or if there are new or recurrent lesions, dosing frequency can be escalated (to a maximum of every other day) while assessing clinical improvement until lesion resolution or until the lesions stabilize without further worsening. If desired clinical change does not occur by 12 weeks, an additional trough plasminogen activity level should be obtained. If the trough level is ≥ 10% (absolute change in plasminogen activity) above baseline, surgical removal of the lesions should be considered in addition to plasminogen treatment. If the trough level is < 10% baseline (in combination with no clinical efficacy), consider discontinuing plasminogen treatment due to the possibility of neutralizing antibodies.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Ryplazim. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval duration is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ryplazim as well as the monitoring required for adverse events and long-term efficacy, approval requires Ryplazim to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ryplazim is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Plasminogen Deficiency Type 1 (Hypoplasminogenemia).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets the following (i, ii, and iii):
     - **i.** Patient has a diagnosis of plasminogen deficiency type 1 confirmed by both of the following:
       - **a)** Biallelic mutations in the *PLG* gene; AND
       - **b)** Baseline plasminogen activity level (prior to initiating Ryplazim) ≤ 45% of normal based on the reference range for the reporting laboratory; AND
     - **ii.** Patient has a history of lesions and symptoms consistent with a diagnosis of congenital plasminogen deficiency; AND
     - **iii.** Ryplazim is prescribed by or in consultation with a hematologist.
   - **B)** Patient is Currently Receiving Ryplazim. Approve for 1 year if the patient meets the following (i and ii):
     - **i.** Patient meets ONE of the following (a or b):
       - **a)** Patient has had a clinical response to Ryplazim, as determined by the prescriber; OR
         Note: Examples of clinical response include resolution of active lesions, stabilization of current lesions, and prevention of new or recurrent lesions.
       - **b)** Patient has a trough plasminogen activity level ≥ 10% (absolute change in plasminogen activity) above the baseline trough level (prior to initiating Ryplazim); AND
     - **ii.** Ryplazim is prescribed by or in consultation with a hematologist.

   Dosing. Approve a dose of 6.6 mg/kg body weight intravenously, not more frequency than once every other day.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ryplazim is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Ryplazim® intravenous infusion [prescribing information]. Laval, Quebec, Canada and Fort Lee, NY: Prometic; November 2021.
2. Shapiro AD, Menegatti M, Palla R, et al. An international registry of patients with plasminogen deficiency (HISTORY). *Haematologica*. 2020;105(3):554-561.
3. Schuster V, Hügle B, Tefs K. Plasminogen deficiency. *J Thromb Haemost*. 2007;5(12):2315-2322.
4. Congenital Plasminogen Deficiency. National Organization for Rare Disorders. Updated October 29, 2021. Available at: https://rarediseases.org/rare-diseases/congenital-plasminogen-deficiency/. Accessed on December 30, 2023.
5. Shapiro AD, Naker C, Parker JM, et al. Plasminogen, human-tvmh for the treatment of children and adults with plasminogen deficiency type 1. *Haemophilia*. 2023;29(6):1556-1564.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	No criteria changes.	01/04/2023
Annual Revision	No criteria changes.	01/03/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Tretten Utilization Management Medical Policy
- Tretten® (coagulation Factor XIII A-Subunit [recombinant] intravenous infusion – NovoNordisk)

REVIEW DATE: 11/08/2023

OVERVIEW

Tretten, a coagulation Factor XIII A-subunit, is indicated for routine prophylaxis of bleeding in patients with congenital factor XIII A-subunit deficiency.[1] The agent is not indicated for use in patients with congenital Factor XIII B-subunit deficiency.

Disease Overview

Congenital Factor XIII deficiency is caused by defects in both Factor XIIIA and Factor XIIIB genes.[2,3] However, most cases are due to genetic alterations on the Factor XIIIA gene. The estimated prevalence of Factor XIIIA deficiency is one case in 1 to 2 million people. Clinical symptoms include delayed wound healing, bleeding of soft and subcutaneous tissue, recurrent spontaneous miscarriage, and central nervous system (CNS) bleeding, which may be life-threatening. If patients have severe Factor XIII deficiency, early manifestations include bleeding from the umbilical cord or CNS. Prospective data showed that a level of 30% Factor XIII clotting activity is an adequate therapeutic target for most patients. Treatment of Factor XIII deficiency involves use of fresh frozen plasma, cryoprecipitate, Corifact® (Factor XIII concentration intravenous infusion), or Tretten.

Guidelines

The National Bleeding Disorders Foundation Medical and Scientific Advisory Council (MASAC) has guidelines for the treatment of hemophilia and other bleeding disorders (revised August 2023).[4] Tretten is recommended in patients who have factor XIII deficiency who lack the factor XIII-A subunit. It will not work in patients who only lack factor XIII-B subunit.

Dosing Considerations

Dosing of clotting factor concentrates is highly individualized. MASAC provides recommendations regarding doses of clotting factor concentrate in the home (2016).[5] The number of required doses varies greatly and is dependent on the severity of the disorder and the prescribed regimen. Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough bleeding in addition to the prophylactic doses used monthly. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for prophylactic dosing plus three days of acute bleeding or perioperative management per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage Tretten. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director

or Pharmacist). Because of the specialized skills required for evaluation and diagnosis of patients treated with Tretten, as well as the monitoring required for adverse events and long-term efficacy, the agent is required to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tretten is recommended for patients who meet the following criteria:

FDA-Approved Indication

1. **Congenital Factor XIII A-Subunit Deficiency.** Approve for 1 year if the agent is prescribed by or in consultation with a hematologist.

   Dosing. Approve up to 140 IU/kg intravenously no more frequently than once every 28 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tretten is not recommended in the following situations:

1. **Congenital Factor XIII B-Subunit Deficiency.** Tretten will not work in patients who only lack Factor XIII-B subunit.[1,2]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Tretten® intravenous infusion [prescribing information]. Plainsboro, NJ: Novo Nordisk; June 2020.
2. Menegatti M, Peyvandi F. Treatment of rare factor deficiencies other than hemophilia. *Blood*. 2019;133(5):415-424.
3. Pelcovits A, Schiffman F, Niroula R. Factor XIII deficiency: a review of clinical presentation and management. *Hematol Oncol Clin North Am*. 2021;35(6):1171-1180.
4. National Bleeding Disorders Foundation. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system (August 2023). MASAC Document #280. Available at: https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed on November 5, 2023.
5. National Hemophilia Foundation. MASAC (Medical and Scientific Advisory Council) recommendations regarding doses of clotting factor concentrate in the home (Revised June 7, 2016). MASAC Document #242. Adopted on June 7, 2016. Available at: https://www.hemophilia.org/sites/default/files/document/files/242.pdf. Accessed on November 5, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	10/19/2022
Annual Revision	No criteria changes.	11/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Vonvendi Management Medical Policy
- Vonvendi® (von Willebrand factor [recombinant] intravenous infusion – Baxalta)

REVIEW DATE: 11/08/2023

OVERVIEW

Vonvendi, a recombinant von Willebrand factor (VWF), is indicated for use in adults ≥ 18 years of age diagnosed with von Willebrand disease (VWD) for:[1]

- **On-demand treatment and control** of bleeding episodes.
- **Perioperative management** of bleeding.
- **Routine prophylaxis to reduce the frequency of bleeding episodes in patients with severe Type 3 VWD** receiving on-demand therapy.

Disease Overview

VWD is an inherited bleeding disorder caused by a deficiency or impairment of a protein found in blood called VWF.[3-6] VWF is a plasma protein with a dual role in hemostasis by mediating platelet adhesion at sites of vascular injury and by binding and stabilizing Factor VIII. The disease is rather common as it affects 1 in 100 people; both genders are impacted equally. Symptoms of VWD include mucocutaneous bleeding and excessive hemorrhage following invasive procedures; occasionally, soft tissue hematomas and joint bleeding may also occur. Women who have VWD may experience heavy menorrhagia or experience excessive bleeding at childbirth. Bleeding episodes may be life-threatening in patients with severe forms of VWD. VWD is classified into six types (1, 2A, 2B, 2M, 2N, and 3) according to distinct genotypic, clinical, and laboratory phenotypic characteristics. Type 1 VWD is the most common type (60% to 80% of patients) and represents a partial quantitative deficiency of VWF. Bleeding symptoms are generally mild to moderate. Type 2 VWD affects 15% to 30% of patients and consists of four disease subtypes (2A, 2B, 2M, and 2N) dependent on the specific gene mutation (e.g., decreased VWF-dependent platelet adhesion, decreased binding affinity for Factor VIII). This type is due to a qualitative VWF defect, and the bleeding is generally moderate, but can vary among patients. Type 3 VWD is uncommon (5% to 10% of patients) but is usually severe because it is due to a virtually complete deficiency of VWF. Many patients with VWD also have reduced Factor VIII levels. Treatment options for VWD include desmopressin either parenterally or by a highly concentrated nasal spray (Stimate), Vonvendi, or plasma-derived Factor VIII product that contain VWF.

Guidelines

The National Bleeding Disorders Foundation Medical and Scientific Advisory Council (MASAC) has guidelines for the treatment of hemophilia and other bleeding disorders (revised August 2023).[3] Most patients with type 1 VWD may be treated with a desmopressin product (DDAVP injection or Stimate nasal spray). Some patients with type 2A VWD may respond to DDAVP; a clinical trial with DDAVP should be performed to determine if DDAVP can be used for these particular patients. The guidelines recommend that both DDAVP injection and Stimate not be used in children aged < 2 years and in patients with VWD in whom desmopressin does not provide adequate VWF levels. Also, they should be used cautiously in pregnant women during labor and delivery. Use of plasma-derived VWF-containing Factor VIII concentrates that have VWF is recommended in certain types of VWD that do not respond to therapy with desmopressin (i.e., type 2B VWD and type 3 VWD). Also, plasma-derived Factor VIII concentrates that contain VWF are recommended in types 1, 2A, 2M, and 2N VWD who have become transiently

unresponsive to DDAVP, as well as in surgical situations, especially in young children < 2 years of age. Alphanate, Humate-P, and Wilate are indicated for use in VWD; in certain patients Koāte® (antihemophilic Factor [plasma-derived] intravenous infusion) may also be effective. Use of cryoprecipitate is not recommended as it has not undergone any viral attenuation steps. Cryoprecipitate should not be utilized to treat patients with VWD except in life- and limb-threatening emergencies when VWD-containing factor VIII concentrate is not immediately available. Vonvendi is available to treat patients with Type 2B and Type 3 VWD; it can also be used in patients with Types 1, 2A, 2M, and 2N VWD who are not responsive to DDAVP and in children < 2 years of age, regardless of VWD type. Vonvendi is approved for use as routine prophylaxis only in patients with severe Type 3 VWD who were previously treated with VWF (recombinant or plasma-derived) on demand. It is produced in Chinese hamster ovary cells and it does not contain human or animal-derived proteins in its cell culture or in its final formulation (a third generation product). Vonvendi contains ultra-large VWF multimers, in addition to the high, medium, and low molecular weight VWF multimers normally found in plasma. Trace amounts of recombinant Factor VIII is in the product as well.

Dosing Considerations

Dosing of clotting factor concentrates is highly individualized. MASAC provides recommendations regarding doses of clotting factor concentrate in the home (2016).[7] The number of required doses varies greatly and is dependent on the severity of the disorder and the prescribed regimen. Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough bleeding in addition to the prophylactic doses used monthly. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for prophylactic dosing plus three days of acute bleeding or perioperative management per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage Vonvendi. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). Because of the specialized skills required for evaluation and diagnosis of patients treated with Vonvendi, as well as the monitoring required for adverse events and long-term efficacy, the agent is required to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vonvendi is recommended for patients who meet the following criteria:

FDA-Approved Indication

1. **Von Willebrand Disease.** Approve for 1 year if the agent is prescribed by or in consultation with a hematologist.

   Dosing. Approve the following dosing regimens (A, B, and/or C):

A) On demand treatment and control of bleeding episodes: approve up to 900 IU/kg intravenously no more frequently than once every 28 days; AND/OR
B) Perioperative management: approve up to 900 IU/kg intravenously no more frequently than once every 28 days; AND/OR
C) Routine prophylaxis: approve up to 60 IU/kg intravenously no more frequently than twice weekly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vonvendi is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Vonvendi® intravenous infusion [prescribing information]. Lexington, MA: Baxalta; March 2023.
2. Gill JC, Castaman G, Windyga J, et al. Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. *Blood*. 2015;126(17):2038-2046.
3. Franchini M, Mannucci PM. Von Willebrand factor (Vonvendi®): the first recombinant product licensed for the treatment of von Willebrand disease. *Expert Rev Hematol*. 2016;9(9):825-830.
4. National Bleeding Disorders Foundation. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system (August 2023). MASAC Document #280. Available at: https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed on November 5, 2023.
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6. Connell NT, Flood VH, Brignardello-Petersen R, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand Disease. *Blood Adv*. 2021;5(1):301-325.
7. National Hemophilia Foundation. MASAC (Medical and Scientific Advisory Council) recommendations regarding doses of clotting factor concentrate in the home (Revised June 7, 2016). MASAC Document #242. Adopted on September 3, 2020. Available at: https://www.hemophilia.org/sites/default/files/document/files/242.pdf. Accessed on November 5, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	**Von Willebrand Disease:** Added dosing for routine prophylaxis to approve up to 60 IU/kg intravenously no more frequently than twice weekly.	02/16/2022
Annual Revision	No criteria changes.	10/19/2022
Annual Revision	No criteria changes.	11/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hemophilia – Altuviiio Utilization Management Medical Policy
- Altuviiio™ (antihemophilic factor [recombinant] Fc-VWF-XTEN fusion protein-ehtl intravenous infusion – Bioverativ/Sanofi)

REVIEW DATE: 02/28/2024

OVERVIEW

Altuviiio, a recombinant DNA-derived Factor VIII concentrate, is indicated for use in **hemophilia A** in adults and children for:[1]
- **Routine prophylaxis** to reduce the frequency of bleeding episodes.
- **On-demand treatment and control** of bleeding episodes.
- **Perioperative management** of bleeding.

It is notable that Altuviiio has demonstrated a 3- to 4-fold prolonged half-life relative to other standard and extended half-life products.[1]

Disease Overview

Hemophilia A is an X-linked bleeding disorder primarily impacting males caused by a deficiency in Factor VIII.[2-5] In the US, the incidence of hemophilia A in males is 1:5,000 with an estimated 20,000 people in the US living with hemophilia A. The condition is characterized by bleeding in joints, either spontaneously or in a provoked joint by trauma. Bleeding can occur in many different body areas as well (e.g., muscles, central nervous system). The bleeding manifestations can lead to substantial morbidity such as hemophilic arthropathy. Disease severity is usually defined by the plasma levels or activity of Factor VIII classified as follows: severe (levels < 1% of normal), moderate (levels 1% to 5% of normal), and mild (levels > 5% to < 40% of normal); phenotypic expression may vary. Approximately 50% of patients with hemophilia A are categorized as having severe disease.

Guidelines

Guidelines have not addressed Altuviiio. Guidelines for hemophilia from the National Hemophilia Foundation (March 2023)[6] and the World Federation of Hemophilia (2020)[7] recognize the important role of Factor VIII products and Hemlibra® (emicizumab-kxwh subcutaneous injection) in the management of hemophilia A in patients. The National Bleeding Disorders Foundation recognize Altuviiio as a product with a prolonged half-life.

Dosing Considerations

Dosing of clotting factor concentrates is highly individualized. The National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC) provides recommendations regarding doses of clotting factor concentrate in the home (2016).[8] The number of required doses varies greatly and is dependent on the severity of the disorder and the prescribed regimen. Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough bleeding in addition to the prophylactic doses used monthly. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for prophylactic dosing plus three days of acute bleeding or perioperative management per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

Policy Statement
Prior Authorization is recommended for medical benefit coverage Altuviiio. Approval is recommended for those who meet the Criteria and Dosing for the listed indication. Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Altuviiio, as well as the monitoring required for adverse events and long-term efficacy, the agent is required to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Altuviiio is recommended for patients who meet the following criteria:

FDA-Approved Indication

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1. **Hemophilia A.** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Altuviiio is being used in at least ONE of the following scenarios (a, b, or c).
       - **a)** Routine prophylaxis; OR
       - **b)** On-demand treatment and control of bleeding episodes; OR
       - **c)** Perioperative management of bleeding; AND
     - **ii.** Patient meets BOTH of the following (a and b):
       - **a)** Factor VIII inhibitor testing has been performed within the last 30 days; AND
       - **b)** Patient does not have a positive test for Factor VIII inhibitors ≥ 0.6 Bethesda units/mL; AND
     - **iii.** Medication is prescribed by or in consultation with a hemophilia specialist; OR
   - **B)** Patient is Currently Receiving Altuviiio or Has Received Altuviiio in the Past. Approve if the patient meets the ALL of following (i, ii, and iii):
     - **i.** Altuviiio is being used in at least ONE of the following scenarios (a, b, or c):
       - **a)** Routine prophylaxis; OR
       - **b)** On-demand treatment and control of bleeding episodes; OR
       - **c)** Perioperative management of bleeding; AND
     - **ii.** Patient meets ONE of the following (a or b):
       - **a)** Patient meets BOTH of the following [(1) and (2)]:
         - **(1)** Factor VIII inhibitor testing has been performed within the last 30 days; AND
         - **(2)** Patient does not have a positive test for Factor VIII inhibitors ≥ 0.6 Bethesda units/mL; OR
       - **b)** According to the prescribing physician, patient does not have clinical manifestations suggesting the presence of Factor VIII inhibitors; AND
         Note: Inhibitors may be present if bleeding is not well controlled, there is decreased responsiveness to Factor VIII therapy, and/or if expected Factor VIII activity plasma levels are not achieved.
     - **iii.** Medication is prescribed by or in consultation with a hemophilia specialist.

   Dosing. Approve the following dosing regimens (A, B, and/or C):

A) Routine prophylaxis: approve up to 50 IU per kg intravenously no more frequently than once weekly; AND/OR
B) On demand treatment and control of bleeding episodes: approve up to 50 IU per kg intravenously with additional doses once every 2 to 3 days for up to 10 days per episode; AND/OR
C) Perioperative management of bleeding: approve up to 50 IU per kg intravenously and provide for additional doses once every 2 to 3 days for up to 10 days per procedure.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Altuviiio is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/29/2023
Annual Revision	No criteria changes.	02/28/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hemophilia – Eptacog Products – NovoSeven RT Utilization Management Medical Policy
- NovoSeven® RT (coagulation Factor VIIa [recombinant] intravenous infusion – Novo Nordisk)

REVIEW DATE: 11/08/2023

OVERVIEW

NovoSeven RT is indicated for the treatment of bleeding episodes and perioperative management in the following conditions:
- **Congenital Factor VII deficiency** in adults and children;
- **Glanzmann's thrombasthenia** with refractoriness to platelet transfusions in adults and children, with or without antibodies to platelets;
- **Hemophilia, acquired** in adults; and
- **Hemophilia A or B with inhibitors** in adults and children.[1]

Of note, off-label use of NovoSeven RT in the general population has been suggested in a variety of acute bleeding scenarios (e.g., trauma, intracranial hemorrhage). A 2012 Cochrane Review concluded that the effectiveness of recombinant activated Factor VIIa as a general hemostatic drug in non-hemophiliac patients remains unproven and that use outside its licensed indications should be limited to clinical trials.[2] Various reviews and clinical practice guidelines concur that the evidence is insufficient to support use of NovoSeven RT as a hemostatic agent outside of its labeled uses.[3-5]

Guidelines

The National Bleeding Disorders Foundation Medical and Scientific Advisory Council (MASAC) guidelines (updated August 2023) support NovoSeven RT as a treatment option for inherited **hemophilia A or B with inhibitors**, **acquired hemophilia A** (other forms of acquired hemophilia not addressed), and **Factor VII deficiency**.[6] Glanzmann's thrombasthenia is not addressed in the guideline. MASAC recommendations (2013) also state that recombinant Factor VIIa has demonstrated efficacy and safety for prophylactic use for patients with inhibitors in hemophilia A and hemophilia B.[7]

Regarding **hemophilia A and B with inhibitors**, World Federation of Hemophilia guidelines (2020) support recombinant Factor VIIa for patients with high-titer inhibitors who require acute treatment or around surgery/invasive procedures.[8] For low-titer inhibitors, Factor VIII or IX replacement may be used. These products may also be used for patients with a history of a high-titer inhibitor whose titer has fallen to low or undetectable levels. However, once an anamnestic response occurs, further treatment with Factor replacement is typically no longer effective, and bypass agent therapy (e.g., recombinant Factor VIIa) is needed. National Hemophilia Foundation MASAC guidelines (updated August 2020) have similar recommendations: treatment for patients with inhibitors depends on multiple factors, including type of inhibitor (high- or low-responding), current titer, location of bleed, and previous response.[6]

Dosing Information

Dosing of clotting factor concentrates is highly individualized. MASAC provides recommendations regarding doses of clotting factor concentrate in the home (2016).[9] The number of required doses varies greatly and is dependent on the severity of the disorder and the prescribed regimen. Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for

breakthrough episodes in addition to the prophylactic doses used monthly. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for prophylactic dosing plus three days of acute episodes or perioperative management per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

Dosing considerations for individual indications are as follows:

- **Congenital Factor VII Deficiency:** In the routine prophylactic setting, recombinant Factor VIIa dosing of up to 30 mcg/kg three times weekly has been described in the literature.[10] Per prescribing information, dosing for bleeding episodes and perioperative management ranges up to 30 mcg/kg up to every 4 hours (180 mcg/kg daily dose).[1]
- **Glanzmann's Thrombasthenia:** Prophylactic dosing is not routine. Per the prescribing information, dosing up to 90 mcg/kg every 2 hours may be used for acute episodes or perioperative management (1,080 mcg/kg daily dose).[1]
- **Hemophilia, Acquired:** Data are limited describing prophylactic use of recombinant Factor VIIa in acquired hemophilia; dosing is generally similar to what is used for congenital hemophilia A and B with inhibitors. Per the prescribing information, dosing up to 90 mcg/kg every 2 hours may be used for acute episodes or perioperative management (1,080 mcg/kg daily dose).[1]
- **Hemophilia A with Inhibitors** and **Hemophilia B with Inhibitors:** For congenital hemophilia A and B with inhibitors, MASAC recommendations note that doses of up to 270 mcg/kg per day have been found to be effective.[7] Per the prescribing information, dosing up to 50 mcg/kg per hour by continuous infusion may be used in the perioperative setting (1,200 mcg/kg daily dose).[1]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of NovoSeven RT. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with NovoSeven RT as well as the monitoring required for adverse events and long-term efficacy, approval requires NovoSeven RT to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of NovoSeven RT is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Congenital Factor VII Deficiency.** Approve for 1 year if NovoSeven RT is prescribed by or in consultation with a hemophilia specialist.

   Dosing. Approve up to 900 mcg/kg intravenously per 28 days.

2. **Glanzmann's Thrombasthenia.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is refractory to platelet transfusions; AND
   B) The medication is prescribed by or in consultation with a hematologist.

   Dosing. Approve up to 3,240 mcg/kg intravenously per 28 days.

3. **Hemophilia, Acquired.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) The medication is prescribed by or in consultation with a hemophilia specialist.

   Dosing. Approve up to 10,800 mcg/kg intravenously per 28 days.

4. **Hemophilia A with Inhibitors.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient meets one of the following (i, ii, or iii):
      i. Patient has a positive inhibitor titer ≥ 5 Bethesda Units; OR
      ii. Patient has a history of an inhibitor with anamnestic response to Factor VIII replacement therapy, which, according to the prescriber, precludes the use of Factor VIII replacement to treat bleeding episodes; OR
      iii. Patient has a history of an inhibitor with refractory hemostatic response to increased Factor VIII dosing, which, according to the prescriber, precludes the use of Factor VIII replacement to treat bleeding episodes; AND
   B) The medication is prescribed by or in consultation with a hemophilia specialist.

   Dosing. Approve up to 11,160 mcg/kg intravenously per 28 days.

5. **Hemophilia B with Inhibitors.** Approve for 1 year if the patient meets both of the following (A and B):
   A) Patient meets one of the following (i, ii, or iii):
      i. Patient has a positive inhibitor titer ≥ 5 Bethesda Units; OR
      ii. Patient has a history of an inhibitor with anamnestic response to Factor IX replacement therapy, which, according to the prescriber, precludes the use of Factor IX replacement to treat bleeding episodes; OR
      iii. Patient has a history of an inhibitor with refractory hemostatic response to increased Factor IX dosing, which, according to the prescriber, precludes the use of Factor IX replacement to treat bleeding episodes; AND
   B) The medication is prescribed by or in consultation with a hemophilia specialist.

   Dosing. Approve up to 11,160 mcg/kg intravenously per 28 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of NovoSeven RT is not recommended in the following situations:

1. **Bleeding Associated with Liver Disease.** Randomized trials have failed to show benefit of NovoSeven RT in controlling upper gastrointestinal bleeding and variceal bleeding in patients with advanced liver disease.[11,12] American Association for the Study of Liver Disease guidelines for portal

hypertensive bleeding in cirrhosis (2016) state that recombinant Factor VIIa should not be used to correct coagulopathy in this scenario.[13]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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2. Simpson E, Lin Y, Stanworth S, et al. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database Syst Rev.* 2012;3:CD005011.
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9. MASAC (Medical and Scientific Advisory Council) recommendations regarding doses of clotting factor concentrate in the home. MASAC Document #242. Adopted on June 7, 2016. Available at: https://www.hemophilia.org/sites/default/files/document/files/242.pdf. Accessed on November 5, 2023.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/02/2022
Annual Revision	No criteria changes.	11/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hemophilia – Eptacog Products – Sevenfact Utilization Management Medical Policy
- Sevenfact® (Factor VIIa [recombinant]-jncw intravenous infusion – LFB S.A./Hema Biologics)

REVIEW DATE: 11/08/2023

OVERVIEW

Sevenfact, a recombinant Factor VIIa product, is indicated for the treatment and control of bleeding episodes occurring in adults and adolescents (≥ 12 years of age) with **hemophilia A or B with inhibitors**.[1] As a limitation of use, Sevenfact is not indicated for the treatment of patients with congenital Factor VII deficiency.

Disease Overview

In hemophilia A and B, antibodies to exogenous clotting factor, known as "inhibitors", may develop. Approximately 30% of patients with severe hemophilia A and up to 5% of patients with severe hemophilia B develop inhibitors to Factor VIII or Factor IX during their lifetime.[2] A high-responding inhibitor (≥ 5 Bethesda Units [BU]) tends to persist, whereas low-responding inhibitors of < 5 BU may wane without changes to the treatment regimen. Presence of inhibitors is associated with higher disease burden, increased risk of musculoskeletal complications, pain, physical limitations, and treatment challenges.[2,3]

Dosing Information

Sevenfact is only indicated in the acute treatment setting for treatment of bleeding events. In the prescribing information, it is noted that maximum tolerated doses have not been determined for Sevenfact, and cumulative daily doses greater than 900 mcg/kg, which may be associated with greater risk of thromboembolic complications, have not been studied.[1] The National Hemophilia Foundation Medical and Scientific Advisory Council (MASAC) provides recommendations regarding doses of clotting factor concentrate in the home (2016).[4] Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough episodes. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for three days of acute bleeding per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

Guidelines

National Bleeding Disorders Foundation MASAC guidelines (revised August 2023) recognize both Sevenfact and NovoSeven RT® (coagulation Factor VIIa [recombinant] intravenous infusion) as treatments for **hemophilia A or B with inhibitors**.[5] No preference is stated for one agent over the other. It is noted that choice of product depends on multiple factors, including type of inhibitor (low- or high-responding), current titer, location of bleed, and previous response. Of note, NovoSeven RT, but not Sevenfact, is recognized as a treatment option in other settings, such as acquired hemophilia A and congenital Factor VII deficiency.

World Federation of Hemophilia (WFH) guidelines (2020) support recombinant Factor VIIa for patients with high-titer inhibitors who require acute treatment or around surgery/invasive procedures.[3] For low-titer inhibitors, Factor VIII or IX replacement may be used. These products may also be used for patients with a history of a high-titer inhibitor whose titer has fallen to low or undetectable levels. However, once an

anamnestic response occurs, further treatment with Factor replacement is typically no longer effective, and bypass agent therapy (e.g., recombinant Factor VIIa) is needed.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Sevenfact. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sevenfact as well as the monitoring required for adverse events and long-term efficacy, approval requires Sevenfact to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sevenfact is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. **Hemophilia A with Inhibitors.** Approve for 1 year if the patient meets all of the following (A, B, and C):
   - **A)** Patient is ≥ 12 years of age; AND
   - **B)** Patient meets one of the following (i, ii, or iii):
     - **i.** Patient has a positive inhibitor titer ≥ 5 Bethesda Units; OR
     - **ii.** Patient has a history of anamnestic response to Factor VIII replacement therapy, which, according to the prescriber, precludes the use of Factor VIII replacement to treat bleeding episodes; OR
     - **iii.** Patient has a history of refractory response to increased Factor VIII dosing, which, according to the prescriber, precludes the use of Factor VIII replacement to treat bleeding episodes; AND
   - **C)** The medication is prescribed by or in consultation with a hemophilia specialist.

   Dosing. Approve up to 2,700 mcg/kg intravenously per 28 days.

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2. **Hemophilia B with Inhibitors.** Approve for 1 year if the patient meets all of the following (A, B, and C):
   - **A)** Patient is ≥ 12 years of age; AND
   - **B)** Patient meets one of the following (i, ii, or iii):
     - **i.** Patient has a positive inhibitor titer ≥ 5 Bethesda Units; OR
     - **ii.** Patient has a history of anamnestic response to Factor IX replacement therapy, which, according to the prescriber, precludes the use of Factor IX replacement to treat bleeding episodes; OR
     - **iii.** Patient has a history of refractory response to increased Factor IX dosing, which, according to the prescriber, precludes the use of Factor IX replacement to treat bleeding episodes; AND
   - **C)** The medication is prescribed by or in consultation with a hemophilia specialist.

Dosing. Approve up to 2,700 mcg/kg intravenously per 28 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sevenfact is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Sevenfact® intravenous infusion [prescribing information]. Les Ulis, France/Louisville, KY: LFB S.A./Hema Biologics; November 2022.
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4. MASAC (Medical and Scientific Advisory Council) recommendations regarding doses of clotting factor concentrate in the home. MASAC Document #242. Adopted on June 7, 2016. Available at: https://www.hemophilia.org/sites/default/files/document/files/242.pdf. Accessed on November 5, 2023.
5. National Bleeding Disorders Foundation. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system (August 2023). MASAC Document #280. Available at: https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed on November 5, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/02/2022
Annual Revision	No criteria changes.	11/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hemophilia – Factor IX Products Utilization Management Medical Policy

Extended Half-Life Recombinant Products

- Alprolix® (Coagulation Factor IX [recombinant] Fc fusion protein intravenous infusion – Bioverativ/Sanofi)
- Idelvion® (Coagulation Factor IX [recombinant] albumin fusion protein intravenous infusion – CSL Behring)
- Rebinyn® (Coagulation Factor IX [recombinant] glycoPEGylated intravenous infusion – NovoNordisk)

Standard Half-Life Recombinant Products

- BeneFIX® (Coagulation Factor IX [recombinant] intravenous infusion – Wyeth/Pfizer)
- Ixinity® (Coagulation Factor IX [recombinant] intravenous infusion – Medexus)
- Rixubis® (Coagulation Factor IX [recombinant] intravenous infusion – Baxalta/Takeda)

Plasma-Derived Standard Half-Life Products

- AlphaNine® SD (Coagulation Factor IX [plasma-derived] intravenous infusion – Grifols)
- Profilnine® (Factor IX Complex [plasma-derived] intravenous infusion – Grifols)

REVIEW DATE: 02/28/2024

OVERVIEW

Alprolix, Idelvion, and Rebinyn are extended half-life recombinant Factor IX products; BeneFIX, Ixinity, and Rixubis are standard half-life recombinant Factor IX products; and AlphaNine SD and Profilnine are plasma-derived Factor IX products.[1-8] All agents are indicated in various clinical scenarios for use in the management of patients with hemophilia B.

Profilnine is also used in patients with Factor II and/or X deficiency.[9] Some data are available, albeit limited.

Disease Overview

Hemophilia B is a recessive X-linked bleeding disorder caused by mutations in the factor IX gene that leads to the deficiency or absence of the coagulation factor IX.[10-12] It occurs in 1 out of 30,000 male births and affects about 5,000 people in the US. Hemophilia B predominantly occurs in males; however, approximately 10% of females are carriers and are at risk of usually mild bleeding. The severity of bleeding depends on the degree of the factor IX defect and the phenotypic expression. Factor levels of < 1%, 1% to 5%, and > 5% to < 40% are categorized as severe, moderate, and mild hemophilia B, respectively. Patients with mild hemophilia B may only experience abnormal bleeding during surgery, during tooth extractions, or when injured. Patients with moderate hemophilia B generally have prolonged bleeding responses to minor trauma. Severe hemophilia B is marked by spontaneous bleeding such as spontaneous hemarthrosis, soft-tissue hematomas, retroperitoneal bleeding, intracerebral hemorrhage, and delayed bleeding post-surgery. Complications from recurrent bleeding and soft-tissue hematomas include severe arthropathy, and joint contractures, which may lead to pain and disability. The main treatment of hemophilia B is replacement of missing blood coagulation factor with Factor IX products. Factor IX replacement therapy may be used on-demand when bleeding occurs or given as routine prophylaxis with scheduled infusions. Both plasma-derived and recombinant Factor IX products are available. In general, prophylactic therapy

has been associated with a reduction in bleeds and improved outcomes for selected patients (e.g., patients with moderate or severe factor IX deficiency). The goal of therapy is to prevent uncontrolled internal hemorrhage and severe joint damage, and to properly manage bleeding episodes. The development of inhibitors occurs at a lower frequency in patients with severe hemophilia B compared with severe hemophilia A but can occur in up to 5% of patients. Higher doses than that typically used for the uses of standard half-life products can be given if the patient develops an inhibitor.

Guidelines

Guidelines for hemophilia from the National Bleeding Disorders Foundation (2023)[13] and the World Federation of Hemophilia (2020)[14] recognize the important role of Factor IX products in the management of hemophilia B patients.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of the following Factor IX products: Alprolix, Idelvion, Rebinyn, BeneFIX, Ixinity, Rixubis, AlphaNine, and Profilnine. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with recombinant Factor IX products, as well as the monitoring required for adverse events and long-term efficacy, the agent is required to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of the following Factor IX products is recommended for patients who meet criteria: Alprolix, Idelvion, Rebinyn, BeneFIX, Ixinity, Rixubis, AlphaNine, and Profilnine.

I. Coverage of Alprolix, Idelvion, Rebinyn, BeneFIX, Ixinity, and Rixubis is recommended for patients who meet the following criteria:

FDA-Approved Indication

1. Hemophilia B. Approve for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) For Alprolix, Idelvion, and Rebinyn approve the following dosing regimens (i, ii, and/or iii):
- **i.** Routine prophylaxis: approve up to 100 IU per kg intravenously at an interval no more frequently than once weekly; AND/OR;
- **ii.** On-demand treatment and control of bleeding episodes: approve up to 100 IU per kg intravenously no more frequently than once every 6 hours for up to 10 days per episode; AND/OR
- **iii.** Perioperative management: approve up to 100 IU per kg intravenously no more frequently than once every 24 hours for up to 10 days per procedure; OR

B) For BeneFIX, Ixinity, and Rixubis approve the following dosing regimens (i, ii, iii, and/or iv):

i. Routine prophylaxis: approve up to 100 IU per kg intravenously no more frequently than twice weekly; AND/OR
ii. On-demand treatment and control of bleeding episodes: approve up to 100 IU per kg intravenously no more frequently than once every 12 hours for up to 10 days per episode; AND/OR
iii. Perioperative management: approve up to 100 IU per kg intravenously no more frequently than once every 8 hours for up to 10 days per procedure; AND/OR
iv. Immune tolerance therapy (also known as immune tolerance induction): approve up to 200 IU per kg intravenously no more frequently than once daily.

II. Coverage of AlphaNine SD and Profilnine is recommended for patients who meet the following criteria:

FDA-Approved Indication

1. Hemophilia B. Approve AlphaNine SD and Profilnine for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

Dosing. Approve the following dosing regimens:
A) Routine prophylaxis: approve up to 50 IU per kg intravenously no more frequently than twice weekly; AND/OR
B) On-demand treatment of and control of bleeding episodes and perioperative management: approve up to 100 IU per kg intravenously no more frequently than twice daily for up to 10 days; AND/OR
C) Immune tolerance therapy (also known as immune tolerance induction): approve up to 200 IU per kg intravenously no more frequently than once daily.

III. Coverage of Profilnine is also recommended for patients who meet the following criteria:

Other Uses with Supportive Evidence

1. Factor II Deficiency. Approve Profilnine for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

Dosing. Limited dosing is available. Recommended dosing in hemophilia B (an FDA-approved use) is cited below.
A) Routine prophylaxis: approve up to 50 IU per kg intravenously no more frequently than twice weekly; AND/OR
B) On-demand treatment of and control of bleeding episodes and perioperative management: approve up to 100 IU per kg intravenously no more frequently than twice daily for up to 10 days.

2. Factor X Deficiency. Approve Profilnine for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

Dosing. Limited dosing is available. Recommended dosing in hemophilia B (an FDA-approved use) is cited below.
A) Routine prophylaxis: approve up to 50 IU per kg intravenously no more frequently than twice weekly; AND/OR

B) On-demand treatment of and control of bleeding episodes and perioperative management: approve up to 100 IU per kg intravenously no more frequently than twice daily for up to 10 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of the cited Factor IX products are not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Alprolix® intravenous infusion [prescribing information]. Waltham, MA: Bioverativ/Sanofi; May 2023.
2. Idelvion® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; June 2023.
3. Rebinyn® intravenous infusion [prescribing information]. Plainsboro, NJ: Novo Nordisk; August 2022.
4. BeneFIX® intravenous infusion [prescribing information]. Philadelphia, PA: Wyeth/Pfizer; November 2022.
5. Ixinity® intravenous infusion [prescribing information]. Chicago, IL: Medexus; November 2022.
6. Rixubis® intravenous infusion [prescribing information]. Lexington, MA: Baxalta/Takeda; March 2023.
7. AlphaNine® SD intravenous infusion [prescribing information]. Los Angeles, CA: Grifols; November 2022.
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9. Menegatti M, Peyvandi F. Treatment of rare factor deficiencies other than hemophilia. *Blood*. 2019;133(5):415-424.
10. Sidonio RF, Malec L. Hemophilia B (Factor IX Deficiency). *Hematol Oncol Clin North Am*. 2021;35(6):1143-1155.
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14. Srivastava A, Santagostino E, Dougall A, on behalf of the WFH guidelines for the management of hemophilia panelists and co-authors. Guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26(Suppl 6):1-158.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	03/22/2023
Annual Revision	Mononine was removed from the policy as it is obsolete.	02/28/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hemophilia – Factor VIII Products Utilization Management Medical Policy

Extended Half-Life Products

- Adynovate® (Antihemophilic Factor PEGylated intravenous infusion – Baxalta/Takeda)
- Eloctate® (Antihemophilic Factor Fc fusion protein intravenous infusion – Bioverativ/Sanofi)
- Esperoct® (Antihemophilic factor glycopegylated intravenous infusion – Novo Nordisk)
- Jivi® (Antihemophilic Factor PEGylated-aucl intravenous infusion – Bayer HealthCare)

Standard Half-Life Products

- Advate® (Antihemophilic Factor intravenous infusion – Baxalta/Takeda)
- Afstyla® (Antihemophilic Factor single chain intravenous infusion – CSL Behring)
- Kogenate® FS (Antihemophilic Factor intravenous infusion – Bayer HealthCare)
- Kovaltry® (Antihemophilic Factor intravenous infusion – Bayer HealthCare)
- Novoeight® (Antihemophilic Factor intravenous infusion – Novo Nordisk)
- Nuwiq® (Antihemophilic Factor intravenous infusion – Octapharma)
- Recombinate® (Antihemophilic Factor intravenous infusion – Baxalta/Takeda)
- Xyntha®/Xyntha® Solofuse™ (Antihemophilic Factor intravenous infusion, plasma/albumin-free – Wyeth/Pfizer)

Plasma-Derived Standard Half-Life Products without Von Willebrand Factor

- Hemofil® M (Antihemophilic Factor intravenous infusion – Baxalta/Takeda)

Plasma-Derived Standard Half-Life Products with Von Willebrand Factor

- Alphanate® (Antihemophilic Factor/von Willebrand Factor Complex [human] intravenous infusion – Grifols)
- Humate-P® (Antihemophilic Factor/von Willebrand Factor Complex intravenous infusion – CSL Behring)
- Koāte® (Antihemophilic Factor intravenous infusion – Grifols/Kedrion Biopharma)
- Wilate® (von Willebrand Factor/Coagulation Factor VIII Complex for intravenous infusion – Octapharma)

REVIEW DATE: 02/28/2024

OVERVIEW

For the management of hemophilia A, many recombinant Factor VIII products are available, including extended half-life products[1-4] (Adynovate, Eloctate, Esperoct, and Jivi) as well as standard half-life products (Advate, Afstyla, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, and Xyntha).[5-13] In general, these products are utilized in various clinical scenarios in the management of patients with hemophilia A. Several standard half-life Factor VIII plasma-derived products are available. Hemofil M is a plasma-derived standard half-life product that does not contain substantial amounts of von Willebrand Factor which is indicated for use in the management of hemophilia A.[14] Plasma-derived Factor VIII products that contain von Willebrand Factor include Alphanate, Humate P, Koate, and Wilate.[15-18] Alphanate, Humate P, and Wilate are indicated for use in clinical scenarios for the management of hemophilia A, as well as in patients with von Willebrand disease (VWD).[15,16,18] Wilate is the only agent FDA-approved for use in routine prophylaxis in children 6 years of age and older and adults with VWD.[18] However, the other agents have

been used in this clinical scenario as well.[29] Koate is indicated for the control and prevention of bleeding episodes or in order to perform emergency elective surgery in patients with hemophilia A.[17] This policy does not involve Altuviiio™ (antihemophilic factor [recombinant] Fc-VWF-XTEN fusion protein-ehtl intravenous infusion).[19]

Disease Overview

Hemophilia A is an X-linked bleeding disorder primarily impacting males caused by a deficiency in Factor VIII.[20-24] In the US, the incidence of hemophilia A in males is 1:5,000 with an estimated 20,000 people in the US living with hemophilia A. The condition is characterized by bleeding in joints, either spontaneously or in a provoked joint. Bleeding can occur in many different body areas as well (e.g., muscles, central nervous system). The bleeding manifestations can lead to substantial morbidity such as hemophilic arthropathy. Disease severity is usually defined by the plasma levels or activity of Factor VIII classified as follows: severe (levels < 1% of normal), moderate (levels 1% to 5% of normal), and mild (levels > 5% to < 40% of normal); phenotypic expression may vary. Approximately 50% of patients with hemophilia A are categorized as having severe disease which may require routine prophylactic Factor VIII therapy.

VWD is a group of inherited bleeding disorders related to defects of von Willebrand Factor (vWF), which is needed to achieve hemostasis.[25-27] It occurs equally in males and females. The disease leads to bleeding from impaired platelet adhesion and aggregation, which may be accompanied by reduced levels of factor VIII. Mucous membrane and skin bleeding symptoms, as well as bleeding with surgical or other hematostatic challenges may occur. The prevalence of the disease is approximately 1.3%. Pregnancy can increase vWF levels and confound the diagnosis. The three major subtypes of VWD include: partial quantitative vWF deficiency (type 1, 75% of patients); qualitative vWF deficiency (type 2, 25% of patients); and complete vWF deficiency (type 3, rare). Type 2 disease is further divided into four variants (2A, 2B, 2M, 2N) on the basis of the phenotype. In type 3 VWD, Factor VIII levels are usually very low. Acquired von Willebrand syndrome may result but is rare, occurring in fewer than one in 100,000 adults. The bleeding risk varies between modest increases in bleeding which occur only with procedures to a major risk of spontaneous hemorrhage. Approaches to the management of VWD involve increasing plasma concentrations of vWF through stimulation with desmopressin, replacing vWF by using human plasma-derived viral inactivated concentrates, promoting hemostasis by use of hemostatic agents with mechanisms other than increasing vWF, and Vonvendi® (von Willebrand factor [recombinant] intravenous infusion). Regular prophylaxis is not frequently required.

Guidelines

Guidelines for hemophilia from the National Hemophilia Foundation (2023)[20] and the World Federation of Hemophilia (2020)[28] recognize the important role of Factor VIII products in the management of hemophilia A. Also, Factor VIII products that contain vWF have a role in the management of VWD.[23]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of the following Factor VIII products: Adynovate, Eloctate, Esperoct, Jivi, Advate, Afstyla, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, Xyntha, Hemofil M, Alphanate, Humate-P, Koate, and Wilate. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with recombinant Factor VIII products, as well as

the monitoring required for adverse events and long-term efficacy, the agent is required to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Adynovate, Eloctate, Esperoct, Jivi, Advate, Afstyla, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, and Xyntha is recommended in those who meet the following criteria.

FDA-Approved Indication

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1. Hemophilia A. Approve the requested agent for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) For Adynovate, Eloctate, Esperoct, and Jivi approve the following dosing regimens (i, ii, and/or iii):
- **i.** Routine prophylaxis: approve up to 100 IU per kg intravenously no more frequently than twice weekly; AND/OR
- **ii.** On-demand treatment and control of bleeding episodes: approve up to 65 IU per kg intravenously no more frequently than once every 8 hours for up to 10 days per episode; AND/OR
- **iii.** Perioperative management: approve up to 65 IU per kg intravenously no more frequently than once every 6 hours for up to 10 days per procedure; OR

B) For Advate, Afstyla, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, and Xyntha approve the following dosing regimens (i, ii, iii, and/or iv):
- **i.** Routine prophylaxis: approve up to 60 IU per kg intravenously no more frequently than every other day (three or four times weekly); AND/OR
- **ii.** On-demand treatment and control of bleeding episodes: approve up to 50 IU per kg intravenously no more frequently than once every 6 hours for up to 10 days per episode; AND/OR
- **iii.** Perioperative management: approve up to 60 IU per kg intravenously no more frequently than once every 6 hours for up to 10 days per procedure; AND/OR
- **iv.** Immune tolerance therapy (also known as immune tolerance induction): approve up to 200 IU per kg intravenously no more frequently than once daily.

II. Coverage of Hemofil M and Koate is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. Hemophilia A. Approve for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

Dosing. Approve the following dosing regimens (A, B, and/or C):

A) Routine prophylaxis: approve up to 50 IU per kg intravenously no more frequently than every other day (three or four times weekly); AND/OR

B) On-demand treatment and control of bleeding episodes and perioperative management: approve up to 50 IU per kg intravenously no more frequently than once every 6 hours for up to 10 days per episode or procedure; AND/OR
C) Immune tolerance therapy (also known as immune tolerance induction): approve up to 200 IU per kg intravenously no more frequently than once daily.

III. Coverage of Alphanate, Humate-P, and Wilate is recommended in those who meet the following criteria:

FDA-Approved Indications

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1. Hemophilia A. Approve for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

Dosing. Approve the following dosing regimens (A, B, and/or C):
A) Routine prophylaxis: approve up to 50 IU per kg intravenously no more frequently than every other day (three or four times weekly); AND/OR
B) On-demand treatment and control of bleeding episodes and perioperative management: approve up to 50 IU per kg intravenously no more frequently than once every 6 hours for up to 10 days per episode or procedure; AND/OR
C) Immune tolerance therapy (also known as immune tolerance induction): approve up to 200 IU per kg intravenously no more frequently than once daily.

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2. Von Willebrand Disease. Approve for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

Dosing. Approve the following dosing regimens (A and/or B):
A) On-demand treatment and control of bleeding episodes and perioperative management: approve up to 80 IU VWF:RCo (Von Willebrand Factor activity as measured with the Ristocetin cofactor assay) per kg intravenously no more frequently than once every 8 hours for up to 10 days per episode or procedure; AND/OR
B) Routine prophylaxis: approve up to 40 IU VWF:RCo per kg intravenously no more frequently than once every 2 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of the cited Factor VIII Products is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Adynovate® intravenous infusion [prescribing information]. Lexington, MA: Baxalta/Takeda; August 2023.
2. Eloctate® intravenous infusion [prescribing information]. Waltham, MA: Bioverativ/Sanofi; May 2023.
3. Jivi® intravenous infusion [prescribing information]. Whippany, NJ: Bayer; August 2018.
4. Esperoct® intravenous infusion [prescribing information]. Plainsboro, NJ: Novo Nordisk; August 2022.
5. Advate® intravenous infusion [prescribing information]. Lexington, MA: Baxalta/Takeda; March 2023.
6. Kovaltry® intravenous infusion [prescribing information]. Whippany, NJ: Bayer; December 2022.
7. Afstyla® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; April 2021.

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8. Kogenate® FS lyophilized powder for reconstitution for intravenous infusion [prescribing information]. Whippany, NJ: Bayer; December 2019.
9. Novoeight® intravenous infusion [prescribing information]. Plainsboro, NJ: Novo Nordisk; July 2020.
10. Nuwiq® intravenous infusion [prescribing information]. Paramus, NJ: Octapharma; June 2021.
11. Recombinate™ intravenous infusion [prescribing information]. Lexington, MA: Baxalta/Takeda; March 2023.
12. Xyntha® intravenous infusion [prescribing information]. Philadelphia, PA: Wyeth/Pfizer; July 2022.
13. Xyntha® Solofuse™ intravenous infusion [prescribing information]. Philadelphia, PA: Wyeth/Pfizer; July 2022.
14. Hemofil® M intravenous infusion [prescribing information]. Lexington, MA: Baxalta/Takeda; March 2023.
15. Alphanate® intravenous infusion [prescribing information]. Los Angeles, CA: Grifols; November 2022.
16. Humate-P® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; June 2020.
17. Koāte® intravenous infusion [prescribing information]. Fort Lee, NJ and Research Triangle Park, NC: Kedrion and Grifols; June 2018.
18. Wilate® intravenous infusion [prescribing information]. Hoboken, NJ: Octapharma; December 2023.
19. Altuviiio™ intravenous infusion [prescribing information]. Waltham, MA: Bioverativ/Sanofi; March 2023.
20. National Bleeding Disorders Foundation. Medical and Scientific Advisory Council (MASAC) recommendations concerning products licensed for the treatment of hemophilia selected disorders of the coagulation system (Revised August 19, 2023 and endorsed on August 20, 2023). MASAC document #280. Available at: https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed on February 22, 2024.
21. Mancuso ME, Mahlangu JN, Pipe SW. The changing treatment landscape in haemophilia: from standard half-life clotting factor concentrates to gene editing. *Lancet*. 2021;397:630-640.
22. Croteau SE. Hemophilia A/B. *Hematol Oncol Clin North Am*. 2022;36(4):797-812.
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24. Peyvandi F, Garagiola I, Young G. The past and future of haemophilia: diagnosis, treatments and its complications. *Lancet*. 2016;388(10040):187-197.
25. Neff AT, Sidonio RF. Management of VWD. *Hematology Am Soc Hematol Educ Program*. 2014;(1):536-541.
26. Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (vWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Report (USA). *Haemophilia*. 2008;14(2):171-232.
27. Favaloro EJ, Bodo I, Israels SJ, Brown SA. Von Willebrand disease and platelet disorders. *Hemophilia*. 2014;20(Suppl 4):59-64.
28. Srivastava A, Santagostino E, Dougall A, on behalf of the WFH guidelines for the management of hemophilia panelists and co-authors. Guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26(Suppl 6):1-158.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Removed Helixate/Helixate FS and Monoclate P from the policy as both products are obsolete.	03/22/2023
Selected Revision	Added dosing for Humate P, Alphanate, and Wilate for Von Willebrand disease for routine prophylaxis.	12/13/2023
Annual Revision	No criteria changes.	02/28/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hemophilia – FEIBA Utilization Management Medical Policy
- Hemophilia – FEIBA® (anti-inhibitor coagulant complex intravenous infusion – Baxalta/Takeda)

REVIEW DATE: 11/08/2023

OVERVIEW

FEIBA, a human plasma fraction with Factor VIII bypassing activity, is indicated for use in **hemophilia A and B patients with inhibitors** for control and prevention of bleeding episodes, perioperative management, and routine prophylaxis to prevent or reduce the frequency of bleeding episodes.[1] It contains both activated and inactivated forms of Factors II, VII, IX, and X and is thus referred to as activated prothrombin complex concentrate (aPCC).[1,2] FEIBA is produced from pooled human plasma.[1]

Guidelines

Regarding **hemophilia A with inhibitors** and **hemophilia B with inhibitors** (without history of anaphylaxis/allergy to Factor IX), World Federation of Hemophilia guidelines (2020) support aPCC for patients with high-titer inhibitors who require acute treatment or around surgery/invasive procedures.[3] For low-titer inhibitors, Factor VIII or IX replacement may be used. These products may also be used for patients with a history of a high-titer inhibitor whose titer has fallen to low or undetectable levels. However, once an anamnestic response occurs, further treatment with Factor replacement is typically no longer effective, and bypass agent therapy (e.g., aPCC) is needed. National Bleeding Disorders Foundation Medical and Scientific Advisory Council (MASAC) guidelines (updated August 2023) have similar recommendations: treatment for patients with inhibitors depends on multiple factors, including type of inhibitor (high- or low-responding), current titer, location of bleed, and previous response.[2]

Dosing Information

Dosing of clotting factor concentrates is highly individualized. MASAC provides recommendations regarding doses of clotting factor concentrate in the home (2016).[4] The number of required doses varies greatly and is dependent on the severity of the disorder and the prescribed regimen. Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough episodes in addition to the prophylactic doses used monthly. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for prophylactic dosing plus three days of acute episodes or perioperative management per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

Dosing considerations for individual indications are as follows:

- **Hemophilia A with Inhibitors** and **Hemophilia B with Inhibitors:** For routine prophylaxis, a dose of 85 units/kg every other day is recommended.[1] Dosing for acute episodes and perioperative management can range up to 100 units/kg every 6 hours (400 units/kg daily dose).

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of FEIBA. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing

documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with FEIBA as well as the monitoring required for adverse events and long-term efficacy, approval requires this agent to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of FEIBA is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Hemophilia A with Inhibitors.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient meets one of the following (i, ii, or iii):
     - **i.** Patient has a positive inhibitor titer ≥ 5 Bethesda Units; OR
     - **ii.** Patient has a history of an inhibitor with anamnestic response to Factor VIII replacement therapy, which, according to the prescriber, precludes the use of Factor VIII replacement to treat bleeding episodes; OR
     - **iii.** Patient has a history of an inhibitor with refractory hemostatic response to increased Factor VIII dosing, which, according to the prescriber, precludes the use of Factor VIII replacement to treat bleeding episodes; AND
   - **B)** The medication is prescribed by or in consultation with a hemophilia specialist.

   Dosing. Approve up to a maximum of 2,390 units/kg intravenously per 28 days.

2. **Hemophilia B with Inhibitors.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient meets one of the following (i, ii, or iii):
     - **i.** Patient has a positive inhibitor titer ≥ 5 Bethesda Units; OR
     - **ii.** Patient has a history of an inhibitor with anamnestic response to Factor IX replacement therapy, which, according to the prescriber, precludes the use of Factor IX replacement to treat bleeding episodes; OR
     - **iii.** Patient has a history of an inhibitor with refractory hemostatic response to increased Factor IX dosing, which, according to the prescriber, precludes the use of Factor IX replacement to treat bleeding episodes; AND
   - **B)** The medication is prescribed by or in consultation with a hemophilia specialist.

   Dosing. Approve up to a maximum of 2,390 units/kg intravenously per 28 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of FEIBA is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. FEIBA® intravenous infusion [prescribing information]. Lexington, MA: Baxalta/Takeda; March 2023.
2. National Bleeding Disorders Foundation. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system (August 2023). MASAC Document #280. Available at: https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed on November 5, 2023.
3. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26 Suppl 6:1-158.
4. MASAC (Medical and Scientific Advisory Council) recommendations regarding doses of clotting factor concentrate in the home. MASAC Document #242. Adopted on June 7, 2016. Available at: https://www.hemophilia.org/sites/default/files/document/files/242.pdf. Accessed on November 8, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/02/2022
Annual Revision	No criteria changes.	11/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hemophilia – Gene Therapy – Beqvez Utilization Management Medical Policy
- Beqvez™ (fidanacogene elaparvovec-dzkt intravenous infusion – Pfizer)

REVIEW DATE: 05/15/2024

OVERVIEW

Beqvez, an adeno-associated virus (AAV) vector-based gene therapy, is indicated for the treatment of **hemophilia B** (congenital Factor IX deficiency) in adults with moderate to severe disease who: 1) currently use Factor IX prophylaxis therapy; or 2) have current or historical life-threatening hemorrhage; or 3) have repeated, serious spontaneous bleeding episodes, AND do not have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid as detected by an FDA-approved test.[1] The recommended dose of Beqvez is 5 x 10^{11} vector genomes per kg of body weight given as a one-time (per lifetime) single dose as an intravenous infusion. Dose based on adjusted body weight for those with a body mass index > 30 kg/m^2.

Disease Overview

Hemophilia B is a genetic bleeding disorder caused by missing or insufficient levels of blood Factor IX, a protein required to produce blood clots to halt bleeding.[2-5] The condition is a rare X-linked bleeding disorder that mainly impacts males. Hemophilia B is four times less common than hemophilia A, which is caused by a relative lack of blood Factor VIII. Approximately 30,000 individuals are living with hemophilia in the US and hemophilia B accounts for around 15% to 20% of hemophilia cases, or around 6,000 patients. Symptoms include heavy or prolonged bleeding following an injury or after a medical procedure. Bleeding can also occur internally into joints, muscles, or internal organs. Spontaneous bleeding events may also occur. Complications in patients with hemophilia B include joint disease and hemarthrosis. Hemophilia B may be diagnosed when bleeding occurs in infancy or later in life for those with milder disease. There is a strong correlation between Factor IX levels and phenotypic expression of bleeding. Normal plasma levels of Factor IX range from 50% to 150%. The disease is classified based on reduced levels. Mild, moderate, and severe hemophilia B is characterized by Factor IX levels ranging from 6% up to 49%, 1% up to 5%, and < 1%, respectively. Besides gene therapies for the treatment of hemophilia B, Factor IX products, both recombinant and plasma-derived, are used routinely to prevent bleeding or are given on-demand to treat bleeding episodes associated with hemophilia B.

Clinical Efficacy

The efficacy of Beqvez was evaluated in one ongoing, prospective, open-label, single-arm, single-dose, multinational, Phase III pivotal trial called BENEGENE-2 involving adult males with moderately severe to severe hemophilia B (Factor IX activity ≤ 2%) [n = 45].[1] All patients completed a prospective lead-in period of at least 6 months in which baseline data were collected while patients were receiving Factor IX products for routine prophylaxis. However, after receipt of Beqvez, use of such products for routine prophylaxis was to be suspended. The trial is ongoing with a planned long-term follow-up of 6 years. Patients were required to be negative for pre-existing neutralizing antibodies to AAVRh74var capsid to participate. Factor IX inhibitors (or a history), uncontrolled human immunodeficiency virus (HIV) infection, or significant liver fibrosis were exclusion criteria. Adequate hepatic and renal function were required. The median follow-up was 2.0 years (range 0.4 to 3.2 years) post-Beqvez administration. The model-derived mean annualized bleeding rate was 4.5 bleeds/year during the baseline lead-in period vs. 2.5 bleeds/year during the post-Beqvez efficacy evaluation period. In total, 60% of patients did not experience any bleeds after receipt of Beqvez; only 29% of patients did not have bleeds in the baseline lead-in period.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Beqvez. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Beqvez as well as the monitoring required for adverse events and long-term efficacy, approval requires Beqvez to be prescribed by a physician who specializes in the condition being treated. All approvals are provided for one-time (per lifetime) as a single dose. If claims history is available, verification is required for certain criteria as noted by **[verification in claims history required]**. For the dosing criteria, verification of the appropriate weight-based dosing is required by a Medical Director as noted by **[verification required]**. In the criteria for Beqvez, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation.

Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with EviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

Documentation: Documentation is required for use of Beqvez as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory results, medical test results, claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Bezvez is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Hemophilia B.** Approve a one-time (per lifetime) single dose if the patient meets ALL of the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, and Q):
   - **A)** Patient is male*; AND
   - **B)** Patient is ≥ 18 years of age; AND
   - **C)** Patient has not received a gene therapy for hemophilia B in the past **[verification in claims history required]**; AND
     Note: If no claim for Beqvez or Hemgenix (etranacogene dezaparvovec-drlb intravenous infusion) is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Beqvez or Hemgenix.
   - **D)** Patient has moderately severe or severe hemophilia B as evidenced by a baseline (without Factor IX replacement therapy) Factor IX level ≤ 2% of normal **[documentation required]**; AND
   - **E)** Patient meets ONE of the following (i, ii, or iii):
     - **i.** According to the prescribing physician, the patient has a history of use of Factor IX therapy for ≥ 150 exposure days; OR
     - **ii.** Patient meets BOTH of the following (a and b):
       - **a)** Patient has a history of life-threatening hemorrhage; AND
       - **b)** On-demand use of Factor IX therapy was required for this life-threatening hemorrhage; OR

iii. Patient meets BOTH of the following (a and b):
- **a)** Patient has a history of repeated, serious spontaneous bleeding episodes; AND
- **b)** On-demand use of Factor IX therapy was required for these serious spontaneous bleeding episodes; AND

F) Patient does not have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid by an approved test **[documentation required]**; AND

G) Patient meets ALL of the following (i, ii, and iii):
- **i.** Factor IX inhibitor titer testing has been performed within 30 days **[documentation required]**; AND
- **ii.** Patient is negative for Factor IX inhibitors **[documentation required]**; AND
- **iii.** Patient does not have a history of Factor IX inhibitors **[documentation required]**; AND

H) Prophylactic therapy with Factor IX will not be given after Beqvez administration once adequate Factor IX levels have been achieved; AND
Note: Use of episodic Factor IX therapy is acceptable for the treatment of bleeds and for surgery/procedures if needed as determined by the hemophilia specialist physician.

I) Patient meets BOTH of the following (i and ii):
- **i.** Patient does not have an active infection with hepatitis B virus or hepatitis C virus **[documentation required]**; AND
- **ii.** Patient is not currently receiving antiviral therapy for a prior hepatitis B virus or hepatitis C virus exposure **[documentation required]**; AND

J) According to the prescribing physician, the patient does not have uncontrolled human immunodeficiency virus infection; AND

K) Patient has undergone liver function testing within 30 days and meets ALL of the following (i, ii, iii, and iv):
- **i.** Alanine aminotransferase level is ≤ two times the upper limit of normal **[documentation required]**; AND
- **ii.** Aspartate aminotransferase level is ≤ two times the upper limit of normal **[documentation required]**; AND
- **iii.** Total bilirubin level is ≤ 1.5 times the upper limit of normal **[documentation required]**; AND
- **iv.** Alkaline phosphatase level is ≤ two times the upper limit of normal **[documentation required]**; AND

L) Patient does not have evidence of advanced liver impairment and/or advanced fibrosis; AND
Note: For example, liver elastography (e.g., ≥ 9 kPA) suggestive of or equal to METAVIR Stage 3 disease.

M) Within 30 days, the platelet count was ≥ 100 x 10^9/L **[documentation required]**; AND

N) Within 30 days, creatinine was ≤ 2.0 mg/dL **[documentation required]**; AND

O) The medication is prescribed by a hemophilia specialist physician; AND

P) Current patient body weight has been obtained within 30 days **[documentation required]**; AND

Q) If criteria A through P are met, approve one dose (vials in a kit) of Beqvez to provide for a one-time (per lifetime) single dose of 5 x 10^{11} vector genomes per kg of body weight by intravenous infusion **[verification required]**. Table 1 provides the number of vials per kit and the National Drug Codes (NDCs) for each kit.
Note: Dose based on adjusted body weight for those with a body mass index > 30 kg/m^2 using the following calculation: Dose Weight (kg) = 30 kg/m^2 x [Height (m)]^2

***** Refer to the Policy Statement.

Dosing. The recommended dose of Beqvez is a one-time (per lifetime) single dose of 5 x 10^{11} vector genomes per kg of body weight by intravenous infusion.

Note: Dose based on adjusted body weight for those with a body mass index > 30 kg/m^2 using the following calculation: Dose Weight (kg) = 30 kg/m^2 x [Height (m)]^2

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Beqvez is not recommended in the following situations:

1. **Prior Receipt of Gene Therapy.** Prior receipt of gene therapy was a reason for patient exclusion in the pivotal study.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

Table 1. Beqvez Multi-Vial Kits.[1]

Patient Dose Weight	Total Number of Vials per Kit	NDC Number
≤ 75 kg	4	0069-2004-04
> 75 to ≤ 95 kg	5	0069-2005-05
> 95 to ≤ 115 kg	6	0069-2006-06
> 115 to ≤ 135 kg	7	0069-2007-07

NDC – National Drug Code.

REFERENCES

1. Beqvez™ intravenous infusion [prescribing information]. New York, NY: Pfizer; April 2024.
2. National Bleeding Disorders Foundation. Hemophilia B. An overview of symptoms, genetics, and treatments to help you understand hemophilia B. Available at: https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-b. Accessed on May 3, 2024.
3. Sidonio RF, Malec L. Hemophilia (Factor IX deficiency). *Hematol Oncol Clin N Am*. 2021;35:1143-1155.
4. Mancuso ME, Mahlangu JN, Pipe SW. The changing treatment landscape in haemophilia: from standard half-life clotting factor concentrates to gene editing. *Lancet*. 2021;397:630-640.
5. Croteau SE. Hemophilia A/B. *Hematol Oncol Clin N Am*. 2022;36:797-812.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	05/15/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hemophilia – Gene Therapy – Hemgenix Utilization Management Medical Policy
- Hemgenix® (etranacogene dezaparvovec-drlb intravenous infusion – CSL Behring and uniQure)

REVIEW DATE: 02/28/2024; selected revision 05/15/2024

OVERVIEW

Hemgenix, an adeno-associated virus (AAV) vector-based gene therapy, is indicated for the treatment of adults with **hemophilia B** (congenital Factor IX deficiency) who: 1) currently use Factor IX prophylaxis therapy; or 2) have current or historical life-threatening hemorrhage; or 3) have repeated, serious spontaneous bleeding episodes.[1,2] The recommended dose of Hemgenix is 2 x 10^{13} genome copies per kg of body weight given as a one-time (per lifetime) single dose as an intravenous infusion.

Disease Overview

Hemophilia B is a genetic bleeding disorder caused by missing or insufficient levels of blood Factor IX, a protein required to produce blood clots to halt bleeding.[3-6] The condition is a rare X-linked bleeding disorder that mainly impacts males. Hemophilia B is four times less common than hemophilia A, which is caused by a relative lack of blood Factor VIII. Approximately 30,000 individuals are living with hemophilia in the US and hemophilia B accounts for around 15% to 20% of hemophilia cases, or around 6,000 patients. Symptoms include heavy or prolonged bleeding following an injury or after a medical procedure. Bleeding can also occur internally into joints, muscles, or internal organs. Spontaneous bleeding events may also occur. Complications in patients with hemophilia B include joint disease and hemarthrosis. Hemophilia B may be diagnosed when bleeding occurs in infancy or later in life for those with milder disease. There is a strong correlation between Factor IX levels and phenotypic expression of bleeding. Normal plasma levels of Factor IX range from 50% to 150%. The disease is classified based on reduced levels. Mild, moderate, and severe hemophilia B is characterized by Factor IX levels ranging from 6% up to 49%, 1% up to 5%, and < 1%, respectively. Besides gene therapies for the treatment of hemophilia B, Factor IX products, both recombinant and plasma-derived, are used routinely to prevent bleeding or are given on-demand to treat bleeding episodes associated with hemophilia B.

Clinical Efficacy

The efficacy of Hemgenix was evaluated in a prospective, open-label, single-dose, single-arm, multinational pivotal study called HOPE-B that involved 54 adult males with moderately severe or severe hemophilia B (Factor IX levels ≤ 2%).[1] Patients prospectively completed a lead-in period of at least 6 months in which standard care routine Factor IX prophylaxis therapy was given. This was followed by a single intravenous dose of Hemgenix. Patients were permitted to continue Factor IX prophylaxis during Months 0 to 6 after dosing, if needed, until Factor IX levels were adequate. Prior to screening, patients had been on stable prophylactic therapy for at least 2 months and had greater than 150 exposure days of treatment with a Factor IX product.[2] Factor IX inhibitors (or a history), uncontrolled human immunodeficiency virus (HIV) infection, or advanced liver fibrosis prevented participation. Adequate hepatic and renal function were required. The estimated mean annualized bleeding rate during Months 7 to 18 following Hemgenix treatment was 1.9 bleeds/year compared with 4.1 bleeds/year during the lead-in period (before Hemgenix administration).[1] At 18 months after treatment, Factor IX activity had increased by 34.3%. The HOPE-B trial is ongoing.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Hemgenix. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Hemgenix as well as the monitoring required for adverse events and long-term efficacy, approval requires Hemgenix to be prescribed by a physician who specializes in the condition being treated. All approvals are provided for one-time (per lifetime) as a single dose. If claims history is available, verification is required for certain criteria as noted by **[verification in claims history required]**. For the dosing criteria, verification of the appropriate weight-based dosing is required by a Medical Director as noted by **[verification required]**. In the criteria for Hemgenix, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation.

Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with EviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

Documentation: Documentation is required for use of Hemgenix as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory results, medical test results, claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Hemgenix is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Hemophilia B.** Approve a one-time (per lifetime) single dose if the patient meets ALL of the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, and P):
   - **A)** Patient is male*; AND
   - **B)** Patient is ≥ 18 years of age; AND
   - **C)** Patient has not received a gene therapy for hemophilia B in the past **[verification in claims history required]**; AND
     Note: If no claim for Hemgenix or Beqvez (fidanacogene elaparvovec intravenous infusion) is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Hemgenix or Beqvez.
   - **D)** Patient has moderately severe or severe hemophilia B as evidenced by a baseline (without Factor IX replacement therapy) Factor IX level ≤ 2% of normal **[documentation required]**; AND
   - **E)** Patient meets ONE of the following (i, ii, or iii):
     - **i.** According to the prescribing physician, the patient has a history of use of Factor IX therapy for ≥ 150 exposure days; OR
     - **ii.** Patient meets BOTH of the following (a and b):
       - **a)** Patient has a history of life-threatening hemorrhage; AND
       - **b)** On-demand use of Factor IX therapy was required for this life-threatening hemorrhage; OR

iii. Patient meets BOTH of the following (a and b):
- **a)** Patient has a history of repeated, serious spontaneous bleeding episodes; AND
- **b)** On-demand use of Factor IX therapy was required for these serious spontaneous bleeding episodes; AND

F) Patient meets ALL of the following (i, ii, and iii):
- **i.** Factor IX inhibitor titer testing has been performed within 30 days **[documentation required]**; AND
- **ii.** Patient is negative for Factor IX inhibitors **[documentation required]**; AND
- **iii.** Patient does not have a history of Factor IX inhibitors **[documentation required]**; AND

G) Prophylactic therapy with Factor IX will not be given after Hemgenix administration once adequate Factor IX levels have been achieved; AND
Note: Use of episodic Factor IX therapy is acceptable for the treatment of bleeds and for surgery/procedures if needed as determined by the hemophilia specialist physician.

H) Patient meets BOTH of the following (i and ii):
- **i.** Patient does not have an active infection with hepatitis B virus or hepatitis C virus **[documentation required]**; AND
- **ii.** Patient is not currently receiving antiviral therapy for a prior hepatitis B virus or hepatitis C virus exposure **[documentation required]**; AND

I) According to the prescribing physician, the patient does not have uncontrolled human immunodeficiency virus infection; AND

J) Patient has undergone liver function testing within 30 days and meets ALL of the following (i, ii, iii, and iv):
- **i.** Alanine aminotransferase level is ≤ two times the upper limit of normal **[documentation required]**; AND
- **ii.** Aspartate aminotransferase level is ≤ two times the upper limit of normal **[documentation required]**; AND
- **iii.** Total bilirubin level is ≤ two times the upper limit of normal **[documentation required]**; AND
- **iv.** Alkaline phosphatase level is ≤ two times the upper limit of normal **[documentation required]**; AND

K) Patient does not have evidence of advanced liver impairment and/or advanced fibrosis; AND
Note: For example, liver elastography (e.g., ≥ 9 kPA) suggestive of or equal to METAVIR Stage 3 disease.

L) Within 30 days, the platelet count was ≥ 50 x 10^9/L **[documentation required]**; AND

M) Within 30 days, patient meets ONE of the following (i or ii):
- **i.** Patient has an estimated creatinine clearance ≥ 30 mL/min **[documentation required]**; OR
- **ii.** Creatinine level is ≤ two times the upper limit of normal **[documentation required]**; AND

N) The medication is prescribed by a hemophilia specialist physician; AND

O) Current patient body weight has been obtained within 30 days **[documentation required]**; AND

P) If criteria A through O are met, approve one dose (kit) of Hemgenix to provide for a one-time (per lifetime) single dose of 2 x 10^{13} genome copies per kg of body weight by intravenous infusion **[verification required]**. Table 1 provides the kit size and the National Drug Codes (NDCs).

***** Refer to the Policy Statement.

Dosing. The recommended dose of Hemgenix is a one-time (per lifetime) single dose of 2 x 10^{13} genome copies per kg of body weight by intravenous infusion.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Hemgenix is not recommended in the following situations:

1. **Prior Receipt of Gene Therapy.** Prior receipt of gene therapy was a reason for patient exclusion in the pivotal study.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

Table 1. Hemgenix Multi-Vial Kits.[1]

Total Number of Vials per Kit	Patient Body Weight	Total Volume per Kit	NDC Number
10	46 to 50 kg	100	0053-0100-10
11	51 to 55 kg	110	0053-0110-11
12	56 to 60 kg	120	0053-0120-12
13	61 to 65 kg	130	0053-0130-13
14	66 to 70 kg	140	0053-0140-14
15	71 to 75 kg	150	0053-0150-15
16	76 to 80 kg	160	0053-0160-16
17	81 to 85 kg	170	0053-0170-17
18	86 to 90 kg	180	0053-0180-18
19	91 to 95 kg	190	0053-0190-19
20	96 to 100 kg	200	0053-0200-20
21	101 to 105 kg	210	0053-0210-21
22	106 to 110 kg	220	0053-0220-22
23	111 to 115 kg	230	0053-0230-23
24	116 to 120 kg	240	0053-0240-24
25	121 to 125 kg	250	0053-0250-25
26	126 to 130 kg	260	0053-0260-26
27	131 to 135 kg	270	0053-0270-27
28	136 to 140 kg	280	0053-0280-28
29	141 to 145 kg	290	0053-0290-29
30	146 to 150 kg	300	0053-0300-30
31	151 to 155 kg	310	0053-0310-31
32	156 to 160 kg	320	0053-0320-32
33	161 to 165 kg	330	0053-0330-33
34	166 to 170 kg	340	0053-0340-34
35	171 to 175 kg	350	0053-0350-35
36	176 to 180 kg	360	0053-0360-36
37	181 to 185 kg	370	0053-0370-37
38	186 to 190 kg	380	0053-0380-38
39	191 to 195 kg	390	0053-0390-39
40	196 to 200 kg	400	0053-0400-40
41	201 to 205 kg	410	0053-0410-41
42	206 to 210 kg	420	0053-0420-42
43	211 to 215 kg	430	0053-0430-43
44	216 to 220 kg	440	0053-0440-44
45	221 to 225 kg	450	0053-0450-45
46	226 to 230 kg	460	0053-0460-46
47	231 to 235 kg	470	0053-0470-47
48	236 to 240 kg	480	0053-0480-48

NDC – National Drug Code.

REFERENCES

1. Hemgenix® intravenous infusion [prescribing information]. King of Prussia, PA; Kankakee, IL; and Lexington, MA: CSL Behring and uniQure; November 2022.
2. Pipe SW, Leebeek FWG, Recht M, et al. Gene therapy with etranacogene dexaparvovec for hemophilia B. *N Engl J Med*. 2023;388:706-718.
3. National Bleeding Disorders Foundation. Hemophilia B. An overview of symptoms, genetics, and treatments to help you understand hemophilia B. Available at: https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-b. Accessed on May 3, 2024.
4. Sidonio RF, Malec L. Hemophilia (Factor IX deficiency). *Hematol Oncol Clin N Am*. 2021;35:1143-1155.
5. Mancuso ME, Mahlangu JN, Pipe SW. The changing treatment landscape in haemophilia: from standard half-life clotting factor concentrates to gene editing. *Lancet*. 2021;397:630-640.
6. Croteau SE. Hemophilia A/B. *Hematol Oncol Clin N Am*. 2022;36:797-812.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/11/2023
Annual Revision	**Hemophilia B:** An overview of the changes are described below. • The documentation requirement was removed regarding the criterion that the "Patient does not have evidence of advanced liver impairment and/or advanced fibrosis". • The following criteria were removed which stated that after the Hemgenix infusion, the physician attests that the following will be performed: 1) liver enzyme testing to monitor for liver enzyme elevations will be done at least weekly for the first 3 months and periodically thereafter; AND implementing a course of corticosteroids will be considered if the patient experiences clinically relevant increases in alanine aminotransferase levels; 2) the patient will undergo monitoring for Factor IX activity at least weekly for the first 3 months and periodically thereafter; and 3) the patient with preexisting risk factors for hepatocellular carcinoma will receive abdominal ultrasound screenings and be monitored at least annually for alpha fetoprotein elevations in the 5 years following receipt of Hemgenix. • The requirement for the specialist physician was changed from "physician who specializes in hemophilia" to "hemophilia specialist physician". • The criterion regarding a current patient body weight be obtained within 30 days was moved to a separate criterion. Previously, this requirement was combined with the Dosing. • Dosing was clarified with emphasis that Hemgenix is given as a "single dose". Also, "documentation required" was replaced with "verification required". A related sentence was added to the Policy Statement that verification of the appropriate weight-based dosing is required by the Medical Director. • Regarding use of Hemgenix in the past, the phrase "verification required by prescriber" was changed to "verification in claims history required". A qualifier was added to reflect that this requirement applies only if a claims history is available; this change was also reflected in the related Policy Statement. Wording regarding "prescriber must attest" was changed to "prescribing physician confirms" regarding the verification that the patient has not previously received Hemgenix. Also, in the Note, the following statement was removed as it is duplicative: verify through claims history that the patient has not previously received Hemgenix. • The phrase "prescriber attests" was removed from the requirement that "prophylactic therapy with Factor IX will not be given after Hemgenix administration once adequate Factor IX levels have been achieved" as well as the to the requirement regarding "patient does not have another coagulation disorder, besides hemophilia B". • In the requirement that Factor IX inhibitor titer testing has been performed "within 30 days", the phrase "before receipt of Hemgenix" was removed. • The phrase regarding liver "health assessment" was changed to liver "function testing". • For the requirement that the patient does not have uncontrolled human immunodeficiency virus, the word "infection" was added after this phrase. **Conditions Not Recommended for Approval:** The condition of "Prior Receipt of Gene Therapy" was added.	02/28/2024

HISTORY (CONTINUED)

Type of Revision	Summary of Changes	Review Date
Selected Revision	**Hemophilia B:** ● Regarding use of Hemgenix in the past, the criterion was changed due to the recent approval of Beqvez (fidanacogene elaparvovec intravenous infusion) for this indication. It now states that the patient has not received "a gene therapy for hemophilia B" in the past. It was added that there should not be claims present for Beqvez and that if claims history is not available, the prescribing physician confirms that the patient has not previously received Beqvez (previously, this only addressed Hemgenix). ● The option of approval was removed that the patient has been receiving routine prophylaxis with Factor IX therapy continuously for ≥ 2 months. ● The requirement that the patient does not currently have an inhibitor to Factor IX was reworded to state that the patient is negative for Factor IX inhibitors. ● The caveat of "According to the prescribing physician" was added to the requirement that the patient does not have uncontrolled human immunodeficiency virus infection; the documentation requirement was removed from this requirement; and the Note that addressed specific laboratory factors was removed. ● The requirement that within 30 days the patient has an estimated creatinine clearance ≥ 30 mL/min AND that the creatinine level is ≤ two times the upper limit of normal was changed to having to meet one of these elements (not both). ● The requirement that the patient does not have another coagulation disorder, besides hemophilia B, was removed.	05/15/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hemophilia – Gene Therapy – Roctavian Utilization Management Medical Policy
- Roctavian® (valoctocogene roxaparvovec-rvox intravenous infusion – BioMarin)

REVIEW DATE: 08/16/2023

OVERVIEW

Roctavian, an adeno-associated virus vector-based gene therapy, is indicated for the treatment of adults with severe hemophilia A (congenital Factor VIII deficiency with Factor VIII activity < 1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test.[1]

Disease Overview

Hemophilia A is an X-linked bleeding disorder primarily impacting males caused by a deficiency in Factor VIII.[2-7] In the US, the incidence of hemophilia A in males is 1:5,000 with an estimated 20,000 people in the US living with hemophilia A. The condition is characterized by bleeding in joints, either spontaneously or in a provoked joint. Bleeding can occur in many different body areas as well (e.g., muscles, central nervous system). The bleeding manifestations can lead to substantial morbidity such as hemophilic arthropathy. Disease severity is usually defined by the plasma levels or activity of Factor VIII classified as follows: severe (< 1 IU/dL), moderate (1 IU/dL to 5 IU/dL), and mild (> 5 IU/dL to < 40 IU/dL); phenotypic expression may vary. Approximately 50% of patients with hemophilia A are categorized as having severe disease. These patients usually require routine prophylaxis with Factor VIII replacement therapy products or Hemlibra® (emicizumab subcutaneous injection) to prevent bleeding.

Clinical Efficacy

The efficacy of Roctavian was evaluated in one open-label, single-group, multinational Phase III trial (GENEr8-1) involving 134 adult males (≥ 18 years of age) with severe hemophilia A (Factor VIII activity level ≤ 1 IU/dL).[1,8,9] Patients involved in the trial did not have Factor VIII inhibitors (or a history of such inhibitors) and were receiving regular prophylaxis with Factor VIII products. Use of prophylactic Factor VIII therapy was not permitted during the trial, but could be used up to 4 weeks post Roctavian administration to allow the agent to have an effect. Other notable exclusion criteria were active infection, chronic or active hepatitis B or C, immunosuppressive disorder (including HIV), Stage 3 or 4 liver fibrosis, cirrhosis, liver function test abnormalities, a history of thrombosis or thrombophilia, serum creatinine ≥ 1.4 mg/dL, and active malignancy. Patients had to be treated or exposed to Factor VIII concentrates previously for a minimum of 150 exposure days. Use of systemic immunosuppressive agents (not including corticosteroids), or live vaccines within 30 days before Roctavian infusion prevented participation. In the 132 patients who completed more than 51 weeks of follow-up (and were HIV-negative), the mean Factor VIII activity level at Weeks 49 through 52 had increased by 41.9 IU/dL (a non-hemophilic range). Among the 112 patients enrolled from a noninterventional study who had baseline annualized bleeding rate information prospectively collected for at least 6 months before receiving Roctavian (the rollover population), the mean annualized rates of Factor VIII concentrate use and treated bleeding after Week 4 had decreased after Roctavian administration by 98.6% and 83.8%, respectively ($P < 0.001$ for both comparisons). At Year 3 post Roctavian dosing the mean annualized bleeding rate in the rollover population in the efficacy evaluation period was 2.6 bleeds/year compared to a mean baseline of 5.4 bleeds/year (while using Factor VIII therapies); mean Factor VIII activity levels were 21 IU/dL at this timepoint (mild hemophilic range).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Roctavian. Because of the specialized skills required for evaluation and diagnosis of patients treated with Roctavian as well as the monitoring required for adverse events and long-term efficacy, approval requires Roctavian to be prescribed by a physician who specializes in the condition being treated. For certain criteria, verification is required as noted by **[verification in claims history required]**. For the dosing criteria, verification of the appropriate weight-based dosing is required by a Medical Director as noted by **[verification required]**. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. In the approval indication for Roctavian, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with eviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Roctavian is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Hemophilia A.** Approve a one-time per lifetime dose if the patient meets the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R, S, T, U, V, W, X, Y, Z, AA, BB, and CC):
   - **A)** Patient is male*; AND
   - **B)** Patient is greater than or equal to 18 years of age; AND
   - **C)** Patient has severe hemophilia A as evidence by a baseline (without Factor VIII replacement therapy) Factor VIII level of < 1 IU/dL **[documentation required]**; AND
   - **D)** Patient does not have detectable pre-existing antibodies to adeno-associated virus 5 (AAV5) by an FDA-approved test **[documentation required]**; AND
   - **E)** Patient has a history of use of Factor VIII therapy for at least 150 exposure days; AND
   - **F)** Patient meets all of the following (i, ii, and iii):
     - **i.** Factor VIII inhibitor titer testing has been performed within 30 days before intended receipt of Roctavian **[documentation required]**; AND
     - **ii.** Patient does not currently have an inhibitor to Factor VIII **[documentation required]**; AND
     - **iii.** Patient does not have a history of Factor VIII inhibitors **[documentation required]**; AND
   - **G)** Prophylactic therapy with Factor VIII will not be given after Roctavian administration once adequate Factor VIII levels have been achieved; AND
     Note: Use of episodic Factor VIII therapy is acceptable for the treatment of bleeds and for surgery/procedures if needed as determined by the hemophilia specialist physician.
   - **H)** Patient has not received Roctavian in the past **[verification in claims history required]**; AND

Note: Verify through claims history that the patient has not previously received Roctavian AND, if no claim for Roctavian is present, the prescribing physician confirms that the patient has not previously received Roctavian.

I) Patient does not have a known hypersensitivity to mannitol; AND

J) Patient does not have an active acute or uncontrolled chronic infection; AND

K) Patient does not have chronic or active hepatitis B **[documentation required]**; AND

L) Patient does not have active hepatitis C **[documentation required]**; AND

M) Patient does not have evidence of significant hepatic fibrosis or cirrhosis; AND

N) Patient meets one of the following (i or ii):

- **i.** Patient has undergone a liver health assessment within 30 days before intended receipt of Roctavian and meets all of the following (a, b, c, d, e, and f):
  - **a)** Alanine aminotransferase levels are ≤ 1.25 times the upper limit of normal **[documentation required]**; AND
  - **b)** Aspartate aminotransferase levels are ≤ 1.25 times the upper limit of normal **[documentation required]**; AND
  - **c)** Total bilirubin levels are ≤ 1.25 times the upper limit of normal **[documentation required]**; AND
  - **d)** Alkaline phosphatase levels are ≤ 1.25 times the upper limit of normal **[documentation required]**; AND
  - **e)** Gamma-glutamyl transferase levels are ≤ 1.25 times the upper limit of normal **[documentation required]**; AND
  - **f)** The International Normalized Ratio is < 1.4 **[documentation required]**; OR
- **ii.** If the patient had one or more of the laboratory values listed in *Criteria a-f* above that was not at the value specified in *Criteria a-f* above, then a hepatologist has evaluated the patient and has determined that use of Roctavian is clinically appropriate **[documentation required]**; AND

O) Within 30 days before intended receipt of Roctavian, the platelet count was ≥ 100 x 10^9/L **[documentation required]**; AND

P) Within 30 days before intended receipt of Roctavian, the creatinine level was < 1.4 mg/dL **[documentation required]**; AND

Q) Patient has not used a systemic immunosuppressive agent within 30 days before intended receipt of Roctavian; AND

Note: Corticosteroids are not included as systemic immunosuppressive agents.

R) Patient does not have any disease or condition that would interfere with the compliance requirements that involve use of systemic corticosteroid therapy or systemic alternative immunosuppressive medications; AND

S) Patient does not have an immunosuppressive disorder; AND

T) Patient is not human immunodeficiency virus positive **[documentation required]**; AND

U) Patient does not have any additional bleeding disorder, besides hemophilia A; AND

V) Patient does not have a history of thrombosis or thrombophilia; AND

W) Patient does not have a current active malignancy; AND

Note: Current active malignancy does not include non-melanoma skin cancer.

X) Patient does not have a history of hepatic malignancy; AND

Y) Patient has not received a live vaccine within 30 days before intended receipt of Roctavian; AND

Z) The hemophilia specialist physician has discussed with the patient that for a period of up to 6 months after administration of Roctavian the following precautions should be taken (i and ii):

- **i.** A male of reproductive potential (and his female partner) should prevent or postpone pregnancy by utilizing an effective form of contraception; AND
- **ii.** A male should not donate semen; AND

AA) Medication is prescribed by a hemophilia specialist physician; AND

BB) Current patient body weight has been obtained within 30 days before intended receipt of Roctavian **[documentation required]**; AND

CC) If criteria A through BB are met, approve one dose of Roctavian to provide a one time (per lifetime) dose of 6 x 10^{13} vector genomes per kg by intravenous infusion **[verification required]**. Note: Roctavian is supplied in a carton (NDC 68135-927-48) that contains one single dose vial (NDC 68135-927-01) with an extractable volume of not less than 8 mL, containing 16 x 10^{13} vector genomes.

***** Refer to the Policy Statement.

Dosing. The recommended dose of Roctavian is a single one time (per lifetime) intravenous infusion of 6 x 10^{13} vector genomes per kg based on current body weight in kg (within the past 30 days).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Roctavian is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Roctavian® intravenous infusion [prescribing information]. Novato, CA: BioMarin; June 2023.
2. Peyvandi F, Garagiola I, Young G. The past and future of haemophilia: diagnosis, treatments and its complications. *Lancet*. 2016;388(10040):187-197.
3. Centers for Disease Control and Prevention. Community Counts: Hemophilia Home Page. Lasted reviewed in July 2023. Available at: https://www.cdc.gov/ncbddd/hemophilia/facts.html. Accessed on August 14, 2023.
4. Mancuso ME, Mahlangu JN, Pipe SW. The changing treatment landscape in haemophilia: from standard half-life clotting Factor concentrates to gene editing. *Lance*t. 2021;397:630-640.
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6. Franchini M, Mannucci PM. The more recent history of hemophilia treatment. *Semin Thromb Hemost*. 2022;48(8):904-910.
7. National Hemophilia Foundation. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and other selected disorders of the coagulation system (endorsed by the National Hemophilia Foundation Board of Directors on May 2, 2023). MASAC Document #276. Available at: https://www.hemophilia.org/sites/default/files/document/files/MASACTreatment.pdf. Accessed on August 13, 2023.
8. Ozelo MC, Mahlangu J, Pasi KJ, et al, for the GENEr8-1 trial group. Valoctocogene roxaparvovec gene therapy for hemophilia A. *N Engl J Med*. 2022;386(11):1013-1025.
9. Mahlangu J, Kaczmarek R, Von Drygalski A, et al, for the GENEr8-1 trial group. Two-year outcomes of valoctocogene roxaparvovec therapy for hemophilia A. *N Engl J Med*. 2023;388(8):694-705.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/16/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hepatology – Givlaari Utilization Management Medical Policy
- Givlaari™ (givosiran subcutaneous injection – Alnylam)

REVIEW DATE: 10/18/2023

OVERVIEW

Givlaari, an aminolevulinate synthase 1-directed small interfering RNA, is indicated for the treatment of patients ≥ 18 years of age with **acute hepatic porphyria** (AHP).[1]

Givlaari is a double-stranded small interfering RNA that causes degradation of aminolevulinate synthase 1 (ALAS1) mRNA in hepatocytes through RNA interference, reducing the elevated levels of liver ALAS1 mRNA.[1] This leads to reduced circulating levels of neurotoxic intermediates aminolevulinic acid and porphobilinogen, factors associated with attacks and other disease manifestations of AHP. In the pivotal trial, inclusion criteria specified a minimum of two porphyria attacks requiring hospitalization, urgent healthcare visit, or intravenous hemin administration at home in the 6 months prior to study entry. Hemin use during the study was permitted for the treatment of acute porphyria attacks.

Disease Overview

Porphyria is a group of metabolic disorders caused by abnormalities in the chemical steps that lead to the production of heme.[2] AHPs are a subgroup of porphyrias in which the enzyme deficiency occurs within the liver.[3] AHPs include acute intermittent porphyria (AIP), variegate porphyria (VP), 5-aminolevulinic acid dehydratase deficiency porphyria (ALAD), and hereditary coproporphyria (HCP) and are characterized by acute neurovisceral symptoms with or without cutaneous manifestations.[3,4] Symptoms and treatments for AIP, VP, ALAD, and HCP are similar; however, VP and HCP patients often develop photosensitivity. Signs and symptoms of AHP usually occur intermittently and include abdominal pain, constipation, muscle weakness, pain in the arms and legs, insomnia, emotional complications, rapid pulse, and high blood pressure. Although most symptomatic patients with AHP have complete resolution of their symptoms between attacks, those with numerous recurrences may develop chronic pain.

Dosing Information

The recommended dose is 2.5 mg/kg administered by subcutaneous injection once monthly by a healthcare professional only.

Guidelines

The Porphyrias Consortium of the National Institutes of Health's Rare Diseases Clinical Research Network has developed recommendations for evaluation and long-term management of AHPs (2017).[5] Initial assessments should include diagnostic confirmation by biochemical testing, subsequent genetic testing to determine the specific AHP, and a complete medical history and physical examination. Preventative measures should be taken to prevent attacks. Hemin therapy (e.g., Panhematin® [hemin injection for intravenous infusion]) is recommended for preventative management in AHP and treatment during acute attacks. Patients with ≥ four attacks per year are candidates for either prophylactic or "on demand" infusions. The need for ongoing prophylaxis should be assessed every 6 to 12 months. Repeated long-term treatment with hemin therapy can lead to iron overload and contribute to hepatic damage and fibrosis. Carbohydrate loading (glucose tablets or dextrose solutions) has been used in early stages of an acute attack, but there are no clear data showing a benefit. Women with AHP can develop cyclic attacks correlated with the menstrual cycle. Options to prevent these attacks include recognizing and removing exacerbating

factors, a gonadotropin releasing-hormone analog, switching to a low dose hormonal contraceptive, or prophylactic hemin therapy infusions.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Givlaari. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Givlaari as well as the monitoring required for adverse events and long-term efficacy, approval requires Givlaari to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Givlaari is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. Acute Hepatic Porphyria. Approve for 1 year if the patient meets the following (A, B, C, and D):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Diagnosis of acute hepatic porphyria was confirmed by both of the following (i and ii):
  - **i.** Patient demonstrated clinical features associated with acute hepatic porphyria; AND
    Note: Examples of clinical features associated with acute intermittent porphyria include neurovisceral symptoms, blistering lesions, hepatic involvement, peripheral neuropathy, abdominal pain, constipation, muscle weakness, pain in the arms and legs.
  - **ii.** Patient meets one of the following (a or b):
    - **a)** Elevated urinary aminolevulinic acid (ALA) greater than the upper limit of normal; OR
    - **b)** Elevated urinary porphobilinogen (PBG) greater than the upper limit of normal; AND
- **C)** Prior to starting treatment with Givlaari, the patient has a history of one porphyria attack in the last 6 months that required a hospitalization, urgent healthcare visit, or intravenous hemin administration at home; AND
- **D)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, or a physician who specializes in acute hepatic porphyria.

Dosing. Approve 2.5 mg/kg administered by subcutaneous injection given no more frequently than once every 30 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Givlaari is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Givlaari™ intravenous infusion [prescribing information]. Cambridge, MA: Alnylam; February 2023.
2. Porphyria. U.S. National Library of Medicine; National Institutes of Health; Department of Health and Human Services. Available at: https://ghr.nlm.nih.gov/condition/porphyria. Accessed on October 10, 2023.
3. Wang B, Rudnick S, Cengia B, et al. Acute hepatic porphyrias: review and recent progress. *Hepatol Commun.* 2018;3(2):193-206.
4. Bissell DM, Wang B. Acute hepatic porphyria. *J Clin Transl Hepat*. 2015;3(1):17-26.
5. Balwani M, Wang B, Anderson K, et al. Acute hepatic porphyrias: recommendations for evaluation and long term management. *Hepatology*. 2017;66(4):1314-1322.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	10/19/2022
Annual Revision	No criteria changes.	10/18/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hepatology – Panhematin Utilization Management Medical Policy
- Panhematin® (hemin intravenous infusion – Recordati Rare Diseases)

REVIEW DATE: 10/18/2023

OVERVIEW

Panhematin, an enzyme inhibitor derived from processed red blood cells, is indicated for the **amelioration of recurrent attacks of acute intermittent porphyria** (AIP) temporally related to the menstrual cycle in susceptible women, after initial carbohydrate therapy is known or suspected to be inadequate.[1]

Safety and effectiveness in patients < 16 years of age have not been established.[1]

Disease Overview

Porphyria is a group of metabolic disorders caused by abnormalities in the chemical steps that lead to the production of heme.[2] Heme is necessary for the transport of oxygen to cells in the body. If synthesis of heme is hindered, an accumulation of porphyrins or porphyrin precursors (intermediate chemicals) accumulates in the cells, resulting in oxygen depletion. Acute hepatic porphyrias (AHPs) are a subgroup of porphyrias in which the enzyme deficiency occurs within the liver.[3] AHPs include AIP, variegate porphyria (VP), 5-aminolevulinic acid dehydratase deficiency porphyria (ALAD), and hereditary coproporphyria (HCP) and are characterized by acute neurovisceral symptoms with or without cutaneous manifestations.[3,4] Symptoms and treatments for AIP, VP, ALAD, and HCP are similar; however, VP and HCP patients often develop photosensitivity. Signs and symptoms of AHP usually occur intermittently and include abdominal pain, constipation, muscle weakness, pain in the arms and legs, insomnia, emotional complications, rapid pulse, and high blood pressure, along with elevated urinary aminolevulinic acid and porphobilinogen. Hospitalization is often required for acute attacks. Although most symptomatic patients with AHP have complete resolution of their symptoms between attacks, those with numerous recurrences may develop chronic pain. Due to the high prevalence of chronic kidney disease, serum creatinine and estimated glomerular filtration rate should be monitored annually for all symptomatic patients.

Dosing Information

The recommended dose of Panhematin is 1 to 4 mg/kg/day administered by intravenous infusion for 3 to 14 days based on the clinical signs.[1] The standard dose in clinical practice is 3 to 4 mg/kg/day. Do not exceed 6 mg/kg in any 24 hour period.

Guidelines

The Porphyrias Consortium of the National Institutes of Health's Rare Diseases Clinical Research Network has developed recommendations for evaluation and long-term management of AHPs (2017).[5] Initial assessments should include diagnostic confirmation by biochemical testing, subsequent genetic testing to determine the specific AHP, and a complete medical history and physical examination. Preventative measures should be taken to prevent attacks. Hemin therapy (e.g., Panhematin) is recommended for preventative management in AHP and treatment during acute attacks. Patients with ≥ four attacks per year are candidates for either prophylactic or "on demand" infusions. The need for ongoing prophylaxis should be assessed every 6 to 12 months. Repeated long-term treatment with hemin therapy can lead to iron overload and contribute to hepatic damage and fibrosis. Carbohydrate loading (glucose tablets or dextrose solutions) has been used in early stages of an acute attack, but there are no clear data showing a benefit. Women with AHP can develop cyclic attacks correlated with the menstrual cycle. Options to prevent these

attacks include recognizing and removing exacerbating factors, a gonadotropin releasing-hormone analog, switching to a low dose hormonal contraceptive, or prophylactic hemin therapy infusions.

Safety

Panhematin is derived from human blood; therefore, there is a potential risk of the transmission of infectious agents (e.g., viruses) that may cause disease.[1] Because increased levels of iron and serum ferritin have been reported in post-marketing experience with Panhematin, providers should monitor iron and serum ferritin in patients receiving multiple doses.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Panhematin. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Panhematin as well as the monitoring required for adverse events and long-term efficacy, approval requires Panhematin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Panhematin is recommended in those who meet one of the following criteria:

FDA-Approved Indication

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1. **Acute Intermittent Porphyria.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Patient is ≥ 16 years of age; AND
   - **B)** Diagnosis of acute intermittent porphyria was confirmed by both of the following (i and ii):
     - **i.** Patient demonstrated clinical features associated with acute intermittent porphyria; AND
       Note: Examples of clinical features associated with acute intermittent porphyria include neurovisceral symptoms, blistering lesions, hepatic involvement, peripheral neuropathy, abdominal pain, constipation, muscle weakness, pain in the arms and legs.
     - **ii.** Patient meets one of the following (a or b):
       - **a)** Elevated urinary aminolevulinic acid (ALA) greater than the upper limit of normal; OR
       - **b)** Elevated urinary porphobilinogen (PBG) greater than the upper limit of normal; AND
   - **C)** Acute intermittent porphyria is related to the menstrual cycle; AND
   - **D)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, or a physician who specializes in acute intermittent porphyria.

   Dosing. Approve up to 6 mg/kg administered by intravenous infusion once daily given no more frequently than 14 days per 30 days.

Other Uses with Supportive Evidence

2. Acute Hepatic Porphyria. Approve for 1 year if the patient meets all of the following (A, B, and C):
- **A)** Patient is ≥ 16 years of age; AND
- **B)** Diagnosis of acute hepatic porphyria was confirmed by both of the following (i and ii):
  - **i.** Patient demonstrated clinical features associated with acute hepatic porphyria; AND
    Note: Examples of clinical features associated with acute intermittent porphyria include neurovisceral symptoms, blistering lesions, hepatic involvement, peripheral neuropathy, abdominal pain, constipation, muscle weakness, pain in the arms and legs.
  - **ii.** Patient meets one of the following (a or b):
    - **a)** Elevated urinary aminolevulinic acid (ALA) greater than the upper limit of normal; OR
    - **b)** Elevated urinary porphobilinogen (PBG) greater than the upper limit of normal; AND
- **C)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, or a physician who specializes in acute hepatic porphyria.

Dosing. Approve up to 6 mg/kg given by intravenous infusion once daily no more frequently than 14 days per 30 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Panhematin is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Panhematin® intravenous infusion [prescribing information]. Lebanon, NJ: Recordati Rare Diseases; May 2020.
2. Porphyria. U.S. National Library of Medicine; National Institutes of Health; Department of Health and Human Services. Available at: https://ghr.nlm.nih.gov/condition/porphyria. Accessed on October 10, 2023.
3. Wang B, Rudnick S, Cengia B, et al. Acute hepatic porphyrias: review and recent progress. *Hepatol Commun.* 2018;3(2):193-206.
4. Bissell DM, Wang B. Acute hepatic porphyria. *J Clin Transl Hepat*. 2015;3(1):17-26.
5. Balwani M, Wang B, Anderson K, et al. Acute hepatic porphyrias: recommendations for evaluation and long term management. *Hepatology*. 2017;66(4):1314-1322.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	No criteria changes	10/19/2022
Annual Revision	No criteria changes.	10/18/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hereditary Angioedema – C1 Esterase Inhibitors (Intravenous) Utilization Management Medical Policy
- Berinert® (C1 esterase inhibitor [human] intravenous infusion – CSL Behring)
- Cinryze® (C1 esterase inhibitor [human] intravenous infusion – Takeda)
- Ruconest® (C1 esterase inhibitor [recombinant] intravenous infusion – Pharming)

REVIEW DATE: 09/20/2023

OVERVIEW

Berinert, Cinryze, and Ruconest are C1 esterase inhibitor (C1-INH) replacement therapies for hereditary angioedema (HAE).[1-3] Cinryze and Berinert are human plasma-derived C1-INH; Ruconest is a recombinant C1-INH purified from milk of transgenic rabbits. Labeled indications are as follows:
- Berinert is indicated for the **treatment of acute abdominal, facial, or laryngeal HAE attacks** in adults and pediatric patients.[1]
- Cinryze is indicated for routine **prophylaxis against HAE attacks** in patients ≥ 6 years of age.[2]
- Ruconest is indicated for the **treatment of acute HAE attacks** in adults and adolescent patients.[3]

Of note, although Cinryze is labeled for use in the prophylactic setting and Berinert is labeled for use in the acute treatment setting, use of Cinryze in the acute setting and Berinert in the prophylactic setting has been reported in the literature.[4,5]

Guidelines

Acute Treatment of HAE Attacks

According to US HAE Association Medical Advisory Board Guidelines (2020), when HAE is suspected based on clinical presentation, appropriate testing includes measurement of the serum C4 level, C1-INH antigenic level, and C1-INH functional level.[6] Low C4 plus low C1-INH antigenic or functional level is consistent with a diagnosis of HAE types I/II. The goal of acute therapy is to minimize morbidity and prevent mortality from an ongoing HAE attack. Patients must have ready access to effective on-demand medication to administer at the onset of an HAE attack. All HAE attacks are eligible for treatment, irrespective of the location of swelling or severity of the attack. First-line treatments include plasma-derived C1-INH, Ruconest, Kalbitor® (ecallantide subcutaneous [SC] injection), and icatibant (Firazyr®, generic).

In guidelines from the World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) [2021], it is recommended that all attacks be treated with either IV C1-INH, Kalbitor, or icatibant (evidence level A for all).[7] Regarding IV C1-INH, it is noted that Berinert and Cinryze are both plasma-derived products available for this use, although indications vary globally. It is essential that patients have on-demand medication to treat all attacks; thus, the guidelines recommend that patients have and carry medication for treatment of at least two attacks.

Long-Term Prophylaxis

US HAE Association Medical Advisory Board Guidelines (2020) note the decision on when to use long-term prophylaxis cannot be made on rigid criteria but should reflect the needs of the individual patient.[6] First-line medications for HAE I/II include intravenous (IV) C1-INH, Haegarda® (C1-INH [human] SC

injection), or Takhzyro® (landelumab-flyo SC injection). The guideline was written prior to approval of Orladeyo® (berotralstat capsules).

According to WAO/EAACI guidelines (2021), it is recommended to evaluate for long-term prophylaxis at every visit, taking disease activity, burden, and control as well as patient preference into consideration.[7] The following therapies are supported as first-line options for long-term prophylaxis: plasma-derived C1-INH (87% agreement), Takhzyro (89% agreement), and Orladeyo (81% agreement). With regard to plasma-derived C1-INH, it is noted that Haegarda provided very good and dose-dependent preventative effects on the occurrence of HAE attacks; the subcutaneous route may provide more convenient administration and maintain improved steady-state plasma concentrations compared with the IV route. Of note, androgens are not recommended in the first-line setting for long-term prophylaxis. Recommendations are not made regarding long-term prophylaxis in HAE with normal C1-INH.

Dosing Information for Plasma-Derived C1-INH (Berinert, Cinryze)

For prophylaxis (Berinert or Cinryze), the maximum allowable dose in the policy comes from the Cinryze prescribing information and is applied to both Berinert and Cinryze prophylactic use requests. For the acute setting (Berinert or Cinryze), dosing recommendations come from the Berinert prescribing information and are applied to both Berinert and Cinryze requests for acute use. Of note, in the pivotal study of Berinert, a maximum of 20 IU/kg of Berinert was administered, and response was assessed for up to 24 hours. For the treatment of acute attacks, the prescribing information states that doses of Berinert lower than 20 IU/kg should not be administered.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Berinert, Cinryze, and Ruconest. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Berinert, Cinryze, and Ruconest, as well as monitoring required for adverse events and long-term efficacy, approval requires the medication to be prescribed by or in consultation with a physician who specializes in the condition being treated. A patient who has previously met initial therapy criteria for Berinert, Cinryze, and Ruconest for the requested indication under the Coverage Review Department and is currently receiving the requested therapy is only required to meet the continuation therapy criteria (i.e., currently receiving Berinert, Cinryze, or Ruconest). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Berinert, Cinryze, or Ruconest, initial therapy criteria must be met.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Berinert or Cinryze is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Prophylaxis. Approve Berinert or Cinryze for 1 year if the patient meets one of the following (A or B):

A) Initial therapy. Approve if the patient meets both of the following (i and ii):

i. Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.

a) Patient has low levels of functional C1-INH protein (< 50% of normal) **at baseline**, as defined by the laboratory reference values **[documentation required]**; AND

b) Patient has lower than normal serum C4 levels **at baseline**, as defined by the laboratory reference values **[documentation required]**; AND

ii. The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

B) Patient is currently receiving Berinert or Cinryze prophylaxis. Approve if the patient meets all of the following (i, ii, and iii):
Note: If the patient is currently receiving the requested therapy, but has not previously received approval of Berinert or Cinryze for this indication through the Coverage Review Department, review under criteria for Initial Therapy.

i. Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.

ii. According to the prescriber, the patient has had a favorable clinical response since initiating Berinert or Cinryze prophylactic therapy compared with baseline (i.e., prior to initiating prophylactic therapy); AND
Note: Examples of a favorable clinical response include decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks.

iii. The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

Dosing. Approve one of the following regimens (A or B):

A) Patient is ≥ 12 years of age: Approve up to a maximum dose of 2,500 units (not exceeding 100 units/kg), administered intravenously no more frequently than twice weekly with doses separated by at least 3 days; OR

B) Patient is < 12 years of age: Approve up to a maximum dose of 1,000 units, administered intravenously no more frequently than twice weekly with doses separated by at least 3 days.

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2. Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Treatment of Acute Attacks. Approve Berinert or Cinryze for 1 year if the patient meets one of the following (A or B):

A) Initial therapy. Approve if the patient meets both of the following (i and ii):

i. Patient has HAE type I or type II as confirmed by following (a and b):
Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.

a) Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND

b) Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND

ii. The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

B) Patient who has treated previous acute HAE attacks with Berinert or Cinryze. Approve if the patient meets all of the following (i, ii, and iii):
Note: If the patient is currently receiving the requested therapy, but has not previously received approval of Berinert or Cinryze for this indication through the Coverage Review Department, review under criteria for Initial Therapy.

i. Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.

ii. According to the prescriber, the patient has had a favorable clinical response with Berinert or Cinryze treatment; AND
Note: Examples of a favorable clinical response include decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, or decrease in HAE acute attack frequency or severity.

iii. The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

Dosing. Approve 20 IU/kg, administered intravenously no more frequently than once daily.

II. Coverage of Ruconest is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Treatment of Acute Attacks.** Approve Ruconest for 1 year if the patient meets one of the following (A or B):

A) Initial therapy. Approve if the patient meets both of the following (i and ii):

i. Patient has HAE type I or type II as confirmed by the following (a and b):
Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.

a) Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND

b) Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND

ii. The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

B) Patient who has treated previous acute HAE attacks with Ruconest. Approve if the patient meets all of the following (i, ii, and iii):
Note: If the patient is currently receiving the requested therapy, but has not previously received approval of Ruconest for this indication through the Coverage Review Department, review under criteria for Initial Therapy.

i. Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.

ii. According to the prescriber, the patient has had a favorable clinical response with Ruconest treatment; AND

Note: Examples of a favorable clinical response include decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, or decrease in HAE acute attack frequency or severity.

iii. The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

Dosing. Approve up to a maximum dose of 4,200 units (not exceeding 50 units/kg), administered intravenously no more frequently than twice daily.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Berinert, Cinryze, or Ruconest is not recommended in the following situations:

1. **Hereditary Angioedema (HAE) Prophylaxis (Ruconest ONLY).** Ruconest is not FDA-approved for prophylaxis of HAE attacks. A small (n = 32) Phase II, randomized, double-blind, placebo-controlled trial in adults and adolescents ≥ 13 years of age showed efficacy of Ruconest over placebo for reducing mean monthly rate of HAE attacks ($P < 0.0001$).[8] At this time, evidence is not sufficient to support Ruconest use for HAE prophylaxis.
   Note: This Condition Not Recommended for Approval does not apply to Berinert or Cinryze.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Berinert® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; September 2021.
2. Cinryze® intravenous infusion [prescribing information]. Lexington, MA: Takeda; January 2021.
3. Ruconest® intravenous infusion [prescribing information]. Warren, NJ: Pharming; April 2020.
4. Zuraw BL. Hereditary angioedema. *N Engl J Med*. 2008;359:1027-1036.
5. Craig T, Shapiro R, Vegh A, et al. Efficacy and safety of an intravenous C1-inhibitor concentrate for long-term prophylaxis in hereditary angioedema. *Allergy Rhinol (Providence)*. 2017;8(1):13-19.
6. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3.
7. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema: the 2021 revision and update. *Allergy*. 2022;77(7):1961-1990.
8. Riedl MA, Grivcheva-Panovska V, Moldovan D, et al. Recombinant human C1 esterase inhibitor for prophylaxis of hereditary angio-oedema: a phase 2, multicentre, randomised, double-blind, placebo-controlled crossover trial. *Lancet.* 2017;390:1595-1602.

HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	**Berinert and Cinryze** **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Prophylaxis:** A Note was added to the initial and continuation criteria that a diagnosis of HAE with normal C1-INH (also known as HAE type III) does not satisfy the requirement for a diagnosis of HAE type I or type II. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Treatment of Acute Attacks:** A Note was added to the initial and continuation criteria that a diagnosis of HAE with normal C1-INH (also known as HAE type III) does not satisfy the requirement for a diagnosis of HAE type I or type II. **Ruconest** **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Treatment of Acute Attacks:** A Note was added to the initial and continuation criteria that a diagnosis of HAE with normal C1-INH (also known as HAE type III) does not satisfy the requirement for a diagnosis of HAE type I or type II.	06/01/2022
Annual Revision	**Berinert and Cinryze** **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Prophylaxis:** In Dosing, the interval was revised to read "no more frequently than twice weekly with doses separated by at least 3 days". Previously, the interval was written as "no more frequently than once every 3 days".	09/21/2022
Annual Revision	It was added to the Policy Statement that a person who has previously met initial therapy criteria for Cinryze, Berinert, or Ruconest for the requested indication under the Coverage Review Department and is currently receiving the medication, is only required to meet continuation of therapy criteria. If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Cinryze, Berinert, or Ruconest, initial therapy criteria must be met. In addition, the following changes were made: **Berinert and Cinryze** **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Prophylaxis:** Deleted [Type I or Type II] from indication heading. Under criteria for "Patient is currently receiving Berinert or Cinryze prophylaxis", added a Note that patient has to meet initial therapy criteria and approval through the Coverage Review Department if they had previously received initial therapy approval through a different entity. Also added the word "type" before II while referring to diagnosis of HAE types. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Treatment of Acute Attacks:** Deleted [Type I or Type II] from indication heading. Under criteria for "Patient has treated previous acute HAE attacks with Berinert or Cinryze", added a Note that patient has to meet initial therapy criteria and approval through the Coverage Review Department if they had previously received initial therapy approval through a different entity. **Ruconest** **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Treatment of Acute Attacks:** Deleted [Type I or Type II] from indication heading. Under criteria for "Patient has treated previous acute HAE attacks with Ruconest", added a Note that patient has to meet initial therapy criteria and approval through the Coverage Review Department if they had previously received initial therapy approval through a different entity.	09/20/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hereditary Angioedema – C1 Esterase Inhibitors (Subcutaneous) Utilization Management Medical Policy
- Haegarda® (C1 esterase inhibitor [human] subcutaneous injection – CSL Behring)

REVIEW DATE: 09/20/2023

OVERVIEW

Haegarda, a human plasma-derived C1 esterase inhibitor (C1-INH), is indicated for **routine prophylaxis to prevent hereditary angioedema (HAE) attacks** in adults and pediatric patients ≥ 6 years of age.[1]

Guidelines

According to US HAE Association Medical Advisory Board Guidelines (2020), when HAE is suspected based on clinical presentation, appropriate testing includes measurement of the serum C4 level, C1-INH antigenic level, and C1-INH functional level.[2] Low C4 plus low C1-INH antigenic or functional level is consistent with a diagnosis of HAE types I/II. The decision on when to use long-term prophylaxis cannot be made on rigid criteria but should reflect the needs of the individual patient. First-line medications for HAE I/II include intravenous C1-INH, Haegarda, or Takhzyro® (lanadelumab-flyo subcutaneous injection). The guideline was written prior to approval of Orladeyo® (berotralstat capsules).

According to World Allergy Organization/European Academy of Allergy and Clinical Immunology guidelines (2021), it is recommended to evaluate for long-term prophylaxis at every visit, taking disease activity, burden, and control as well as patient preference into consideration.[3] The following therapies are supported as first-line options for long-term prophylaxis: plasma-derived C1-INH (87% agreement), Takhzyro (89% agreement), and Orladeyo (81% agreement). With regard to plasma-derived C1-INH, it is noted that Haegarda provided very good and dose-dependent preventative effects on the occurrence of HAE attacks; the subcutaneous route may provide more convenient administration and maintain improved steady-state plasma concentrations compared with the intravenous route. Of note, androgens are not recommended in the first-line setting for long-term prophylaxis. Recommendations are not made regarding long-term prophylaxis in HAE with normal C1-INH.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Haegarda. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Haegarda as well as the monitoring required for adverse events and long-term efficacy, approval requires Haegarda to be prescribed by or in consultation with a physician who specializes in the condition being treated. A patient who has previously met initial therapy criteria for Haegarda for the requested indication under the Coverage Review Department and is currently receiving the requested therapy is only required to meet the continuation therapy criteria (i.e., currently receiving Haegarda). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Haegarda, initial therapy criteria must be met.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Haegarda is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Prophylaxis**. Approve Haegarda for 1 year if the patient meets one of the following (A or B):
   - **A)** Initial therapy. Approve if the patient meets both of the following (i and ii):
     - **i.** Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
       - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) **at baseline**, as defined by the laboratory reference values **[documentation required]**; AND
       - **b)** Patient has lower than normal serum C4 levels **at baseline**, as defined by the laboratory reference values **[documentation required]**; AND
     - **ii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.
   - **B)** Patient is currently receiving Haegarda prophylaxis. Approve if the patient meets all of the following (i, ii, and iii):
     Note: If the patient is currently receiving the requested therapy, but has not previously received approval of Haegarda for this indication through the Coverage Review Department, review under criteria for Initial Therapy.
     - **i.** Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
     - **ii.** According to the prescriber, the patient has had a favorable clinical response since initiating Haegarda prophylactic therapy compared with baseline (i.e., prior to initiating prophylactic therapy); AND
       Note: Examples of a favorable clinical response include decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks.
     - **iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

   Dosing. Approve up to a maximum dose of 60 IU/kg per injection, administered subcutaneously no more frequently than twice weekly with doses separated by at least 3 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Haegarda is not recommended in the following situations:

1. **Concomitant Use with Other Hereditary Angioedema (HAE) Prophylactic Therapies.** Haegarda has not been studied in combination with other prophylactic therapies for HAE, and combination

therapy for long-term prophylactic use is not recommended. Patients may use other medications, including Cinryze® (C1 esterase inhibitor [human] intravenous infusion), for treatment of acute HAE attacks, and for short-term (procedural) prophylaxis.
Note: Examples of other HAE prophylactic therapies include Cinryze (C1 esterase inhibitor [human] intravenous infusion), Orladeyo (berotralstat capsules), and Takhzyro (lanadelumab-flyo subcutaneous injection).

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Haegarda® subcutaneous injection [prescribing information]. Kankakee, IL: CSL Behring; January 2022.
2. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3.
3. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema: the 2021 revision and update. *Allergy*. 2022;77(7):1961-1990.

HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	**Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Prophylaxis:** A Note was added to the initial and continuation criteria that a diagnosis of HAE with normal C1-INH (also known as HAE type III) does not satisfy the requirement for a diagnosis of HAE type I or type II.	06/01/2022
Annual Revision	**Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Prophylaxis:** In Dosing, the interval was revised to read "no more frequently than twice weekly with doses separated by at least 3 days". Previously, the interval was written as "no more frequently than once every 3 days".	09/21/2022
Annual Revision	It was added to the Policy Statement that a person who has previously met initial therapy criteria for Haegarda for the requested indication under the Coverage Review Department and is currently receiving Haegarda, is only required to meet continuation of therapy criteria (i.e., patient is currently receiving Haegarda). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Haegarda, initial criteria must be met. In addition, the following changes were made: **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Prophylaxis:** Deleted [Type I or Type II] from indication heading. Under criteria for "Patient is currently receiving Haegarda prophylaxis", added a Note that patient has to meet initial therapy criteria and approval through the Coverage Review Department if they had previously received initial therapy approval through a different entity. Also added the word "type" before II while referring to diagnosis of HAE types.	09/20/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hereditary Angioedema – Icatibant Utilization Management Medical Policy
- Firazyr® (icatibant subcutaneous injection – Takeda, generic)
- Sajazir™ (icatibant subcutaneous injection – Cycle)

REVIEW DATE: 09/20/2023

OVERVIEW

Icatibant is a synthetic decapeptide that is indicated for the **treatment of acute hereditary angioedema (HAE) attacks** in adults ≥ 18 years of age.[1]

Guidelines

According to US HAE Association Medical Advisory Board Guidelines (2020), when HAE is suspected based on clinical presentation, appropriate testing includes measurement of the serum C4 level, C1 esterase inhibitor (C1-INH) antigenic level, and C1-INH functional level.[2] Low C4 plus low C1-INH antigenic or functional level is consistent with a diagnosis of HAE types I/II. The goal of acute therapy is to minimize morbidity and prevent mortality from an ongoing HAE attack. Patients must have ready access to effective on-demand medication to administer at the onset of an HAE attack. All HAE attacks are eligible for treatment, irrespective of the location of swelling or severity of the attack. First-line treatments include plasma-derived C1-INH, Ruconest® (C1-INH [recombinant] intravenous [IV] infusion), Kalbitor® (ecallantide subcutaneous injection), and icatibant.

In guidelines from the World Allergy Organization/European Academy of Allergy and Clinical Immunology (2021), it is recommended that all attacks be treated with either IV C1-INH, Kalbitor, or icatibant (evidence level A for all).[3] Regarding IV C1-INH, it is noted that Berinert® (C1 esterase inhibitor [human] IV infusion) and Cinryze® (C1 esterase inhibitor [human] IV infusion) are both plasma-derived products available for this use, although indications vary globally. It is essential that patients have on-demand medication to treat all attacks; thus, the guidelines recommend that patients have and carry medication for treatment of at least two attacks.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of icatibant. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). Because of the specialized skills required for evaluation and diagnosis of patients treated with icatibant, approval requires icatibant to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. A patient who has previously met initial therapy criteria for icatibant for the requested indication under the Coverage Review Department and is currently receiving the requested therapy is only required to meet the continuation therapy criteria (i.e., patient who has treated previous HAE attacks with icatibant). If past criteria have not been met under the Coverage Review Department and the patient has treated previous HAE attacks with icatibant, initial therapy criteria must be met.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of icatibant is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Treatment of Acute Attacks**. Approve for 1 year if the patient meets one of the following (A or B):
   - **A)** Initial therapy. Approve if the patient meets both of the following (i and ii):
     - **i.** Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
       - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) **at baseline**, as defined by the laboratory reference values **[documentation required]**; AND
       - **b)** Patient has lower than normal serum C4 levels **at baseline**, as defined by the laboratory reference values **[documentation required]**; AND
     - **ii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.
   - **B)** Patient who has treated previous HAE attacks with icatibant. Approve if the patient meets all of the following (i, ii, and iii):
     Note: If the patient is currently receiving the requested therapy but has not previously received approval of icatibant for this indication through the Coverage Review Department, review under criteria for Initial Therapy.
     - **i.** Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
     - **ii.** According to the prescriber, the patient has had a favorable clinical response with icatibant treatment; AND
       Note: Examples of a favorable clinical response include decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, or decrease in HAE acute attack frequency or severity.
     - **iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

   Dosing. Approve up to 30 mg per injection, administered subcutaneously no more frequently than three times daily.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of icatibant is not recommended in the following circumstances:

1. **Hereditary Angioedema (HAE) Prophylaxis**. Data are not available and icatibant is not indicated for prophylaxis of HAE attacks.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Firazyr® subcutaneous injection [prescribing information]. Lexington, MA: Takeda; October 2021.
2. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3.
3. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema: the 2021 revision and update. *Allergy*. 2022;77(7):1961-1990.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	09/21/2022
Annual Revision	It was added to the Policy Statement that a person who has previously met initial therapy criteria for icatibant for the requested indication under the Coverage Review Department and has treated previous HAE attacks with icatibant, is only required to meet the continuation of therapy criteria (i.e., patient has treated previous HAE attacks with icatibant). If past criteria have not been met under the Coverage Review Department and the patient has treated previous HAE attacks with icatibant, initial criteria must be met. In addition, the following changes were made: **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Treatment of Acute Attacks:** Deleted [Type I or Type II] from indication heading. Under criteria for "Patient who has treated previous HAE attacks with icatibant", added a Note that patient has to meet initial therapy criteria and approval through the Coverage Review Department if they had previously received initial therapy approval through a different entity .	09/20/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hereditary Angioedema – Kalbitor Utilization Management Medical Policy
- Kalbitor® (ecallantide subcutaneous injection – Takeda)

REVIEW DATE: 09/20/2023

OVERVIEW

Kalbitor, a plasma kallikrein inhibitor, is indicated for the **treatment of acute attacks of hereditary angioedema (HAE)** in patients ≥ 12 years of age.[1]

Potentially serious hypersensitivity reactions, including anaphylaxis, have occurred in patients treated with Kalbitor.[1] Kalbitor should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and HAE.

Guidelines

According to US HAE Association Medical Advisory Board Guidelines (2020), when HAE is suspected based on clinical presentation, appropriate testing includes measurement of the serum C4 level, C1 esterase inhibitor (C1-INH) antigenic level, and C1-INH functional level.[2] Low C4 plus low C1-INH antigenic or functional level is consistent with a diagnosis of HAE types I/II. The goal of acute therapy is to minimize morbidity and prevent mortality from an ongoing HAE attack. Patients must have ready access to effective on-demand medication to administer at the onset of an HAE attack. All HAE attacks are eligible for treatment, irrespective of the location of swelling or severity of the attack. First-line treatments include plasma-derived C1-INH, Ruconest® (C1-INH [recombinant] intravenous infusion), Kalbitor, and icatibant.

In guidelines from the World Allergy Organization/European Academy of Allergy and Clinical Immunology (2021), it is recommended that all attacks be treated with either IV C1-INH, Kalbitor, or icatibant (evidence level A for all).[3] Regarding IV C1-INH, it is noted that Berinert® (C1 esterase inhibitor [human] IV infusion) and Cinryze® (C1 esterase inhibitor [human] IV infusion) are both plasma-derived products available for this use, although indications vary globally. It is essential that patients have on-demand medication to treat all attacks; thus, the guidelines recommend that patients have and carry medication for treatment of at least two attacks.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Kalbitor. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kalbitor, as well as monitoring required for adverse events and long-term efficacy, approval requires the medication to be prescribed by or in consultation with a physician who specializes in the condition being treated. A patient who has previously met initial therapy criteria for Kalbitor for the requested indication under the Coverage Review Department and is currently receiving the requested therapy, is only required to meet the continuation criteria (i.e., patient who has treated previous acute HAE attacks with Kalbitor). If past criteria have not been met under the Coverage Review Department and the patient has treated previous HAE attacks with Kalbitor, initial therapy criteria must be met.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kalbitor is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Treatment of Acute Attacks**. Approve Kalbitor for 1 year if the patient meets one of the following (A or B):
   - **A)** Initial therapy. Approve if the patient meets both of the following (i and ii):
     - **i.** Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
       - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) **at baseline**, as defined by the laboratory reference values **[documentation required]**; AND
       - **b)** Patient has lower than normal serum C4 levels **at baseline**, as defined by the laboratory reference values **[documentation required]**; AND
     - **ii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.
   - **B)** Patient who has treated previous acute HAE attacks with Kalbitor. Approve if the patient meets all of the following (i, ii, and iii):
     Note: If the patient is currently receiving the requested therapy but has not previously received approval of Kalbitor for this indication through the Coverage Review Department, review under criteria for Initial Therapy.
     - **i.** Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
     - **ii.** According to the prescriber, the patient has had a favorable clinical response with Kalbitor treatment; AND
       Note: Examples of a favorable clinical response include decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, or decrease in HAE acute attack frequency or severity.
     - **iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

   Dosing. Approve up to a maximum dose of 30 mg per injection, administered subcutaneously no more frequently than twice daily.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kalbitor is not recommended in the following situations:

1. **Hereditary Angioedema (HAE) Prophylaxis**. Data are not available and Kalbitor is not indicated for prophylaxis of HAE attacks.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Kalbitor® subcutaneous injection [prescribing information]. Lexington, MA: Takeda; December 2020.
2. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3.
3. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema: the 2021 revision and update. *Allergy*. 2022;77(7):1961-1990.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	09/21/2022
Annual Revision	It was added to the Policy Statement that a person who has previously met initial therapy criteria for Kalbitor for the requested indication under the Coverage Review Department and has treated previous HAE attacks with Kalbitor, is only required to meet the continuation of therapy criteria (i.e., patient has treated previous HAE attacks with Kalbitor). If past criteria have not been met under the Coverage Review Department and the patient has treated previous HAE attacks with Kalbitor, initial criteria must be met. In addition, the following changes were made: **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Treatment of Acute Attacks:** Deleted [Type I or Type II] from indication heading. Under criteria for "Patient who has treated previous HAE attacks with Kalbitor", added a Note that patient has to meet initial therapy criteria and approval through the Coverage Review Department if they had previously received initial therapy approval through another entity. Also added the word "type" before II while referring to diagnosis of HAE types.	09/20/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hereditary Angioedema – Takhzyro Utilization Management Medical Policy
- Takhzyro® (lanadelumab-flyo subcutaneous injection – Shire/Takeda)

REVIEW DATE: 09/20/2023

OVERVIEW

Takhzyro, a human monoclonal antibody inhibitor of plasma kallikrein, is indicated for **prophylaxis to prevent attacks of hereditary angioedema (HAE)** in patients ≥ 2 years of age.[1]

Guidelines

According to US HAE Association Medical Advisory Board Guidelines (2020), when HAE is suspected based on clinical presentation, appropriate testing includes measurement of the serum C4 level, C1 esterase inhibitor (C1-INH) antigenic level, and C1-INH functional level.[2] Low C4 plus low C1-INH antigenic or functional level is consistent with a diagnosis of HAE types I/II. The decision on when to use long-term prophylaxis cannot be made on rigid criteria but should reflect the needs of the individual patient. First-line medications for HAE I/II include intravenous C1-INH, Haegarda® (C1-INH [human] subcutaneous injection), or Takhzyro. The guideline was written prior to approval of Orladeyo® (berotralstat capsules).

According to World Allergy Organization/European Academy of Allergy and Clinical Immunology guidelines (2021), it is recommended to evaluate for long-term prophylaxis at every visit, taking disease activity, burden, and control as well as patient preference into consideration.[3] The following therapies are supported as first-line options for long-term prophylaxis: plasma-derived C1-INH (87% agreement), Takhzyro (89% agreement), and Orladeyo (81% agreement). With regard to plasma-derived C1-INH, it is noted that Haegarda provided very good and dose-dependent preventative effects on the occurrence of HAE attacks; the subcutaneous route may provide more convenient administration and maintain improved steady-state plasma concentrations compared with the intravenous route. Of note, androgens are not recommended in the first-line setting for long-term prophylaxis. Recommendations are not made regarding long-term prophylaxis in HAE with normal C1-INH.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Takhzyro. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Takhzyro as well as the monitoring required for adverse events and long-term efficacy, approval requires Takhzyro to be prescribed by or in consultation with a physician who specializes in the condition being treated. A patient who has previously met initial therapy criteria for Takhzyro for the requested indication under the Coverage Review Department and is currently receiving the requested therapy is only required to meet the continuation therapy criteria (i.e., currently receiving Takhzyro). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Takhzyro, initial therapy criteria must be met.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Takhzyro is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Prophylaxis**. Approve Takhzyro for 1 year if the patient meets one of the following (A or B):
   - **A)** Initial therapy. Approve if the patient meets both of the following (i and ii):
     - **i.** Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
       - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND
       - **b)** Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND
     - **ii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.
   - **B)** Patient is currently receiving Takhzyro prophylaxis. Approve if the patient meets all of the following (i, ii, and iii):
     Note: If the patient is currently receiving the requested therapy, but has not previously received approval of Takhzyro for this indication through the Coverage Review Department, review under criteria for Initial Therapy.
     - **i.** Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
     - **ii.** According to the prescriber, the patient has had a favorable clinical response since initiating Takhzyro prophylactic therapy compared with baseline (i.e., prior to initiating prophylactic therapy); AND
       Note: Examples of a favorable clinical response include decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks.
     - **iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

   Dosing. Approve the following dosing regimens (A, B, or C):
   - **A)** For patients who are ≥ 12 years of age: Approve a dose of 300 mg per injection, administered subcutaneously no more frequently than once every 2 weeks; OR
   - **B)** For patients who are 6 to < 12 years of age: Approve a dose of 150 mg per injection, administered subcutaneously no more frequently than once every 2 weeks; OR
   - **C)** For patients who are < 6 years of age: Approve a dose up to 150 mg per injection, administered subcutaneously no more frequently than once every 4 weeks

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Takhzyro is not recommended in the following situations:

1. **Concomitant Use with Other Hereditary Angioedema (HAE) Prophylactic Therapies.** Takhzyro has not been studied in combination with other prophylactic therapies for HAE, and combination therapy for long-term prophylactic use is not recommended. Patients may use other medications, including Cinryze® (C1 esterase inhibitor [human] intravenous infusion), for on-demand treatment of acute HAE attacks, and for short-term (procedural) prophylaxis.
   Note: Examples of other HAE prophylactic therapies include Cinryze (C1 esterase inhibitor [human] intravenous infusion), Haegarda (C1 esterase inhibitor [human] subcutaneous injection), and Orladeyo (berotralstat capsules).

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Takhzyro® subcutaneous injection [prescribing information]. Lexington, MA: Takeda; February 2023.
2. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3.
3. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema: the 2021 revision and update. *Allergy*. 2022;77(7):1961-1990.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	09/21/2022
Selected Revision	In the overview section, the age of the FDA labeled indication of Takhzyro was revised from ≥ 12 years to ≥ 2 years. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Prophylaxis:** The age requirement of ≥ 12 years of age was added to the dosing regimen of 300 mg per injection, administered subcutaneously no more frequently than once every 2 weeks. The following two dosing regimens were added: for patients who are 6 to < 12 years of age, 150 mg per injection, administered subcutaneously no more frequently than once every 2 weeks; and for patients who are < 6 years of age, up to 150 mg per injection, administered subcutaneously no more frequently than once every 4 weeks.	02/15/2023
Annual Revision	It was added to the Policy Statement that a person who has previously met initial therapy criteria for Takhzyro for the requested indication under the Coverage Review Department and is currently receiving Takhzyro, is only required to meet continuation of therapy criteria (i.e., patient is currently receiving Takhzyro). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Takhzyro, initial criteria must be met. In addition, the following changes were made: **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Prophylaxis:** Deleted [Type I or Type II] from indication heading. Under criteria for "Patient is currently receiving Takhzyro prophylaxis", added a Note that patient has to meet initial therapy criteria and approval through the Coverage Review Department if they had previously received initial therapy approval through another entity. Also added the word "type" before II while referring to diagnosis of HAE types.	09/20/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Homozygous Familial Hypercholesterolemia – Evkeeza Utilization Management Medical Policy

- Evkeeza® (evinacumab-dgnb intravenous infusion – Regeneron)

REVIEW DATE: 05/08/2024

OVERVIEW

Evkeeza, an angiopoietin-like 3 inhibitor, is indicated as an adjunct to other low-density lipoprotein cholesterol (LDL-C) lowering therapies for the treatment of **homozygous familial hypercholesterolemia** (HoFH) in patients ≥ 5 years of age.[1]

In the pivotal trial that led to approval of Evkeeza, patients were receiving additional medications to lower LDL-C levels such as statins (94% [77% of patients at high-intensity statin doses]), a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor (77%), ezetimibe (75%), and Juxtapid® (lomitapide capsules). Although some Phase II data are available,[3] the safety and effectiveness of Evkeeza have not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH).[1] The effects of Evkeeza on cardiovascular (CV) morbidity and mortality have not been determined.

Disease Overview

Familial hypercholesterolemias, which include HeFH and HoFH, encompass a group of genetic defects that cause severe elevations in LDL-C levels, as well as other lipid parameters.[4,5] HoFH impacts approximately 1 in 300,000 to 1,000,000 persons. The condition is most commonly due to impaired functionality of the low-density lipoprotein (LDL) receptor which leads to a low or absence of clearance of LDL-C from the circulation. Currently known causes of familial hypercholesterolemia include mutations in the LDL receptor, apolipoprotein B, or PCSK9 genes. Patients with familial hypercholesterolemia may have physical findings such as tendon or cutaneous xanthomas, which may occur in childhood. Individuals with familial hypercholesterolemia are at very high risk of atherosclerotic cardiovascular disease (ASCVD) at a premature age. Most guidelines recommended LDL-C targets of < 100 mg/dL for adults and < 70 mg/dL for adults with ASCVD or other risk factors. Statins are the initial treatment for familial hypercholesterolemia. For patients with HoFH, high-intensity statin therapy is recommended, with ezetimibe added as well. Therapy with a PCSK9 inhibitor (e.g., Repatha® [evolocumab subcutaneous injection], Praluent® [alirocumab subcutaneous injection]) is usually the next step. Juxtapid can be added onto maximal lipid-lowering therapy and Evkeeza may be considered. Combination therapy is required for most patients. LDL apheresis is recommended in certain circumstances. The diagnosis of HoFH can be done by genetic or clinical criteria.[5] An untreated LDL-C (> 400 mg/dL) is suggestive of HoFH. Patients may have cutaneous or tendon xanthomas before 10 years of age and/or untreated elevated LDL-C levels consistent with HeFH in both parents. In the digenic form, one parent may have normal LDL-C levels and the other may have LDL-C levels consistent with HoFH.

Guidelines

Guidelines provide strategies for managing familial hypercholesterolemia, including HoFH, and mention the role of Evkeeza.[5,6]

- **American College of Cardiology (2022):** Specialized therapies, one of which includes Evkeeza, may be needed to control LDL-C in certain patients (e.g., those with HoFH) who have had an inadequate response to statins, with or without ezetimibe, and PCSK9 inhibitors.[6]
- **European Atherosclerosis Society (2023):** Clinical guidance by this organization recommends lipid-lowering therapy be initiated with high-intensity statin therapy and ezetimibe.[5] A PCSK9 inhibitor can be added as well. If not at LDL-C goals, other agents can be alternatives as well (e.g., Juxtapid, Evkeeza). Lipoprotein apheresis may also be considered. The goal is to reduce LDL-C to < 115 mg/dL in children and adolescents, < 70 mg/dL in adults if no major ASCVD risk factors are present, and < 55 mg/dL if patients have ASCVD or major ASCVD risk factors.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Evkeeza. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. A patient who has previously met Initial Therapy criteria for Evkeeza for the requested indication under the Coverage Review Department and is currently receiving Evkeeza is only required to meet continuation of therapy criteria (i.e., currently receiving therapy). If past criteria has not been met under the Coverage Review Department and the patient is currently receiving Evkeeza, or is restarting Evkeeza, Initial Therapy criteria must be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Evkeeza is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Homozygous Familial Hypercholesterolemia.** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 5 years of age; AND
     - **ii.** Patient meets ONE of the following (a, b, or c):
       - **a)** Patient has phenotypic confirmation of homozygous familial hypercholesterolemia; OR
         Note: Examples include pathogenic variants at the low-density lipoprotein receptor (LDLR), apolipoprotein B (apo B), proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene.
       - **b)** Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level > 400 mg/dL AND meets ONE of the following [(1) or (2)]:
         Note: Untreated refers to prior to therapy with any antihyperlipidemic agent.
         - **(1)** Patient had clinical manifestations of homozygous familial hypercholesterolemia before the age of 10 years; OR
           Note: Clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma.
         - **(2)** At least one parent of the patient had untreated LDL-C levels or total cholesterol levels consistent with familial hypercholesterolemia; OR

Note: An example of familial hypercholesterolemia is an untreated LDL-C level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL.

c) Patient has a treated LDL-C level ≥ 300 mg/dL AND meets ONE of the following [(1) or (2)]:
Note: Treated refers to after therapy with at least one antihyperlipidemic agent. Some examples of antihyperlipidemic agents include statins (e.g., atorvastatin, rosuvastatin, lovastatin, simvastatin, pravastatin), ezetimibe, a PCSK9 inhibitor (i.e., Repatha [evolocumab subcutaneous injection, Praluent [alirocumab subcutaneous injection]), or Juxtapid (lomitapide capsules).

(1) Patient had clinical manifestations of homozygous familial hypercholesterolemia before the age of 10 years; OR
Note: Examples of clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma.

(2) At least one parent of the patient had untreated LDL-C levels or total cholesterol levels consistent with familial hypercholesterolemia; AND
Note: An example of familial hypercholesterolemia in both parents would be if both had an untreated LDL-C ≥ 190 mg/dL and/or an untreated total cholesterol > 250 mg/dL.

iii. Patient meets ONE of the following (a or b):

a) Patient meets ALL of the following [(1), (2), and (3)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single entity or as a combination product]); AND

(2) Patient has tried one high-intensity statin along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND

(3) Low-density lipoprotein cholesterol level after this treatment regimen remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting ONE of the following [(1) or (2)]:

(1) Patient experienced statin-related rhabdomyolysis; OR
Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).

(2) Patient meets ALL of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND
Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND

(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND
Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

iv. Patient meets ONE of the following (a, b, or c):

a) Patient meets BOTH of the following [(1) and (2)]:

(1) Patient has tried one PCSK9 inhibitor for ≥ 8 continuous weeks; AND

Note: Examples of PCSK9 inhibitors include Repatha (evolocumab subcutaneous injection) and Praluent (alirocumab subcutaneous injection).

(2) The LDL-C level after this PCSK9 inhibitor therapy remains ≥ 70 mg/dL; OR

b) Patient is known to have two LDL-receptor negative alleles; OR

c) Patient is 5 to 9 years of age; OR

B) Patient Currently Receiving Evkeeza. Approve if according to the prescriber, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing LDL-C, total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Evkeeza for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Evkeeza, Initial Therapy criteria must be met.

Dosing. Approve 15 mg/kg administered by intravenous infusion no more frequently than once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Evkeeza is not recommended in the following situations:

1. **Heterozygous Familial Hypercholesterolemia.** The safety and effectiveness of Evkeeza have not been established in patients with hypercholesterolemia who do not have HoFH, including those with HeFH.[1]

2. **Hyperlipidemia.** Although data are available, the prescribing information for Evkeeza states that the safety and efficacy of Evkeeza have not been established in patients with other forms of hypercholesterolemia.[1,3]
   Note: This is not associated with HoFH and is referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated LDL-C levels.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Evkeeza® intravenous infusion [prescribing information]. Tarrytown, NY: Regeneron; March 2023.
2. Raal FJ, Rosenson RS, Reeskamp LF, et al, for the ELIPSE HoFH investigators. Evkeeza for homozygous familial hypercholesterolemia. *N Engl J Med*. 2020;383(8):711-720.
3. Rosenson RS, Burgess LJ, Ebenbichler CF, et al. Evkeeza in patients with refractory hypercholesterolemia. *N Engl J Med.* 2020;383(24):2307-2319.
4. Raal FJ, Hovingh GK Catapano AL. Familial hypercholesterolemia treatments: guidelines and new therapies. *Atherosclerosis*. 2018;277:483-492.
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6. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. *J Am Coll*. 2022;80(14):1366-1418.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	03/08/2023
Selected Revision	**Homozygous Familial Hypercholesterolemia:** The age of approval was changed to ≥ 5 years of age; previously, a patient had to be ≥ 12 years of age. Also, criteria were revised to not require a patient 5 to 9 years of age to try one proprotein convertase subtilisin kexin type 9 inhibitor.	03/29/2023
Early Annual Revision	It was added to the Policy Statement that a patient who has previously met initial therapy criteria for Evkeeza for the requested indication under the Coverage Review Department and is currently receiving Evkeeza is only required to meet continuation of therapy criteria (i.e., currently receiving therapy). If past criteria has not been met under the Coverage Review Department and the patient is currently receiving Evkeeza, or is restarting Evkeeza, initial criteria must be met. In addition, the following changes were made: **Homozygous Familial Hypercholesterolemia:** Requirements were divided to distinguish between initial therapy and patient currently receiving Evkeeza (previously there was only one criteria set). For a patient who is currently receiving Evkeeza and has previously met initial therapy criteria for the requested indication under the Coverage Review Department, only the continuation of therapy criteria has to be met. The continuation of therapy criteria states that according to the prescribing physician, the patient has experienced a response to therapy with examples provided in a Note.	04/26/2023
Annual Revision	It was removed from the Policy Statement that the agent is prescribing by or in consultation with a physician who specializes in the condition being treated. In addition, the following changes were made: **Homozygous Familial Hypercholesterolemia:** For Initial Therapy, the requirement that the medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders was removed. The requirement that the patient has had genetic confirmation by two mutant alleles at the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9, or low-density lipoprotein receptor adaptor protein 1 gene locus was changed to state that the patient has phenotypic confirmation of homozygous familial hypercholesterolemia with the above examples moved to a Note. The diagnostic criterion which stated that the patient has an untreated low-density lipoprotein cholesterol level > 500 mg/dL was changed to > 400 mg/dL. The criterion (which is in two places [those with an untreated low-density lipoprotein cholesterol level > 400 mg/dL and a treated low-density lipoprotein cholesterol level ≥ 300 mg/dL]) that both parents of the patient had untreated low-density lipoprotein cholesterol levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia was changed to state that at least one parent of the patient had untreated low-density lipoprotein cholesterol levels or total cholesterol levels consistent with familial hypercholesterolemia. The related Note that "An example of heterozygous familial hypercholesterolemia in both parents would be if both had an untreated low-density lipoprotein cholesterol level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL" was changed to state "An example of familial hypercholesterolemia is an untreated low-density lipoprotein cholesterol level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL." For a Patient Currently Receiving the Medication, the requirement that the "prescribing physician" notes that the patient has experienced a response to therapy was changed to "prescriber".	05/08/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Human Immunodeficiency Virus – Apretude Utilization Management Medical Policy
- Apretude (cabotegravir intramuscular injection – ViiV)

REVIEW DATE: 01/24/2024

OVERVIEW

Apretude, a human immunodeficiency virus-1 (HIV-1) integrase strand transfer inhibitor (INSTI), is indicated for **pre-exposure prophylaxis (PrEP)** in at-risk adults and adolescents weighing ≥ 35 kg to reduce the risk of sexually acquired HIV-1 infection.[1] Individuals must have a negative HIV-1 test prior to initiating Apretude (with or without an oral lead-in with Vocabria® [cabotegravir tablets]) for HIV-1 PrEP. All individuals should be screened for HIV-1 infection prior to each injection of Apretude.

Dosing

Apretude is administered by intramuscular (IM) gluteal injections and must be given by a healthcare provider. Vocabria *may* be administered for approximately 1 month prior to Apretude (Table 1) or the patient may proceed directly to Apretude without an oral lead-in (Table 2). If an oral lead-in is used, Apretude should be administered on the last day of oral lead-in or within 3 days thereafter (Table 1). Note: Vocabria is only (and will only ever be) available from the manufacturer.

Initial dosing: The recommended initiation dose of Apretude is two, single 600 mg IM injections, given 1 month apart for 2 consecutive months (Months 1 and 2 if no oral lead-in is used [Months 2 and 3 if oral lead-in is used]).[1] After the initiation injection doses, the recommended continuation dose of Apretude is a single 600 mg IM injection every 2 months (Q2M) [starting at Month 4 if no oral-lead in is used or Month 5 if oral lead-in is used]. Apretude may be given up to 7 days before or after the date of the scheduled injection.

Table 1. Recommended Dosing Schedule (with Oral Lead-in) for PrEP.[1]

Oral Lead-in (at Least 28 Days)	IM (Gluteal) Initiation Injection (Month 2 and Month 3)	IM (Gluteal) Continuation Injection (Month 5 and Q2M Onwards)
Vocabria 30 mg QD for 28 days	Apretude 600 mg (3 mL)[a]	Apretude 600 mg (3 mL)[b]

PrEP – Pre-exposure prophylaxis; IM – Intramuscular; Q2M – Every 2 months; QD – Once daily; [a] Should be administered on the last day of oral lead-in or within 3 days thereafter; [b] Individuals may be given Apretude up to 7 days before or after the date the individual is scheduled to receive the injections.

Table 2. Recommended Dosing Schedule (Direct to Injection) for PrEP.[1]

IM (Gluteal) Initiation Injection (Month 1 and Month 2)	IM (Gluteal) Continuation Injection (Month 4 and Q2M Onwards)
Apretude 600 mg (3 mL)[a]	Apretude 600 mg (3 mL)[a]

PrEP – Pre-exposure prophylaxis; IM – Intramuscular; Q2M – Every 2 months; [a] Individuals may be given Apretude up to 7 days before or after the date the individual is scheduled to receive the injections.

Adherence to the injection dosing schedule is strongly recommended. Individuals who miss a scheduled injection visit should be clinically reassessed to ensure resumption of Apretude remains appropriate.

Planned Missed Injections: If an individual plans to miss a scheduled (Q2M) continuation injection visit by > 7 days, take Vocabria 30 mg once daily (QD) for a duration of up to 2 months to replace one missed scheduled (Q2M) injection. The first dose of Vocabria should be taken approximately 2 months after the

last injection dose of Apretude. Restart Apretude on the day Vocabria dosing completes or within 3 days (Table 3). For Vocabria durations > 2 months, an alternative oral regimen is recommended.

Unplanned Missed Injections: If a scheduled injection visit is missed or delayed by > 7 days and oral dosing has not been taken in the interim, clinically reassess the individual to determine if resumption of Apretude remains appropriate (if the injection schedule will be continued, see Table 3).

Table 3. Apretude Dosing Recommendations After Missed Injections.[1]

Time Since Last Injection	Recommendation
Initiation Injection – If the second injection is missed and time since first injection is:	
≤ 2 months	Administer Apretude (600 mg) as soon as possible, then continue to follow the Q2M injection dosing schedule.
> 2 months	Restart Apretude (600 mg) with one injection, followed by a second injection (600 mg) 1 month later. Then continue to follow the Q2M injection dosing schedule thereafter (starting at Month 4).
Maintenance Injection – If third or subsequent injection is missed and time since prior injection is:	
≤ 3 months	Administer Apretude as soon as possible, then continue with the Q2M injection dosing schedule.
> 3 months	Restart Apretude (600 mg) with one injection, followed by a second injection (600 mg) 1 month later. Then continue to follow the Q2M injection dosing schedule thereafter (starting at Month 4).

Q2M – Every 2 months.

Dose modifications for Apretude are needed when administered with rifabutin. When rifabutin is started before or concomitantly with the first initiation injection of Apretude, the recommended dosing of Apretude is one 600 mg injection, followed 2 weeks later by a second 600 mg initiation injection and monthly thereafter while on rifabutin. When rifabutin is started at the time of the second initiation injection or later, the recommended dosing schedule of Apretude is 600 mg monthly while on rifabutin. After stopping rifabutin, the recommended dosing schedule of Apretude is 600 mg Q2M.

Guidelines

Apretude has been incorporated into the US Public Health Service PrEP for the Prevention of HIV Infection in the US Clinical Practice Guidelines (December 2021).[2] The update was published just prior to the FDA approval of Apretude.[2] A guideline available from the International Antiviral Society-USA (IAS-USA) [December 2022] provides similar guidance to the US Public Health Services guidelines.[3] The World Health Organization (WHO) published a guideline on Apretude for PrEP in 2022 to serve as a supplement to their other oral PrEP recommendations.[4] These guidelines are intended for a broader, world-wide audience, but generally echo the US Public Health Service PrEP and IAS-USA guideline recommendations. Table 4 provides a summary of the recommendations for daily oral PrEP and Apretude (every 2 months).

Table 4. US Public Health Service PrEP Recommendations (December 2021).[2]

	Recommendation for PrEP	Evidence Rating
Apretude[a]	For adults and adolescents who report sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition.	IA
FTC/TDF	For adult and adolescent (≥ 35 kg) **men and women**: • **Sexually active individuals** who report sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition; OR • **IDU** and report injection practices that place them at substantial ongoing risk of HIV exposure and acquisition.	1A

Table 4 (continued). US Public Health Service PrEP Recommendations (December 2021).[2]

	Recommendation for PrEP	Evidence Rating
Descovy	For adult and adolescent (≥ 35 kg) **cis-gender men**[*] and **transgender women**[†]**:** • **Sexually active individuals** who report sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition. Descovy PrEP has **not been studied in cis-gender women**[‡] and is **not recommended** for HIV prevention for women or other individuals at risk through receptive vaginal sex (IA).	IA (cis-gender men) IIB (transgender women)

PrEP – Pre-exposure prophylaxis; [a] Conditioned on FDA-approval at the time of guideline publication; HIV – Human immunodeficiency virus; FTC/TDF – Emtricitabine/tenofovir disoproxil fumarate; IDU – Injection drug user(s); [*] Individuals assigned male sex at birth whose gender identity is male; [†] Individuals assigned male sex at birth whose gender identity is female; [‡] Individuals assigned female sex at birth whose gender identity is female.

The US Public Health Service Guidelines also make the following points related to monitoring for PrEP.[2] Prior to prescribing PrEP, acute and chronic HIV infection must be excluded by symptom history and HIV testing must be performed immediately before any PrEP regimen is started (IA). Clinicians should document a negative HIV test result within the week before initiating (or reinitiating) PrEP medications, ideally with an antigen/antibody test conducted by a laboratory. The required HIV test prior to initiation of PrEP can be accomplished in one of two ways: 1) drawing blood and sending the specimen to a laboratory for an antigen/antibody test or 2) performing a rapid, point-of-care, FDA-approved, fingerstick antigen/antibody blood test. For PrEP, rapid tests that use oral fluid should not be used to screen for HIV infection because they are less sensitive for the detection of acute or recent infection than blood tests. HIV infection should be assessed every 2 months for patients receiving Apretude so that individuals with incident infection do not continue taking PrEP. When PrEP is prescribed, clinicians should provide access to support for medication adherence and continuation in follow-up PrEP care (IIA) and additional proven effective risk-reduction services to enable the use of PrEP in combination with other effective prevention methods to reduce risk for sexual acquisition of sexually transmitted infections or blood borne bacterial and viral infections though intravenous drug use (IIIA).

Guidelines from the IAS-USA state that for Apretude, HIV testing at initiation and at all visits should ideally include an HIV RNA tests with a lower limit of quantification of ≤ 50 copies/mL AND a laboratory-based antigen-antibody test.[3] If RNA testing is not available, Apretude can still be considered using antigen/antibody screening only. Results of such testing do not need to be available to provide injections.

The WHO guidelines for Apretude in PrEP enforce that HIV testing prior to offering Apretude is required and should be continued prior to each injection with Apretude.[4] Only individuals who are HIV-negative should be initiated on PrEP. HIV testing can be conducted using quality-assured serology assays (i.e., rapid diagnostic tests and enzyme immunoassays).

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Apretude. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Apretude as well as the monitoring required for adverse events and long-term efficacy, approval requires Apretude to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Apretude is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Pre-exposure Prophylaxis (PrEP) of Human Immunodeficiency Virus (HIV)-1 Infection.** Approve for 2 months if the patient meets the following (A, B, C, and D):
   - **A)** Patient is ≥ 35 kg; AND
   - **B)** Patient meets both of the following conditions (i and ii):
     - **i.** The medication will be administered only if the patient has a negative HIV-1 test result ≤ 1 week prior to the dose of Apretude; AND
     - **ii.** The medication will be administered only if the patient has no signs or symptoms of acute HIV infection, according to the prescriber: AND
   - **C)** The medication is prescribed as part of a comprehensive HIV-1 prevention strategy (i.e., adherence to administration schedule and safer sex practices, including condoms); AND
   - **D)** The medication is prescribed by or in consultation with a physician who specializes in the treatment of HIV infection.

   Dosing. Approve the following dosing regimens (A or B):
   - **A)** Approve 600 mg intramuscularly for one dose, followed by 600 mg for a second dose 1 month later, then approve 600 mg intramuscularly once every 2 months thereafter.
   - **B)** If Apretude will be given concomitantly with rifabutin, approve Apretude 600 mg intramuscularly for one dose, followed by 600 mg for a second dose 2 weeks later, then approve 600 mg intramuscularly once-monthly thereafter.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Apretude is not recommended in the following situations:

1. **Treatment of Human Immunodeficiency Virus (HIV).** Apretude is not indicated for the treatment of HIV. It is inadequate therapy for established HIV infection and use in persons with early HIV infection may encourage resistance of one or more of the PrEP medications.[2]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	01/25/2023
Annual Revision	No criteria changes.	01/24/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Human Immunodeficiency Virus – Cabenuva Utilization Management Medical Policy
- Cabenuva® (cabotegravir extended-release intramuscular injection; rilpivirine extended-release intramuscular injection, co-packaged – ViiV/GlaxoSmithKline)

REVIEW DATE: 02/07/2024

OVERVIEW

Cabenuva is a two-drug co-packaged product of cabotegravir, a human immunodeficiency virus type-1 (HIV-1) integrase strand-transfer inhibitor, and rilpivirine, an HIV-1 non-nucleoside reverse transcriptase inhibitor.[1] It is indicated as a complete regimen for the treatment of **HIV-1 infection** in patients ≥ 12 years of age and ≥ 35 kg to replace their current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to cabotegravir or rilpivirine.[1]

Dosing

Cabenuva must be administered by a healthcare professional. Prior to starting Cabenuva, healthcare professionals should carefully select patients who agree to the required monthly injection dosing schedule and counsel patients about the importance of adherence to scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance with missed doses.[1]

Oral lead-in with Vocabria® (cabotegravir tablets) + Edurant® (rilpivirine tablets) may be used for approximately 1 month (at least 28 days) prior to the initiation of Cabenuva to assess the tolerability of cabotegravir and rilpivirine. Cabenuva may be administered as a once-monthly injection or once every 2-month injection. Table 1 provides the recommended oral lead-in and monthly injection dosing schedule. Table 2 provides the recommended oral lead-in and every 2-month injection dosing schedule.

Table 1. Recommended Oral Lead-In and Monthly Intramuscular Injection Dosing Schedule.[1]

Vocabria + Edurant Lead-In (at Least 28 Days)	Cabenuva Initiation Injections (One-Time Dosing)	Cabenuva Continuation Injections (Once-Monthly Dosing)
Month 1	At Month 2 (On the Last Day of Oral Lead-In Dosing)	Month 3 Onwards
Vocabria (30 mg) QD with a meal	cabotegravir 600 mg (3 mL)	cabotegravir 400 mg (2 mL)
Edurant (25 mg) QD with a meal	rilpivirine 900 mg (3 mL)	rilpivirine 600 mg (2 mL)

QD – Once daily.

Table 2. Recommended Oral Lead-In and Every 2-Month Intramuscular Injection Dosing Schedule.[1]

Vocabria + Edurant Lead-In (at Least 28 Days)	Cabenuva Initiation Dosing	Cabenuva Continuation Injections (Once Every 2-Month Dosing)
Month 1	At Month 2 and Month 3	Month 5 Onwards
Vocabria (30 mg) QD with a meal	cabotegravir 600 mg (3 mL)	cabotegravir 600 mg (3 mL)
Edurant (25 mg) QD with a meal	rilpivirine 900 mg (3 mL)	rilpivirine 900 mg (3 mL)

QD – Once daily.

Guidelines

The Department of Health and Human Services (DHHS) Guidelines for the Use of Antiviral Agents in Adults and Adolescents with HIV (December 6, 2023) recognize Cabenuva as a long-acting antiretroviral regimen that is an optimization option for patients who are engaged with their health care providers, virologically suppressed on oral therapy for 3 to 6 months, and who agree to make the frequent clinic visits

needed.[5] Both FDA-approved dosing regimens are appropriate for Cabenuva in virally suppressed patients (once monthly or every 2-month dosing and with or without oral lead-in). The Guidelines point out that the tablet formulation of cabotegravir (Vocabria®) is only available through the manufacturer, not in community pharmacies. Cabenuva is not recommended as initial therapy for people with HIV because of the lack of data supporting efficacy in this patient population.

International Antiviral Society-USA (IAS-USA) Recommendations on Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults (2022) have similar recommendations to the DHHS guidelines for Cabenuva.[7] In individuals with no history of treatment failure and no known or suspected resistance to either agent, Cabenuva is an option. Cabenuva is noted to give greater patient satisfaction vs. oral antiretrovirals (ARVs) to those interested in non-oral options for treatment because of privacy, stigma, or convenience reasons. Both approved dosing regimens (with and without oral lead-in) are considered acceptable based on patient preference. If scheduled doses of Cabenuva are missed, resumption of therapy should follow the Prescribing Information. Cabenuva is not recommended for initial therapy in ARV-naïve individuals.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Cabenuva. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cabenuva as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Cabenuva to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Cabenuva as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cabenuva is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. **Human Immunodeficiency Virus (HIV)-1, Treatment.** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, iv, and v):
     - **i.** Patient is ≥ 12 years of age; AND
     - **ii.** Patient weighs ≥ 35 kg; AND
     - **iii.** Patient has HIV-1 RNA < 50 copies/mL (viral suppression) **[documentation required]**; AND
     - **iv.** Prior to initiating Cabenuva or 1 month lead-in with Vocabria (cabotegravir tablets), the patient was treated with a stable regimen (≥ 3 months) of antiretrovirals for HIV-1 **[documentation required]**; AND

v. The medication is prescribed by or in consultation with a physician who specializes in the treatment of HIV infection.

B) Patient is Currently Receiving Cabenuva. Approve if the patient has HIV-1 RNA < 50 copies/mL (viral suppression) **[documentation required]**.

Dosing. Approve one of the following dosing regimens (A or B):

A) Once Monthly Dosing Regimen: Approve 600 mg/900 mg intramuscularly for one dose, then approve 400 mg/600 mg intramuscularly once-monthly thereafter (every 4 weeks).

B) Every 2 Months Dosing Regimen: Approve 600 mg/900 mg intramuscularly for two doses, 1 month apart, then approve 600 mg/900 mg intramuscularly once every 2 months thereafter (every 8 weeks).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cabenuva is not recommended in the following situations:

1. **Pre-Exposure Prophylaxis (PrEP) of Human Immunodeficiency Virus (HIV)-1 Infection.** Cabenuva is not indicated for the prevention of HIV.

2. **Co-administration with Antiretrovirals for Human Immunodeficiency Virus (HIV) Treatment.** Because Cabenuva is a complete regimen, co-administration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended.[1]

3. **Human Immunodeficiency Virus (HIV)-2 Infection.** Cabenuva is not indicated in patients with HIV-2 infection.[1] The Department of Health and Human Services guidelines further note that HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors, therefore, Cabenuva is not recommended for people with HIV-2.[5]

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	02/01/2023
Selected Revision	**Human Immunodeficiency Virus Type-1 (HIV-1), Treatment:** Criteria requiring that, according to the prescriber, the patient either has difficulty maintaining compliance with a daily antiretroviral regimen for HIV-1 OR has severe gastrointestinal issues that may limit absorption or tolerance of oral medications was removed.	12/06/2023
Annual Revision	**Human Immunodeficiency Virus Type-1 (HIV-1), Treatment:** The criterion requiring that prior to initiating Cabenuva or 1 month lead-in with Vocabria (cabotegravir tablets), the patient was treated with a stable regimen (≥ 4 months) of antiretrovirals for HIV-1, was modified. The timeframe for the stable regimen was changed from ≥ 4 months to ≥ 3 months. **Human Immunodeficiency Virus (HIV)-2 Infection.** This condition was added to the Conditions not Recommended for Approval.	02/07/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Human Immunodeficiency Virus – Sunlenca Prior Authorization Policy
- Sunlenca® (lenacapavir subcutaneous injection – Gilead)

REVIEW DATE: 01/03/2024

OVERVIEW

Sunlenca, a human immunodeficiency virus type 1 (HIV-1) capsid inhibitor, is indicated in combination with other antiretroviral(s) for the treatment of **multidrug resistant HIV-1 infection** in heavily treatment-experienced adults failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.[1] Of note, Sunlenca is also available as tablets which are not addressed in this policy.

Clinical Efficacy

The efficacy of Sunlenca was evaluated in one Phase II/III, randomized, double-blind, placebo-controlled, multicenter, pivotal study in patients with multidrug resistant HIV-1.[2] Eligible patients had documented resistance to two or more agents from three of four main antiretroviral classes (nucleoside reverse transcriptase inhibitor [NRTI], non-nucleoside reverse transcriptase inhibitor [NNRTI], protease inhibitor, and integrase strand-transfer inhibitor [INSTI]) and two or fewer active antiretrovirals from the four main classes that could be effectively combined for optimized background therapy.

Dosing

Initial treatment with Sunlenca has two scheduling options. Option 1: Two subcutaneous (SC) injections (927 mg) and two tablets (600 mg) on Day 1, then two tablets (600 mg) on Day 2. Option 2: Two tablets (600 mg) on Days 1 and 2, one tablet (300 mg) on Day 8, and two SC injections (927 mg) on Day 15. For either option, maintenance treatment begins 26 weeks (± 2 weeks) after the initial dosing regimen is completed and continues as two SC injections (927 mg) once every 6 months (Q6M). Injections are given by a healthcare provider. Missed dose. During the maintenance period, if > 28 weeks have elapsed since the last injection and if clinically appropriate to continue Sunlenca treatment, restart the initiation dosage regimen from Day 1 using either Option 1 or Option 2.

Guidelines

According to the Department of Health and Human Services Guidelines for the use of antiretrovirals in adults and adolescents with HIV (December 6, 2023), in patients with multidrug resistance without fully active antiretroviral options, consensus on optimal management is lacking.[4] Maximal virologic suppression remains the goal of treatment; however, if it cannot be achieved, the goals are to preserve immune function, prevention clinical progression, and minimize the development of further resistance that may compromise future regimens. The Guidelines note that that even partial virologic suppression of HIV-1 RNA to > 0.5 $\log_{10}$ copies/mL from baseline correlates with clinical benefit. There is evidence that continuing antiretroviral therapy even in the presence of viremia and the absence of CD4+ count increases, reduces the risk of disease progression. Additional data suggest that even modest reductions in HIV-1 RNA levels continue to confer immunologic and clinical benefits. In general, adding a single, fully active antiretroviral to the regimen is not recommended because of the risk of rapid development of resistance. Patients with ongoing detectable viremia who lack sufficient treatment options to construct a fully suppressive regimen are noted to be candidates for Rukobia™ (fostemsavir extended-release tablets), Sunlenca, and/or Trogarzo® (ibalizumab-uiyk intravenous infusion). For people with multidrug-resistant HIV-2, Trogarzo and Sunlenca may be considered based on *in vitro* data. Optimal treatment strategies for individuals with HIV-2 are not defined.

The International Antiviral Society-USA (December 2022) provides some guidance on patients with viral failure; Sunlenca is mentioned in patients with INSTI resistance as a product under FDA review.[5] Management of INSTI resistance can be difficult and guidance from an expert in HIV drug resistance is recommended for selection of the optimal regimen. If INSTI resistance is relatively limited, and a new regimen is to include an INSTI, dolutegravir should be administered twice daily. The regimen should also include at least one, and preferably two other fully active drugs, optimally from drug classes not previously used. Therapies may include Rukobia, Sunlenca (currently under FDA review), Selzentry® (maraviroc tablets, generic and oral solution), Trogarzo, or Fuzeon® (enfuviritide SC injection).

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Sunlenca. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sunlenca as well as the monitoring required for adverse events and long-term efficacy, approval requires Sunlenca to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sunlenca is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Human Immunodeficiency Virus (HIV)-1 Infection, Treatment.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, and v):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** According to the prescriber, the patient is failing a current antiretroviral regimen for HIV; AND
     - **iii.** According to the prescriber, the patient has resistance to two or more agents from at least THREE of the following antiviral classes (a, b, c, d):
       - **a)** Nucleoside reverse transcriptase inhibitor;
         Note: Examples of nucleoside reverse transcriptase inhibitors include abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate, tenofovir alafenamide, zidovudine.
       - **b)** Non-nucleoside reverse transcriptase inhibitor;
         Note: Examples of non-nucleoside reverse transcriptase inhibitors include delaviridine, efavirenz, etravirine, nevirapine, nevirapine XR, rilpivirine.
       - **c)** Protease inhibitor;
         Note: Examples of protease inhibitors include atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, tipranavir.
       - **d)** Integrase strand transfer inhibitor; AND

Note: Examples of integrase strand transfer inhibitors include raltegravir, dolutegravir, elvitegravir.

iv. The medication will be taken in combination with an optimized antiviral background regimen including one or more other antiretroviral agents; AND

v. The medication is prescribed by or in consultation with a physician who specializes in the treatment of HIV infection.

B) Patient is Currently Receiving Sunlenca. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. The medication will continue to be taken in combination with an optimized antiviral background regimen including one or more other antiretroviral agents; AND

ii. Patient has responded to a Sunlenca-containing regimen, as determined by the prescriber. Note: Examples of a response are HIV RNA < 50 cells/mm^3, HIV-1 RNA ≥ 0.5 $\log_{10}$ reduction from baseline in viral load.

Dosing. Approve an initial dose of 927 mg subcutaneously one time, and maintenance dose of 927 mg subcutaneously every 6 months (± 2 weeks from the date of the last injection).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sunlenca is not recommended in the following situations:

1. **Pre-Exposure Prophylaxis (PrEP) of Human Immunodeficiency Virus (HIV).** Sunlenca is not approved for this indication; however, it is under investigation in two Phase III, unpublished, and ongoing clinical trials for PrEP (PURPOSE 1 and PURPOSE 2).[7,8]

2. **Human Immunodeficiency Virus (HIV), Use in Treatment-Naïve Patients.** Sunlenca is not approved for this indication; however, it is under investigation in one Phase II ongoing clinical trial in treatment-naïve adults with HIV-1 (CALIBRATE).[3]

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/04/2023
Selected Revision	**Human Immunodeficiency Virus (HIV)-1 Infection, Treatment**: Dosing was updated to approve an initial dose of 927 mg subcutaneously one time and a maintenance dose of 927 mg every 6 months (± 2 weeks from the date of the last injection). Previously, two dosing options were provided: an initial dose of 927 mg subcutaneously one time (Day 1), and maintenance dose of 927 mg subcutaneously every 6 months (26 weeks) from the date of the last injection ± 2 weeks; OR an initial dose of 927 mg two times (Day 1 and Day 15), and maintenance dose of 927 mg subcutaneously every 6 months (26 weeks) from the date of the last injection ± 2 weeks.	04/12/2023
Annual Revision	No criteria changes.	01/03/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Human Immunodeficiency Virus – Trogarzo Utilization Management Medical Policy
- Trogarzo® (ibalizumab-uiyk intravenous infusion – Theratechnologies)

REVIEW DATE: 03/27/2024

OVERVIEW

Trogarzo is a long-acting humanized immunoglobulin G4 monoclonal antibody indicated in combination with other antiretroviral(s) for the treatment of **human immunodeficiency virus type-1 (HIV-1) infection** in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen.[1] Patients should receive a single intravenous loading dose of 2,000 mg followed by a maintenance dose of 800 mg once every 2 weeks. The loading dose and maintenance doses of Trogarzo can be administered as a diluted intravenous (IV) infusion or undiluted IV push.

Disease Overview

Multiclass or three-class drug resistant HIV-1 infection is usually defined as the presence of phenotypic or genotypic resistance to at least one drug in each of the following three classes: the nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors classes.[2] Trogarzo blocks HIV-1 from infecting CD4+ T cells by binding to domain 2 of CD4.[1] This interferes with post-attachment steps required for the entry of HIV-1 virus particles into host cells and prevents the viral transmission that occurs via cell-cell fusion. The binding specificity to domain 2 of CD4 allows Trogarzo to block viral entry into host cells without causing immunosuppression. There is no antagonism with other antiretrovirals. In the pivotal trial for Trogarzo, all patients had documented resistance to at least one antiretroviral from the nucleoside reverse transcriptase inhibitor, non-nucleoside reverse transcriptase inhibitor, and protease inhibitor classes.

Guidelines

According to the Department of Health and Human Services Guidelines for the use of antiretrovirals in adults and adolescents with HIV (February 27, 2024), in patients with multidrug resistance without fully active antiretroviral options, consensus on optimal management is lacking.[4] Maximal virologic suppression remains the goal of treatment; however, if it cannot be achieved, the goals are to preserve immune function, prevention clinical progression, and minimize the development of further resistance that may compromise future regimens. The Guidelines note that that even partial virologic suppression of HIV-1 RNA to > 0.5 $\log_{10}$ copies/mL from baseline correlates with clinical benefit. There is evidence that continuing antiretroviral therapy even in the presence of viremia and the absence of CD4+ count increases, reduces the risk of disease progression. Additional data suggest that even modest reductions in HIV-1 RNA levels continue to confer immunologic and clinical benefits. In general, adding a single, fully active antiretroviral to the regimen is not recommended because of the risk of rapid development of resistance. Patients with ongoing detectable viremia who lack sufficient treatment options to construct a fully suppressive regimen are noted to be candidates for Rukobia™ (fostemsavir extended-release tablets), Sunlenca® (lenacapavir subcutaneous [SC] injection) and/or Trogarzo. For people with multidrug-resistant HIV-2, Trogarzo and Sunlenca may be considered based on *in vitro* data. Optimal treatment strategies for individuals with HIV-2 are not defined.

The International Antiviral Society-USA (December 2022) provides some guidance on patients with viral failure.[4] The regimen should also include at least one, and preferably two other fully active drugs, optimally from drug classes not previously used. Therapies may include Rukobia, Sunlenca (currently under FDA

review), Selzentry® (maraviroc tablets, generic and oral solution), Trogarzo, or Fuzeon® (enfuviritide SC injection).

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Trogarzo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Trogarzo as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Trogarzo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Trogarzo is recommended in those who meet the following:

FDA-Approved Indication

1. **Human Immunodeficiency Virus (HIV)-1.** Approve for the duration outlined below if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, and v):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** According to the prescriber, the patient is failing a current antiretroviral regimen for HIV; AND
     - **iii.** Patient has multiple antiretroviral drug resistance as demonstrated by resistance to at least one antiretroviral from at least THREE of the following antiviral classes (a, b, c, d, e, f):
       - **a)** Nucleoside reverse transcriptase inhibitor;
         Note: Examples of nucleoside reverse transcriptase inhibitors include but are not limited to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate, tenofovir alafenamide, zidovudine.
       - **b)** Non-nucleoside reverse transcriptase inhibitor;
         Note: Examples of non-nucleoside reverse transcriptase inhibitors include but are not limited to delavirdine, efavirenz, etravirine, nevirapine, nevirapine XR, rilpivirine.
       - **c)** Protease inhibitor;
         Note: Examples of protease inhibitors include but are not limited to atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, tipranavir.
       - **d)** Fusion inhibitor;
         Note: An example of a fusion inhibitor includes but is not limited to Fuzeon (enfuviritide subcutaneous injection).
       - **e)** Integrase strand transfer inhibitor;
         Note: Examples of integrase strand transfer inhibitors include but are not limited to raltegravir, dolutegravir, elvitegravir.
       - **f)** CCR5-antagonist; AND
         Note: An example of a CCR5-antagonist includes but is not limited to Selzentry (maraviroc tablets).

iv. The medication will be taken in combination with an optimized antiviral background regimen including one or more other antiretroviral agents; AND
v. The medication is prescribed by or in consultation with a physician who specializes in the treatment of HIV infection.

B) Patient is Currently Receiving Trogarzo. Approve for 1 year if the patient meets BOTH of the following (i and ii):
i. The medication will continue to be taken in combination with an optimized antiviral background regimen including one or more other antiretroviral agents; AND
ii. Patient has responded (e.g., HIV-1 RNA ≥ 0.5 $\log_{10}$ reduction from baseline in viral load) to a Trogarzo-containing regimen, as determined by the prescriber.

Dosing. Approve the following dosing regimens (A and B):
A) Loading dose of 2,000 mg as an intravenous infusion or intravenous push, given one time; AND
Note: Approve an additional 2,000 mg loading dose if an 800-mg maintenance dose is missed by ≥ 3 days of the scheduled dosing day, with maintenance dosing (800 mg intravenously every 2 weeks) resumed thereafter.
B) Maintenance dose of 800 mg, as an intravenous infusion or intravenous push, given every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Trogarzo is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. Last Updated: February 27, 2024. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/whats-new-adult-adolescent-arv.pdf. Accessed on March 7, 2024.
4. Gandhi RT, Bedimo R, Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults 2022 recommendations of the International Antiviral Society–USA Panel. *JAMA*. 2023;329(1):63-84.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Human Immunodeficiency Virus (HIV)-1 Infection.** Examples of antiretroviral therapies tried were moved to notes.	03/29/2023
Selected Revision	**Human Immunodeficiency Virus (HIV)-1 Infection.** Dosing was updated to include loading dose by intravenous push.	12/20/2023
Annual Revision	**Conditions Not Recommended for Approval. Human Immunodeficiency Virus (HIV-2):** This condition not recommended for approval was removed.	03/27/2024

CARECONTINUUM™

MEDICAL STEP MANAGEMENT POLICY

POLICY: Hyaluronic Acid Derivatives (Intraarticular) Medical Step Management Policy

- Durolane® (sodium hyaluronate injection – Bioventus)
- Euflexxa® (sodium hyaluronate injection – Ferring)
- Gel-One® (sodium hyaluronate injection – Seikagaku/Zimmer)
- Gelsyn-3™ (sodium hyaluronate injection – Bioventus)
- GenVisc® 850 (sodium hyaluronate injection – OrthogenRx)
- Hyalgan® (sodium hyaluronate injection – Fidia)
- Hymovis® (high molecular weight viscoelastic hyaluronan injection – Fidia)
- Monovisc™ (high molecular weight hyaluronan injection – Anika)
- Orthovisc® (high molecular weight hyaluronan injection – Anika)
- Supartz FX™ (sodium hyaluronate injection – Seikagaku/Bioventus)
- Sodium hyaluronate 1% injection – Teva
- SynoJoynt™ (sodium hyaluronate injection – Arthrex)
- Synvisc® (hylan G-F 20 sodium hyaluronate injection – Genzyme)
- Synvisc-One® (hylan G-F 20 sodium hyaluronate injection – Genzyme)
- Triluron™ (sodium hyaluronate injection – Fidia)
- TriVisc™ (sodium hyaluronate injection – OrthogenRx)
- Visco-3™ (sodium hyaluronate injection – Seikagaku/Bioventus)

REVIEW DATE: 09/27/2023

OVERVIEW

Hyaluronic acid derivatives are indicated for the treatment of **pain related to knee osteoarthritis** in patients who have failed to respond adequately to conservative nonpharmacologic therapy and to simple analgesics (e.g., acetaminophen).[1-17] This policy involves the use of the intraarticular hyaluronic acid derivatives used for knee osteoarthritis.

Table 1. Number of Injections per Course for Hyaluronic Acid Derivatives.[1-17*]

Product	Number of injections per course
Durolane, Gel-One, Monovisc, Synvisc-One	One injection given one time
Hymovis	Two injections given 1 week apart
Euflexxa, Gelsyn-3, Sodium Hyaluronate, SynoJoynt, Synvisc, Triluron, TriVisc, Visco-3	Three injections given 1 week apart
Orthovisc	Three or four injections given 1 week apart
GenVisc 850, Hyalgan, Supartz FX	Five injections given 1 week apart

* Dose is for one knee. If two knees are being treated, then each knee requires a syringe or vial of product.

POLICY STATEMENT

This Medical Step Management program has been developed to encourage the use of Preferred Products. For all products (Preferred and Non-Preferred), the patient is required to meet the standard *Hyaluronic Acid Derivatives (Intraarticular) Utilization Management Medical* criteria. The program also directs the patient to try at least one Preferred Product prior to the approval of a Non-Preferred Product. Patients with a history of using the Non-Preferred Products who require additional therapy with a hyaluronic acid derivative are directed to the Preferred Products. Requests for Non-Preferred Products will also be reviewed using the

exception criteria (below). All approvals are provided for the number of injections required to complete one course, as directed in the standard *Hyaluronic Acid Derivatives (Intraarticular) Utilization Management Medical Policy*.

Documentation: Documentation of previous therapy will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, and prescription receipts.

Automation: None.

Preferred Products: Euflexxa, Orthovisc, Monovisc
Non-Preferred Products: Durolane, Gel-One, Gelsyn-3, GenVisc 850, Hyalgan, Hymovis, Supartz FX, Sodium hyaluronate injection, SynoJoynt, Synvisc, Synvisc-One, Triluron, TriVisc, Visco-3

RECOMMENDED EXCEPTION CRITERIA

Non-Preferred Products	Exception Criteria
Durolane Gel-One Gelsyn-3 GenVisc 850 Hyalgan Hymovis Supartz FX Sodium hyaluronate injection SynoJoynt Synvisc Synvisc-One Triluron TriVisc Visco-3	**1.** Approve one course of therapy per treated knee if the patient meets the following (A and B): **A)** Patient meets the standard *Hyaluronic Acid Derivatives (Intraarticular) Utilization Management Medical Policy* criteria; AND **B)** Patient meets ONE of the following (i, ii, or iii): **i.** Patient has tried a course of Orthovisc (one course equals 3 or 4 injections) OR Euflexxa (one course equals 3 injections) **[documentation required]**; OR **ii.** Patient has tried a single injection of Monovisc **[documentation required]**; OR **iii.** Patient meets both of the following (a and b): **a)** The request is for product that requires more than one injection to complete a course; AND Note: Examples of products that are given as more than one injection to complete a course include Gelsyn-3, GenVisc 850, Hyalgan, Hymovis, Supartz FX, Sodium hyaluronate injection, SynoJoynt, Synvisc, Triluron, TriVisc, or Visco-3. **b)** Patient has already started a course of injections with one of these agents. Note: If a course of therapy has already been started, the patient can continue with the same product to complete the entire course. After completing this course, if further therapy is required with a hyaluronic acid derivative, then a Preferred Product must be tried.

REFERENCES

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3. Gel-One® intraarticular injection [prescribing information]. Warsaw, IN: Zimmer; May 2011.
4. Gelsyn-3® intraarticular injection [prescribing information]. Durham, NC: Bioventus; 2016.
5. GenVisc® 850 intraarticular injection [prescribing information]. Doylestown, PA: OrthogenRx; not dated.
6. Hyalgan® intraarticular injection [prescribing information]. Parsippany, NJ: Fidia Pharma; May 2014.
7. Hymovis® intraarticular injection [prescribing information]. Parsippany, NJ: Fidia Pharma; October 2015.
8. Monovisc® intraarticular injection [prescribing information]. Bedford, MA: DePuy Synthes; not dated.
9. Orthovisc® intraarticular injection [prescribing information]. Raynham, MA: DePuy Synthes; September 2014.
10. Sodium hyaluronate 1% intraarticular injection [prescribing information]. North Wales, PA: Teva; March 2019.
11. Supartz® FX™ intraarticular injection [prescribing information]. Durham, NC: Bioventus; April 2015.
12. Synvisc® intraarticular injection [prescribing information]. Ridgefield, NJ: Genzyme; September 2014.
13. Synvisc-One® intraarticular injection [prescribing information]. Ridgefield, NJ: Genzyme; September 2014.
14. Triluron intraarticular injection [prescribing information]. Florham Park, NJ: Fidia Pharma; March 2019.
15. Trivisc intraarticular injection [prescribing information]. Doylestown, PA: OrthogenRx; not dated.
16. Visco-3 intraarticular injection [prescribing information]. Durhan, NC: Bioventus; not dated.
17. SynoJoynt™ injection [prescribing information]. Naples, FL: Arthrex; 2022.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	SynoJoynt was added to the policy as a Non-Preferred Product.	09/21/2022
Annual Revision	No criteria changes.	09/27/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hyaluronic Acid Derivatives (Intraarticular) Utilization Management Medical Policy

- Durolane® (sodium hyaluronate injection – Bioventus)
- Euflexxa® (sodium hyaluronate injection – Ferring)
- Gel-One® (sodium hyaluronate injection – Seikagaku/Zimmer)
- Gelsyn-3™ (sodium hyaluronate injection – Bioventus)
- GenVisc® 850 (sodium hyaluronate injection – OrthogenRx)
- Hyalgan® (sodium hyaluronate injection – Fidia)
- Hymovis® (high molecular weight viscoelastic hyaluronan injection – Fidia)
- Monovisc™ (high molecular weight hyaluronan injection – Anika)
- Orthovisc® (high molecular weight hyaluronan injection –Anika)
- Supartz FX™ (sodium hyaluronate injection – Seikagaku/Bioventus)
- Sodium hyaluronate 1% injection – Teva
- SynoJoynt™ (sodium hyaluronate injection – Arthrex)
- Synvisc® (hylan G-F 20 sodium hyaluronate injection – Genzyme)
- Synvisc-One® (hylan G-F 20 sodium hyaluronate injection – Genzyme)
- Triluron™ (sodium hyaluronate injection – Fidia)
- TriVisc™ (sodium hyaluronate injection – OrthogenRx)
- Visco-3™ (sodium hyaluronate injection – Seikagaku/Bioventus)

REVIEW DATE: 09/27/2023

OVERVIEW

Hyaluronic acid derivatives are indicated for the treatment of **pain related to knee osteoarthritis** in patients who have failed to respond adequately to conservative nonpharmacologic therapy and to simple analgesics (e.g., acetaminophen).[1-16,43] The use of intraarticular injections are to restore the normal properties (viscosity and elasticity) of the synovial fluid. Gel-One, Hyalgan, Supartz FX, Synvisc/Synvisc-One, Triluron, and Visco-3 are derived from rooster or chicken combs. The remaining products are derived from non-avian sources and may be useful for patients with allergies to eggs or poultry products. GenVisc 850 has data to support similarity to Supartz FX.[9] Although retreatment data are limited, all of these products have data concerning efficacy and/or safety of repeat courses. In many cases, at least 6 months was required or a minimum of 6 months had elapsed prior to injection of a repeat course.

Guidelines

Guidelines for the medical management of osteoarthritis of the hand, hip, and knee are available from the American College of Rheumatology (2019).[17] Multiple non-pharmacological modalities are recommended for knee osteoarthritis, including exercise, self-management programs, weight loss, Tai Chi, and use of assistive devices (i.e., bracing or a cane). Pharmacologic therapy for knee osteoarthritis consists of acetaminophen, oral and topical non-steroidal anti-inflammatory drugs (NSAIDs), tramadol, intraarticular corticosteroid injections, duloxetine, and topical capsaicin. There is limited evidence establishing a benefit of hyaluronic acid intraarticular injections, which contributes to the conditional recommendation against use in knee osteoarthritis. However, when other alternatives have been exhausted or have failed to provide satisfactory benefit, use of intraarticular hyaluronic acid injections may be viewed more favorably than offering no intervention. In the guidelines, no distinction is made between the available intraarticular hyaluronic acid products or between products with various molecular weights.

The Osteoarthritis Research Society International also has guidelines for knee osteoarthritis (2019).[19] These guidelines note that use of intraarticular hyaluronic acid injections are conditionally recommended for patients with knee osteoarthritis. The guidelines comment on the long-term treatment effect with intraarticular hyaluronic acid injections which is associated with symptom improvement beyond 12 weeks and a more favorable safety profile than intraarticular corticosteroid injections.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of hyaluronic acid derivatives indicated for knee osteoarthritis. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Because of the specialized skills required for evaluation and diagnosis of patients treated with hyaluronic acid derivative intraarticular products as well as the specialized administration technique, these products are required to be administered by or under the supervision of a physician specializing in rheumatology, orthopedic surgery, or physical medicine and rehabilitation (physiatrist). Previous therapy is required to be verified by a clinician in the Coverage Review Department when noted in the criteria as **[verification of therapies required].** All approvals for initial therapy are provided for the number of injections noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of hyaluronic acid derivatives is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. **Osteoarthritis of the Knee**. Approve one course of therapy per treated knee if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve an initial course if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Diagnosis of the knee to be treated is confirmed by radiologic evidence of knee osteoarthritis; AND
       Note: Examples of radiographic evidence includes x-ray, magnetic resonance imaging (MRI), computed tomography (CT) scan, ultrasound.
     - **ii.** Patient has tried at least TWO of the following three modalities of therapy for osteoarthritis (a, b, c):
       - **a)** At least one course of physical therapy for knee osteoarthritis;
       - **b)** At least TWO of the following pharmacologic therapies [(1), (2), (3), (4)] **[verification of therapies required]**:
         - **(1)** Oral or topical nonsteroidal anti-inflammatory drug(s) [NSAID(s)];
           Note: Examples of oral NSAIDs include naproxen, ibuprofen, celecoxib. Examples of topical NSAIDs include diclofenac solution or diclofenac gel. A trial of two or more NSAIDs (oral and/or topical) counts as one pharmacologic therapy.
         - **(2)** Acetaminophen;
         - **(3)** Tramadol (Ultram/XR, generic);
         - **(4)** Duloxetine (Cymbalta, generic);
       - **c)** At least TWO injections of intraarticular corticosteroids to the affected knee; AND
     - **iii.** The product is administered by or under the supervision of a physician specializing in rheumatology, orthopedic surgery, or physical medicine and rehabilitation (physiatrist).

B) Patient has Already Received One or More Courses of a Hyaluronic Acid Derivative in the Same Knee. Approve one repeat course if the patient meets ALL of the following (i, ii, and iii):
- **i.** At least 6 months have elapsed since the last injection with any hyaluronic acid derivative; AND
- **ii.** According to the prescriber, the patient had a response to the previous course of hyaluronic acid derivative therapy for osteoarthritis of the knee and now requires additional therapy for osteoarthritis symptoms; AND
  Note: Examples of a response include reduced joint pain, tenderness, morning stiffness, or improved mobility.
- **iii.** The product is administered by or under the supervision of a physician specializing in rheumatology, orthopedic surgery, or physical medicine and rehabilitation (physiatrist).

Dosing. Approve the following dosing regimens:
Note: Dose listed is for one knee. If two knees are being treated, then each knee requires a syringe or vial of product.

A) Durolane, Gel-One, Monovisc, Synvisc-One: Approve one injection.
B) Hymovisc: Approve up to two injections given 1 week apart.
C) Euflexxa, Gelsyn-3, sodium hyaluronate 1% injection, SynoJoynt, Synvisc, Triluron, TriVisc, Visco-3: Approve up to three injections given 1 week apart.
D) Orthovisc: Approve up to 4 injections given 1 week apart.
E) GenVisc 850, Hyalgan, Supartz FX: Approve up to 5 injections given 1 week apart.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of hyaluronic acid derivatives is not recommended in the following situations:

1. **Acute Ankle Sprain.** A randomized, controlled, prospective trial was conducted which assessed the use of intraarticular hyaluronic acid in acute ankle sprains.[20-21] Patients treated with intraarticular hyaluronic acid (n = 79) within 48 hours of injury and again on Day 4 reported a time to pain-free and disability-free return to sport of 11 days (± 8 days) compared with 17 days (± 8 days) for placebo ($P < 0.05$). All patients were also treated with standard of care (rest, ice, compression, and elevation). At 24 months, the placebo group experienced an increase in repeat sprains when compared with those treated with an intraarticular hyaluronic acid product (21 recurrent ankle sprains in the placebo group compared with 7 recurrent ankle sprains in the intraarticular hyaluronic acid treatment group [$P < 0.001$]) as well as a significant difference in missed days from participation in sport activity (49 days vs. 12 days for the placebo and hyaluronic acid groups, respectively; $P < 0.001$).[21] More data are needed to determine the role of intraarticular hyaluronic acid products in the treatment of acute ankle sprains.

2. **Osteoarthritis and Other Pathologic Conditions Involving Joints Other than the Knee** (e.g., hand, hip, ankle, shoulder osteoarthritis, temporomandibular joint [TMJ], adhesive capsulitis of the shoulder, subacromial impingement). The prescribing information for these agents state in the precautions section that the safety and effectiveness of hyaluronic acid derivatives injections into joints other than the knee have not been established.[1-16] Due to the absence of evidence to support use of intraarticular hyaluronic acid and potential for harm, the guidelines for the management of hand, hip, and knee osteoarthritis by American College of Rheumatology (2019) do not recommend use of intraarticular hyaluronic acid in patients with hand or hip osteoarthritis.[17] Small trials have also investigated intraarticular hyaluronic acid in other joints, including ankle osteoarthritis and hip osteoarthritis.[23-38] More data are needed to determine if there is a role for intraarticular hyaluronic acid for the treatment of osteoarthritis involving other joints. A small trial (n = 70) found that intraarticular hyaluronic acid

did not result in increased benefit for adhesive capsulitis of the shoulder (also known as frozen shoulder) in patients who were already receiving physical therapy.[39] Another small study (n = 159) did not show benefit of intraarticular hyaluronic acid over corticosteroid or placebo injections in patients with subacromial impingement.[40]

3. **Pathologic Conditions of the Knee Other than Osteoarthritis** (e.g., chondromalacia patellae, osteochondritis dissecans, patellofemoral syndrome, post-anterior cruciate ligament [ACL] reconstruction). Intraarticular hyaluronic acid derivatives are indicated in knee osteoarthritis.[1-16] Adequate, well-designed trials have not clearly established the use of these products in other conditions of the knee.[41-42]

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	09/28/2022
Annual Revision	No criteria changes.	09/27/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immune Globulin – Atgam Utilization Management Medical Policy
- Atgam® (lymphocyte immune globulin, anti-thymocyte globulin [equine] intravenous infusion – Pfizer)

REVIEW DATE: 01/03/2024

OVERVIEW

Atgam, an immune globulin, is indicated for the following uses:[1]
- **Allograft rejection**, for the management of allograft rejection in renal transplant patients. When administered with conventional therapy at the time of rejection, Atgam increases the frequency of resolution of the acute rejection episode.
- **Aplastic anemia,** for the treatment of moderate to severe aplastic anemia in patients unsuitable for bone marrow transplantation. The usefulness of Atgam has not been demonstrated in patients with aplastic anemia who are suitable candidates for bone marrow transplantation or in patients with aplastic anemia secondary to neoplastic disease, storage disease, myelofibrosis, Fanconi's syndrome, or in patients known to have been exposed to myelotoxic agents or radiation.

Dosing Information

- **Aplastic anemia.** A more common high dose regimen used for aplastic anemia is 40 mg/kg/day for 4 days in combination with cyclosporine.[16] It is noted that when given over longer timeframes, such as 8 to 14 days, the incidence and severity of serum sickness is greater.[17] A recent study investigating eltrombopag added to standard immunosuppressive therapy used Atgam administered at a dose of 40 mg/kg on 4 consecutive days.[18]
- **Acute Graft-Versus-Host Disease.** Atgam has been used for steroid-resistant acute graft-versus-host disease at a dose of 15 mg/kg per dose over 3 hours twice daily for 5 days for a total of 10 doses.[19]
- **Immunotherapy-related cardiovascular toxicity.** One case report has been published which summarized the use of equine ATG for the treatment of a patient with fulminant myocarditis secondary to Opdivo® (nivolumab intravenous infusion) therapy.[10] Equine ATG was administered according to the local protocol for acute cellular rejection and consisted of 500 mg on Day 1 and the dose was titrated by 250 mg daily to maintain a CD2/3 level of 50 – 100/µL for a total of 5 days of treatment. Resolution of ventricular arrhythmias occurred within 3 days of beginning ATG and cardiac enzymes normalized by Day 5. Cardiac biopsy 10 days after beginning ATG treatment revealed histologic improvement with significantly less myocyte necrosis.
- **Myelodysplastic syndrome.** In one study in patients with myelodysplastic syndrome to improve cytopenia, horse anti-thymocyte globulin was given at a dose of 15 mg/kg for 5 days.[20] Another older study dosed Atgam at 40 mg/kg/day intravenously for 4 days.[21]

Guidelines

The use of Atgam is supported in a number of clinical guidelines.[2-9]
- **Acute cellular rejection**: The Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Care of Kidney Transplant Recipients (2009) recommends anti-thymocyte globulin (ATG) as a treatment option for induction therapy, given prior to, at the time of, or immediately after transplant.[2] The KDIGO guidelines recommend ATG for the treatment of

acute cellular rejection unresponsive to corticosteroids, recurrent acute cellular rejection, and for acute antibody-mediated rejection.

- **Aplastic anemia**: The British Society of Haematology guidelines for the diagnosis and management of aplastic anemia recommend immunosuppressive therapy with Atgam plus cyclosporine for the first-line treatment of patients with non-severe aplastic anemia requiring treatment, severe or very severe aplastic anemia in those who lack a matched sibling donor, and severe or very severe aplastic anemia in patients > 35 to 50 years of age.[3,4] A second course of Atgam is recommended following a relapse after the first course of therapy, or after failure to respond to the first course if the patient is ineligible for a matched unrelated donor hematopoietic stem cell transplant. In addition, Atgam is included in conditioning regimens for bone marrow transplantation.[5]
- National Comprehensive Cancer Network (NCCN) guidelines:[6-9]
  - **Graft-vs-host disease:** The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines (version 3.2023 – October 9, 2023) recommend ATG as additional therapy in conjunction with corticosteroids for the management of acute steroid-refractory disease.[9]
  - **Immunotherapy-related cardiovascular toxicity:** The NCCN Guidelines for the Management of Immunotherapy-Related Toxicities (version 1.2024 – December 7, 2023), recommend Atgam as additional treatment for life-threatening cardiac immune-related adverse events if there is no improvement within 24 hours of starting pulse-dose methylprednisolone.[6,7] Atgam can also be considered for elevated liver transaminases if there is worsening or no improvement after use with corticosteroids, such as prednisone or methylprednisolone.
  - **Myelodysplastic syndrome:** The NCCN Clinical Practice Guidelines (version 3.2023 – November 10, 2023) recommend Atgam as a treatment option for the management of lower risk disease.[7,8] Treatment with Atgam alone or in combination with cyclosporine and/or Promacta® (eltrombopag olamine tablets) is recommended for select patients with clinically relevant thrombocytopenia or neutropenia; or for select patients with symptomatic anemia.

Other Uses With Supportive Evidence

- **Induction Therapy.** Atgam has been utilized as a component of induction therapy for heart and lung transplantation.[11-15]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Atgam. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Atgam as well as the monitoring required for adverse events and long-term efficacy, approval requires Atgam to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Atgam is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Allograft Rejection in Solid Organ Transplant.** Approve for 1 month if the patient meets the following (A and B):
   - **A)** Patient meets ONE of the following (i or ii):
     - **i.** Atgam is used for induction therapy, prior to, at the time of, or immediately following transplantation; OR
     - **ii.** Atgam is used for the treatment of acute rejection; AND
   - **B)** The medication is prescribed by or in consultation with a transplant specialist physician or a physician associated with a transplant center.

   Dosing. Approve ONE of the following dosing regimens (A or B):
   - **A)** Up to 15 mg/kg administered intravenously daily for up to 14 days with an additional alternate-day therapy up to a total of 21 doses, if needed; OR
   - **B)** The dosing regimen is based on a transplant center's protocol.

2. **Aplastic Anemia.** Approve for 1 month if the patient meets the following (A and B):
   - **A)** Patient has moderate to severe disease; AND
   - **B)** The medication is prescribed by or in consultation with a hematologist or a physician who specializes in the treatment of aplastic anemia.

   Dosing. Approve ONE of the following dosing regimens (A or B):
   - **A)** Up to 20 mg/kg administered intravenously daily for up to 14 days with an additional alternate-day therapy up to a total of 21 doses, if needed; OR
   - **B)** Up to 40 mg/kg intravenously daily for up to 4 consecutive days.

Other Uses with Supportive Evidence

3. **Hematopoietic Stem Cell Transplantation or Umbilical Cord Transplantation**. Approve for 1 month if the patient meets the following (A and B):
   - **A)** Atgam is used as part of a conditioning regimen beginning prior to hematopoietic stem cell transplantation or umbilical cord transplantation; AND
   - **B)** The medication is prescribed by or consultation with an oncologist or a physician who specializes in stem cell or umbilical cord transplantation.

   Dosing. Approve ONE of the following dosing regimens (A or B):
   - **A)** Up to 40 mg/kg administered intravenously daily as a single dose, or divided and given twice daily for up to 4 days; OR
   - **B)** The dosing regimen is based on a transplant center's protocol.

4. **Graft-Versus-Host Disease**. Approve for 1 month if the patient meets the following (A, B, and C):
   - **A)** Patient has acute disease; AND
   - **B)** Patient's disease is refractory or resistant to corticosteroid therapy; AND
   - **C)** The medication is prescribed by or consultation with an oncologist or a physician who specializes in transplantation.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) Up to 40 mg/kg/day administered intravenously daily or twice daily for up to 10 doses; OR
B) The dosing regimen is based on a transplant center's protocol.

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5. Immune Checkpoint Inhibitor-Related Toxicities. Approve for 1 month if the patient meets the following (A, B, C, and D):
A) Patient has received at least one immune checkpoint inhibitor; AND
Note: Immune checkpoint inhibitors include Opdivo (nivolumab intravenous infusion), Keytruda (pembrolizumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion), Bavencio (avelumab intravenous infusion), Imfinzi (durvalumab intravenous infusion), Yervoy (ipilimumab intravenous infusion), Libtayo (cemiplimab intravenous infusion), Jemperli (dostarlimab intravenous infusion).
B) Patient meets ONE of the following (i or ii):
i. Patient has cardiac immune-related adverse events; OR
Note: Examples of cardiac immune-related adverse events are myocarditis, pericarditis, arrhythmias, impaired ventricular function, large vessel vasculitis.
ii. Patient has elevated liver enzymes or toxic liver disease; AND
C) Patient has not improved after therapy with corticosteroids; AND
Note: Examples of corticosteroids include prednisone, dexamethasone, methylprednisolone.
D) The medication is prescribed by or consultation with a cardiologist, oncologist, gastroenterologist, or a physician who specializes in the treatment of immune checkpoint inhibitor-related toxicity.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) Up to 15 mg/kg administered intravenously daily for 14 days with an additional alternate-day therapy up to a total of 21 doses, if needed; OR
B) Up to 30 mg/kg/day administered intravenously.

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6. Myelodysplastic Syndrome. Approve for 1 month if the patient meets the following (A and B):
A) Patient has lower risk disease; AND
Note: Lower risk disease is defined as International Prognostic Scoring System (IPSS) risk of low or intermediate-1; IPSS-Revised (IPSS-R) risk of very low, low, or intermediate; IPSS-Molecular (IPSS-M) risk of very low, low, moderate low. Other risk stratification models may also be used (e.g., the MD Anderson Cancer Center or the World Health Organization Prognostic Scoring System).
B) The medication is prescribed by or in consultation with an oncologist or a physician who specializes in the treatment of myelodysplastic syndromes.

Dosing. Approve ONE of the following dosing regimens (A or B)
A) Up to 40 mg/kg/day administered intravenously for up to 4 days; OR
B) Up to 15 mg/kg administered intravenously daily for 5 days

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CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Atgam is not recommended in the following situations.

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/14/2022
Annual Revision	**Allograft Rejection in Solid Organ Transplant**. Updated dosing to up to 15 mg/kg administered intravenously daily for up to 14 days with additional alternate-day therapy up to a total of 21 doses, if needed; previously was up to 15 mg/kg administered intravenously daily for up to 14 days AND up to seven additional doses can be administered intravenously every other day for a maximum total of 21 doses in 28 days. Added a dosing regimen based on a transplant center's protocol. **Aplastic Anemia**. Removed the requirement that the patient is unsuitable for bone marrow transplantation. Added a dosing regimen of up to 40 mg/kg intravenously daily for up to 4 consecutive days. **Hematopoietic Stem Cell Transplantation or Umbilical Cord Transplantation**. Updated condition of approval, previously was Allogeneic Hematopoietic Stem Cell Transplantation. Removed allogeneic wording and added umbilical cord transplantation wording throughout the criteria. Added a dosing regimen based on a transplant center's protocol. **Graft-Versus-Host Disease**. Removed 'allogeneic hematopoietic stem cell' wording from prescriber's or consultant prescriber's specialty. Added 'daily or twice daily' wording to the dosing regimen of 40 mg/kg/day. Added a dosing regimen based on a transplant center's protocol. **Immune Checkpoint Inhibitor-Related Toxicities**. Added additional examples of immune checkpoint inhibitors. Added option for approval that a patient has elevated liver enzymes or toxic liver disease. The option for approval that the patient has life-threatening myocarditis, pericarditis, arrhythmias, impaired ventricular function criterion was updated to patient has cardiac immune-related adverse events and examples of these events were listed in a note. The requirement that the patient has not improved within 24 hours of starting pulse dose methylprednisolone was updated to patient has not improved after therapy with corticosteroids and examples of corticosteroids were listed in a note. Gastroenterologist was added to the list of prescribers or consultant prescribers. Updated dosing to up to 15 mg/kg administered intravenously daily for 14 days with an additional alternate-day therapy up to a total of 21 doses, if needed; previously was up to 15 mg/kg administered intravenously daily for 14 days and up to seven additional doses can be administered intravenously every other day for maximum total of 21 doses in 28 days. Added a new dosing regimen of up to 30 mg/kg/day administered intravenously. **Myelodysplastic Syndrome**. Added International Prognostic Scoring System-Molecular risk of very low, low, moderate low to the note. Additionally, added in the note that other risk stratification models may also be used (e.g., the MD Anderson Cancer Center or the World Health Organization Prognostic Scoring System). Removed the following requirement: Patient has one of the following according to the prescriber: (i) Clinically relevant thrombocytopenia (ii) Clinically relevant neutropenia (iii) Increased marrow blasts (iv) Symptomatic anemia. A physician who specializes in the treatment of myelodysplastic syndromes was added to the list of prescribers or consultant prescribers. Added a new dosing regimen of up to 15 mg/kg administered intravenously daily for 5 days.	01/03/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immune Globulin – Cytogam Utilization Management Medical Policy
- Cytogam® (human cytomegalovirus immune globulin intravenous infusion – Kamada)

REVIEW DATE: 01/17/2024

OVERVIEW

Cytogam, a human cytomegalovirus (CMV) immune globulin intravenous (IGIV), is indicated for the **prophylaxis of CMV disease** associated with transplantation of kidney, lung, liver, pancreas, and heart.[1]

Other Uses With Supportive Evidence

Maternal transmission of CMV to the fetus may occur at any time during gestation, leading to congenital CMV.[2] A study of 304 pregnant women with a primary CMV infection were offered CMV IGIV. In the therapy group, 157 women were treated with CMV IGIV low dose (100 mg/kg/infusion given once every month) or high dose (200 mg/kg/infusion given once every 2 weeks for up to 3 doses if needed). The trial demonstrated that 56% of patients without CMV IGIV vs. 30% of patients receiving CMV IGIV developed congenital CMV infection.

CMV can cause complications in immunocompromised patients, including patients who have received a stem cell transplant or who have human immunodeficiency virus.[3,4] Small analyses have shown that CMV hyperimmune globulin, given as salvage or rescue therapy (after standard antiviral drug therapy), may be beneficial.[4,5] Additionally, CMV immune globulin has been designated as an orphan drug by the FDA for use in conjunction with ganciclovir for the treatment of CMV pneumonitis.[6] Higher doses of 400 mg/kg intravenously have been given off-label for the treatment of CMV pneumonitis.

Dosing Information

The maximum recommended dosage for prophylaxis of CMV disease associated with transplantation of kidney, lung, liver, pancreas, and heart is 150 mg/kg per intravenous infusion with a total of 7 infusions.[1] The first infusion should be within 72 hours of transplant followed by infusions at Week 2, 4, 6, 8, 12, and 16 post-transplant.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Cytogam. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cytogam as well as the monitoring required for adverse events and long-term efficacy, approval requires Cytogam to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cytogam is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **Prophylaxis of Cytomegalovirus Associated with Solid Organ Transplant.** Approve for 4 months if the medication is prescribed by or in consultation with a physician affiliated with a transplant center, hematologist, or an infectious disease physician.

   Dosing. Approve up to 150 mg/kg given by intravenous infusion no more frequently than every 2 weeks.

Other Uses with Supportive Evidence

2. **Cytomegalovirus Associated with Pregnancy.** Approve for 6 months if the medication is prescribed by or in consultation with an infectious disease physician or an obstetrician-gynecologist.

   Dosing. Approve the following dosing regimens (A or B):
   A) Up to 100 mg/kg given by intravenous infusion no more frequently than every month; OR
   B) Up to 200 mg/kg given by intravenous infusion and the number of doses given does not exceed 3 doses total.

3. **Cytomegalovirus, Treatment.** Approve for 6 months if the patient meets the following (A and B):
   A) Patient meets one of the following (i or ii):
      i. Patient is being treated for cytomegalovirus pneumonitis; OR
      ii. Patient meets both of the following (a and b):
      Note: For cytomegalovirus retinitis, use of the following medications given by intravitreal or by an ocular implant would satisfy the requirement.
         a) Patient has tried or is unable to use one of the following systemic therapies:
            (1) Ganciclovir; OR
            (2) Valganciclovir; AND
         b) Patient has tried or is unable to use foscarnet (Foscavir intravenous infusion); AND
   B) Cytogam has been prescribed by or in consultation with an infectious disease specialist, an ophthalmologist, a physician associated with a transplant center, an oncologist, or a hematologist.

   Dosing. Approve the following dosing regimens (A or B):
   A) Up to 400 mg/kg given daily by intravenous infusion; OR
   B) The dosing regimen is based on a transplant center's protocol.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cytogam is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/08/2021
Annual Revision	No criteria changes.	12/14/2022
Annual Revision	**Cytomegalovirus, Treatment**. This new condition of approval and criteria was added to the policy	01/17/2024

CARECONTINUUM™

MEDICAL STEP MANAGEMENT POLICY

POLICY: Immune Globulin – Intravenous Medical Step Management Policy

- Alyglo™ (immune globulin intravenous solution-stwk – GC Biopharma)
- Asceniv™ (immune globulin intravenous solution-sira – ADMA Biologics)
- Bivigam® (immune globulin intravenous solution – ADMA Biologics)
- Flebogamma® DIF (immune globulin intravenous solution – Grifols)
- Gammagard® Liquid (immune globulin solution – Takeda)
- Gammagard® S/D < 1 mcg/mL in 5% solution (immune globulin intravenous solution – Takeda)
- Gammaked™ (immune globulin solution caprylate/chromatography purified – Kedrion)
- Gammaplex® (immune globulin intravenous solution – BPL)
- Gamunex®-C (immune globulin solution caprylate/chromatography purified – Grifols)
- Octagam® (immune globulin intravenous solution – Octapharma)
- Panzyga® (immune globulin intravenous solution-ifas – Octapharma/Pfizer)
- Privigen® (immune globulin intravenous solution – CSL Behring)

REVIEW DATE: 04/10/2024

OVERVIEW

Immune globulin intravenous (IVIG) products are concentrated human immunoglobulins, primarily immunoglobulin G (IgG).

All of these products (except Octagam 10%) are FDA-approved for replacement therapy in patients with **primary immune deficiencies** due to defects in humoral immunity. The following indications are FDA approved:

- **B-cell chronic lymphocytic leukemia (CLL)**, for prevention of infections in patients with hypogammaglobulinemia and/or recurrent infections.[5,16]
- **Chronic inflammatory demyelinating polyneuropathy (CIDP)**, to improve neuromuscular disability and impairment, and for maintenance therapy to prevent relapse.[4,6,9,12,13]
- **Dermatomyositis (or polymyositis)**. Octagam 10% is indicated for the treatment of dermatomyositis in adults.[11]
- **Idiopathic (immune) thrombocytopenic purpura (ITP)**, acute and chronic, when a rapid rise in platelet count is needed to prevent and/or control bleeding or to allow a patient with ITP to undergo surgery.[2,5-9,11-13]
- **Kawasaki disease** in pediatric patients for the prevention of coronary artery aneurysm.[5]
- **Multifocal motor neuropathy** in adults as maintenance therapy to improve muscle strength and disability.[4]
- **Primary humoral immune deficiency (PID)**, for replacement therapy, including but not limited to the humoral immune defect in the following conditions: common variable immunodeficiency, X-linked agammaglobulinemia [congenital agammaglobulinemia], Wiskott-Aldrich Syndrome, and severe combined immunodeficiencies.[1-10,12-15] Gammagard Liquid 10%, Gammaked, and Gamunex-C may be administered via intravenous (IV) or subcutaneous infusion for primary immunodeficiency.[4,6,9] IVIG is also indicated for measles prophylaxis in individuals with PID who have been exposed to measles or who are at high risk of measles exposure.[2-10,12,13,15]

IVIG also is used for many off-label indications.[16] Much of the evidence for clinical effectiveness of IVIG is anecdotal (i.e., case reports, open series, or cohort studies). Some conditions have been studied in controlled trials. Usually, IVIG is indicated only if standard approaches have failed, become intolerable, or are contraindicated.

IVIG products are generally considered therapeutically equivalent and interchangeable with other IVIG products.

POLICY STATEMENT

This Medical Step Management program has been developed to encourage the use of Preferred Products. For all medications (Preferred and Non-Preferred), the patient is required to meet the respective *Immune Globulin Intravenous Utilization Management Medical Policy* criteria. The program also directs the patient to try two Preferred Products prior to the approval of a Non-Preferred Product. Requests for Non-Preferred Products will also be reviewed using the exception criteria (below). All approvals are provided for the duration noted in the *Immune Globulin Intravenous Utilization Management Medical Policy* criteria.

Automation: None.

Preferred Products: Flebogamma DIF, Gammagard Liquid, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Octagam, Privigen

Non-Preferred Products: Alyglo, Asceniv, Bivigam, Panzyga

RECOMMENDED EXCEPTION CRITERIA

Non-Preferred Product(s)	Exception Criteria
Alyglo	**1.** Approve if the patient meets BOTH of the following (A and B): **A)** Patient meets the standard *Immune Globulin Intravenous Utilization Management Medical Policy* criteria; AND **B)** Patient meets ONE of the following conditions (i or ii): **i.** Patient has tried TWO of the following products: Flebogamma DIF, Gammagard Liquid, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Octagam, Privigen; OR **ii.** According to the prescriber, a product with minimal content of coagulation factor XIa is needed based on a comorbidity of the patient.
Asceniv	**1.** Approve if the patient meets BOTH of the following (A and B): **A)** Patient meets the standard *Immune Globulin Intravenous Utilization Management Medical Policy* criteria; AND **B)** Patient meets ONE of the following conditions (i or ii): **i.** Patient has tried TWO of the following products: Flebogamma DIF, Gammagard Liquid, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Octagam, Privigen; OR **ii.** According to the prescriber, the patient requires an immune globulin with elevated levels of respiratory syncytial virus (RSV) antibodies.

	Note: An example of when a patient would require elevated levels of RSV antibodies is if the patient has repeated RSV infections despite adequate immune globulin dosing in a compliant patient.
Bivigam, Panzyga	**1.** Approve if the patient meets BOTH of the following (A and B): **A)** Patient meets the standard *Immune Globulin Intravenous Utilization Management Medical Policy* criteria; AND **B)** Patient has tried TWO of the following products: Flebogamma DIF, Gammagard Liquid, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Octagam, Privigen.

REFERENCES

1. Bivigam® 10% intravenous solution [prescribing information]. Boca Raton, FL: ADMA Biologics; December 2022.
2. Flebogamma® 5% DIF intravenous solution [prescribing information]. Los Angeles, CA: Grifols; September 2019.
3. Flebogamma DIF 10% intravenous solution [prescribing information]. Los Angeles, CA: Grifols; September 2019.
4. Gammagard® Liquid 10% solution [prescribing information]. Lexington, MA: Takeda; January 2024.
5. Gammagard® S/D IgA < 1 mcg/mL in a 5% intravenous solution [prescribing information]. Lexington, MA: Takeda; March 2023.
6. Gammaked™ 10% solution [prescribing information]. Fort Lee, NJ: Kedrion; January 2020.
7. Gammaplex® 5% intravenous solution [prescribing information]. Durham, NC: BPL; November 2021.
8. Gammaplex 10% intravenous solution [prescribing information]. Durham, NC: BPL; November 2021.
9. Gamunex®-C 10% solution [prescribing information]. Los Angeles, CA: Grifols; January 2020.
10. Octagam® 5% intravenous solution [prescribing information]. Paramus, NJ: Octapharma; April 2022.
11. Octagam® 10% intravenous solution [prescribing information]. Paramus, NJ: Octapharma; April 2022.
12. Privigen® 10% intravenous solution [prescribing information]. Kankakee, IL: CSL Behring; March 2022.
13. Panzyga 10% intravenous solution [prescribing information]. New York; NY: Pfizer; February 2021.
14. Asceniv 10% intravenous solution [prescribing information]. Boca Raton, FL. ADMA Biologics; April 2019.
15. Alyglo™ 10% intravenous solution [prescribing information]. Teaneck, NJ: GC Biopharma; December 2023.
16. Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol.* 2017;139(3S):S1-S46.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	04/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT ADVANCED CLINICAL EVALUATION MEDICAL POLICY

POLICY: Immune Globulin Intravenous Utilization Management Medical Policy – Advanced Clinical Evaluation

- Alyglo™ (immune globulin intravenous solution-stwk – GC Biopharma)
- Asceniv™ (immune globulin intravenous solution-sira – ADMA Biologics)
- Bivigam® (immune globulin intravenous solution – AMDA Biologics)
- Flebogamma® DIF (immune globulin intravenous solution – Grifols)
- Gammagard® Liquid (immune globulin solution – Takeda)
- Gammagard® S/D < 1 mcg/mL in 5% solution (immune globulin intravenous solution – Takeda)
- Gammaked™ (immune globulin intravenous solution caprylate/chromatography purified – Kedrion)
- Gammaplex® (immune globulin intravenous solution – BPL)
- Gamunex®-C (immune globulin solution caprylate/chromatography purified – Grifols)
- Octagam® (immune globulin intravenous solution – Octapharma)
- Panzyga® (immune globulin intravenous solution-ifas – Octapharma/Pfizer)
- Privigen® (immune globulin intravenous solution – CSL Behring)

REVIEW DATE: 10/25/2023; selected revision 02/07/2024 and 04/10/2024

OVERVIEW

Immune globulin intravenous (IVIG) products are concentrated human immunoglobulins, primarily immunoglobulin G (IgG).

All of these products (except Octagam 10%) are FDA-approved for replacement therapy in patients with **primary immune deficiencies** due to defects in humoral immunity. The following indications are FDA approved:

- **B-cell chronic lymphocytic leukemia (CLL)**, for prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent infections.[6,18,21]
- **Chronic inflammatory demyelinating polyneuropathy (CIDP)**, to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.[5,7,9,12,15,67]
- **Dermatomyositis (or polymyositis)**. Octagam 10% is indicated for the treatment of dermatomyositis in adults.[11] Patients with dermatomyositis treated with Octagam were under treatment with corticosteroids and/or maximally two immune-suppressants OR patients had previous failure or intolerance with a corticosteroid and at least one additional immunosuppressive drug.[33] IVIG may be considered amongst the treatment options for patients with polymyositis not responding to first line immunosuppressive treatment.[32]
- **Idiopathic (immune) thrombocytopenic purpura (ITP)**, acute and chronic, when a rapid rise in platelet count is needed to prevent and/or control bleeding or to allow a patient with ITP to undergo surgery.[2,4,6-9,11,12,15,23-25]
- **Kawasaki disease,** in pediatric patients for the prevention of coronary artery aneurysm.[6,26] The American Heart Association and the American Academy of Pediatrics recommend initial therapy with 2 g of IVIG per kg as a single intravenous (IV) dose given over 10 to 12 hours.[26] The dose can be repeated if needed.

- **Multifocal motor neuropathy,** in adults as maintenance therapy to improve muscle strength and disability.[5]
- **Primary humoral immune deficiency (PID)**, for replacement therapy, including but not limited to the humoral immune defect in the following conditions: common variable immunodeficiency, X-linked agammaglobulinemia (congenital agammaglobulinemia), Wiskott-Aldrich Syndrome, and severe combined immunodeficiencies.[1-10,12,15,16,25,80] Gammagard Liquid 10%, Gammaked, and Gamunex-C may be administered via IV or subcutaneous infusion for primary immunodeficiency.[5,7,9] IVIG is also indicated for measles prophylaxis in individuals with PID who have been exposed to measles or who are at high risk of measles exposure.[3,4,7-10,12,13,17,24,45,80]

IVIG is prepared from pooled plasma collected from a large number of human donors.[1-12,15,16,25] The donors in a typical pool of plasma have a wide range of antibodies against infectious agents. These products have IgG subclasses similar to that found in normal humans. Asceniv contains not only antibodies which satisfy the requirement to treat patients with PID, it also has elevated levels of respiratory syncytial virus (RSV) antibodies.[19]

IVIG also is used for many off-label indications. Much of the evidence for clinical effectiveness of IVIG is anecdotal (i.e., case reports, open series, or cohort studies). Some conditions have been studied in controlled trials. Usually, IVIG is indicated only if standard approaches have failed, become intolerable, or are contraindicated.

- **Antibody-mediated rejection (ABMR) in transplantation:** Current strategies for treatment of antibody-mediated rejection include plasmapheresis, IVIG, and T-cell or B-cell-depleting agents.[75] Although there are no controlled trials regarding the most appropriate treatments, the benefits of immune globulin have been well described and has been used as the standard-of-care (along with plasmapheresis) in multiple studies.[18,76] Clinical practice guidelines (2009 Kidney Disease: Improving Global Outcomes) recommend a combination of corticosteroids, plasmapheresis, IVIG, anti-CD20 antibody, and lymphocyte-depleting antibody for antibody-mediated rejection.[76,77] As in desensitization therapy, much of the information of IVIG use is in patients with kidney transplants, but the same principles apply to transplantation of other organs and tissues. Immune globulin has been used in lung transplant patients to treat ABMR[20,44,78] and a scientific statement from the American Heart Association states that primary therapy for ABMR in patients with heart transplants may include IVIG, plasmapheresis, high-dose corticosteroids, and anti-lymphocyte antibodies.[36]
- **Autoimmune mucocutaneous blistering diseases (pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid [cicatricial pemphigoid], and epidermolysis bullosa acquisita):** Conventional therapy (a systemic corticosteroid and an immunosuppressive agent) is started at the same time or before IVIG. Many case reports and uncontrolled case series suggest benefit of IVIG in patients with recalcitrant disease or in those with contraindications to conventional therapy.[28-30] International expert recommendations for the management of pemphigus note that first-line treatment includes corticosteroids and anti-CD20 monoclonal antibodies. First-line corticosteroid-sparing agents include azathioprine and mycophenolate mofetil, and other corticosteroid-sparing agents include IVIG.[2]
- **Cytomegalovirus (CMV) pneumonitis or pneumonia in patients with cancer or transplant-related infection:** For CMV pneumonia, therapy generally consists of antivirals (e.g., ganciclovir, foscarnet). The National Comprehensive Cancer Network (NCCN) guidelines on prevention and treatment of cancer-related infections (version 1.2023 – June 28, 2023) lists IVIG as an adjunctive therapy for CMV pneumonitis, but notes that IVIG use as an antiviral is contraversial.[31]
- **Desensitization therapy prior to and immediately after transplantation:** Most of the information on use of IVIG for desensitization is in patients with kidney transplantation but many

of the same principles apply to transplantation of other organs and tissues.[34,35] Current protocols include using low-dose IVIG with plasma exchange or high-dose IVIG with or without B-cell depletion with rituximab.[18]

- **Guillain-Barré syndrome (GBS):** The American Academy of Neurology recommends IVIG in patients who require aid to walk within 2 or 4 weeks from the onset of neuropathic symptoms.[37] The effect of IVIG in GBS has only been investigated in randomized controlled trials in patients who are unable to walk at nadir (i.e., severely affected patients), not in mildly affected patients who are able to walk unaided at nadir.[38] IVIG is not indicated or proven to be effective in patients mildly affected with GBS.[32,38]
- **Hematologic neoplasm-associated hypogammaglobulinemia or hypogammaglobulinemia after B-cell targeted therapies (secondary immunodeficiency):** Clinical guidelines for immunoglobulin use by the National Health Service-England note secondary antibody deficiency can be hypogammaglobinemia associated with therapeutic monoclonals targeted at B-cells and plasma cells, non-Hodgkin's lymphoma, CLL, multiple myeloma, or other relevant B-cell malignancies.[27] NCCN guidelines regarding management of immunotherapy-related toxicities (version 2.2023 – May 9, 2023) recommends that after anti-CD19 chimeric antigen receptor (CAR)-T cell therapy, IVIG replacement should be considered for patients with serum IgG levels < 400 to 600 mg/dL and serious or recurrent infections.[73]
- **Hematopoietic cell transplantation (HCT) to prevent infections:** HCT is defined as transplantation of any blood- or marrow-derived hematopoietic stem cells, regardless of transplant type (i.e., allogeneic or autologous) or cell source (i.e., bone marrow, peripheral blood, or umbilical cord blood). With regard to IVIG, guidelines recommend IVIG for prevention or preemptive treatment of specific infections in HCT recipients.[39] In adult or adolescent HCT recipients (allogeneic or autologous), IVIG is used to prevent infections in those with severe hypogammaglobulinemia (i.e., serum IgG < 400 mg/dL) during the first 100 days after HCT. In pediatric patients, IVIG is indicated in those with an allogeneic HCT if hypogammaglobulinemia is severe during the first 100 days after HCT. For prevention of infections beyond 100 days post-HCT (allogeneic or autologous), IVIG is recommended in recipients with severe hypogammaglobulinemia (i.e., serum IgG < 400 mg/dL). Guidelines from the American Society for Blood and Marrow Transplantation make recommendations for IVIG dosing in HCT recipients to prevent infectious complication.[39] During the first 100 days after HCT, the dose in adults and adolescents is 0.5 g/kg per week. The IVIG dose should be individualized to maintain trough (pre-dose) serum IgG > 400 to 500 mg/dL. The dose in allogeneic pediatric HCT patients is 0.4 g/kg per month, adjusted to keep IgG > 400 mg/dL. Higher and more frequent dosing may be necessary in patients for prevention of early disease after HCT because the half-life of IVIG is reduced to between 1 to 10 days in this population. Dosing for > 100 days post-HCT is 0.5 g/kg given every 3 to 4 weeks. The dose is not adjusted using serum IgG level in patients with multiple myeloma or malignant macroglobulinemia. NCCN guidelines on prevention and treatment of cancer-related infections discussed similar recommendations.[31]
- **Human immunodeficiency virus (HIV)- or Hepatitis C-associated thrombocytopenia:** Secondary ITP can occur in patients with HIV infection.[23,24] It can also occur in patients with Hepatitis C. The American Society of Hematology (ASH) guidelines for ITP recommend initial treatment with corticosteroids, IVIG, or Rh0(D) immune globulin for patients with secondary ITP due to HIV. ASH also recommends IVIG for secondary ITP associated with Hepatitis C.[23,24]
- **HIV-infected infants and children, to prevent recurrent infections:** IVIG is recommended to prevent serious bacterial infections in HIV-infected children who have hypogammaglobulinemia (IgG < 400 mg/dL).[40] Clinicians providing care for adolescents are advised to use the US Department of Health and Human Services Adult and Adolescent HIV-guideline for the care of

post-pubertal adolescents (sexual maturity rating [SMR] four and five) and to use the pediatric guideline for guidance on the care of adolescents at SMR III or lower.[40]

- **Immunotherapy-related toxicities associated with checkpoint inhibitor therapy:** NCCN guidelines for the management of immunotherapy-related toxicities (version 2.2023 – May 9, 2023) recommend IVIG for the management of severe pneumonitis after 48 hours of methylprednisolone therapy, as treatment for severe myasthenia gravis, encephalitis, cardiovascular adverse events, musculoskeletal adverse events, moderate or severe GBS, severe transverse myelitis, bullous dermatitis, and Stevens-Johnson syndrome/toxic epidermal necrolysis.[73] The American Society of Clinical Oncology also has practice guidelines on the management of immune-related adverse events in patients treated with checkpoint inhibitor therapy.[74] These practice guidelines address the above mentioned indications along with other conditions (e.g., severe cutaneous adverse reactions, myositis, autoimmune hemolytic anemia, immune thrombocytopenia).
- **Lambert-Eaton Myasthenic Syndrome:** Limited but moderate- to high-quality evidence from randomized controlled trials have shown that 3,4-diaminopyridine or IVIG was associated with improved muscle strength score and compounded muscle action potential amplitudes. IVIG may be used as an alternative in patients who do not respond or do not tolerate other therapies.[18]
- **Multiple myeloma:** Patients with multiple myeloma are often functionally hypogammaglobulinemic with total immunoglobulin production being elevated, but the repertoire of antibody production restricted.[31] The NCCN guidelines on multiple myeloma (version 1.2024 – September 22, 2023) notes that IVIG replacement during CAR-T cell and bispecific antibody therapies are not guided by the presence of infections.[24] It also should be considered in the setting of recurrent serious infections and/or hypogammaglobulinemia (IgG < 400 mg/dL).
- **Multiple sclerosis, acute severe exacerbation or relapse:** Medication options for relapse management include high dose corticosteroids, intramuscular adrenocorticotrophic hormone, plasmapheresis, and IVIG. IVIG is sometimes used to treat relapses that do not respond to corticosteroids.[43] During pregnancy, relapses severe enough to require treatment can be safely managed with a short-term course of corticosteroids after the first trimester. Methylprednisolone is the preferred agent because it is metabolized before crossing the placenta.[43]
- **Myasthenia gravis:** Recommendations from an international consensus guidance statement for management of adult or juvenile myasthenia gravis include the use of IVIG in some patients.[65] Symptomatic and immunosuppressive treatment of myasthenia gravis includes pyridostigmine as initial therapy in most patients. Corticosteroids or immunosuppressive therapies are used in all patients with myasthenia gravis who have not met treatment goals after an adequate trial of pyridostigmine. A nonsteroidal immunosuppressive agent (e.g., azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus) should be used alone when corticosteroids are contraindicated or refused. In patients with refractory myasthenia gravis, chronic IVIG and chronic plasma exchange (PLEX), cyclophosphamide, or rituximab may be used. PLEX and IVIG are recommended as short-term treatments in patients with myasthenia gravis with life-threatening effects such as respiratory insufficiency or dysphagia, to prepare for surgery in patients with significant bulbar dysfunction, when rapid response is needed, when other treatments are not adequate, and before starting corticosteroids, if necessary to prevent or minimize exacerbations. IVIG can be considered as maintenance therapy in patients with refractory myasthenia gravis or in patients with relative contraindications to immunosuppressive agents. Refractory myasthenia gravis is defined as the post intervention status of unchanged or worse after corticosteroids and at least two other immunosuppressive agents used in adequate doses for an adequate duration, with persistent symptoms or side effects that limit functioning, as defined by the patient or physician. The international consensus guidance statement for myasthenia gravis[65] recommends an initial dose of 2 g/kg given in divided doses over 2 to 5 days. For maintenance therapy, the recommended dose

is 0.4 to 1 g/kg given every 4 weeks; an attempt to decrease frequency can be made over time. If additional treatment is required, the dose should be adjusted based on the response.

- **Passive immunization for measles (post-exposure prophylaxis):** When administered within 6 days of exposure, immune globulin (IG) can prevent or modify measles in patients who are nonimmune.[13] IG therapy is not indicated in persons who have received one dose of measles-containing vaccine at ≥ 12 months, unless the patient is severely immunocompromised. The Advisory Committee on Immunization Practices recommends the use of IG therapy for post-exposure prophylaxis of measles in the following patients who are at risk for severe disease and complication from measles: infants < 12 months of age, pregnant women without evidence of measles immunity, and severely immunocompromised persons.[13] For infants < 12 months of age, intramuscular IG is used; infants 6 through 11 months of age can receive measles, mumps, and rubella vaccine instead of IG if given within 72 hours of exposure. IVIG is used for pregnant women and severely immunocompromised patients. ACIP recommends 400 mg/kg as an IV infusion.[13]
- **Post-exposure prophylaxis for varicella OR treatment or post-exposure prophylaxis for tetanus:** Children infected with HIV without a history of previous varicella infection OR children who have not received two doses of varicella vaccine should receive VariZIG® or, if not available, IVIG within 10 days after close contact with a person who has chickenpox or shingles.[41,46] VariZIG is indicated for post-exposure prophylaxis in certain patients without immunity to varicella and is given as soon as possible after exposure, preferably within 4 days, and as late as 10 days after exposure.[47] In situations where administration of VariZIG does not appear possible within 10 days of exposure, IVIG is considered an alternative and should be given within 10 days of exposure[48] (and ideally within 96 hours of exposure).[40] The dose is 400 mg/kg given once.[40,41,46] Per the Centers for Disease Control and Prevention, if tetanus immune globulin is not available, clinicians can use immune globulin at a dose of 200 to 400 mg/kg.[48]
- **Parvovirus B19 infection and pure red blood cell aplasia, immunologic subtype:** In immunosuppressed patients lacking neutralizing antibodies, IVIG has been useful for the treatment of persistent B19 infection.[49] The guidelines from the American Society of Transplantation Infectious Diseases Community of Practice state that IVIG is frequently used for the treatment of solid organ transplant recipients with symptomatic parvovirus B19 infection.[66] A Canadian expert panel of hematologists recommend prednisone followed by cyclophosphamide or cyclosporine as first-line therapy for immunologic type pure red cell aplasia.[22] The panel considers IVIG a reasonable second-line option for this serious condition. Recent reviews note that 200 to 400 mg/kg/day for 5 to 10 days is considered the recommended treatment course.[79]
- **Stiff-person syndrome (Moersch-Woltman syndrome):** Per the European Federation of Neurological Societies, IVIG should be reserved for patients who have no symptomatic relief after the use of diazepam and/or baclofen and have severe disability in carrying out daily activities.[32]
- **Thrombocytopenia, feto-neonatal alloimmune:** Antenatal therapy with IVIG administered to the mother is effective in increasing fetal platelet counts in neonatal alloimmune thrombocytopenia.[50,51] First-line therapy for newborns with fetal/neonatal alloimmune thrombocytopenia is antigen-negative compatible platelets; IVIG is adjunctive therapy.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of IVIG products. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where

the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with IVIG products as well as the monitoring required for adverse events and long-term efficacy, some approvals require IVIG products to be prescribed by or in consultation with a physician who specializes in the condition being treated. All reviews will be forwarded to a Physician Medical Director for evaluation.

If the prescriber is switching between IVIG products and a case has already been approved by a clinician, a new approval may be entered without another clinical review. The new approval should only be extended for the remaining doses and duration which were granted on the original review. The indication (or diagnosis code) and dosing need to be the same as the original review. If the indication or dosing is different, a new clinical review would need to be completed. If the client is using the *Immune Globulin – Intravenous Medical Step Management Policy* in tandem with this Utilization Management policy, the new approval may be entered without another clinical review for a preferred product only.

Documentation: Documentation is required for use of IVIG as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Immune Globulin Intravenous Advanced Clinical Evaluation Medical Policy*, and who is requesting reauthorization, the criteria utilized do NOT require re-submission of documentation for reauthorization, except for the criterion requiring documentation of a continued benefit from Immune Globulin therapy.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of immune globulin intravenous products is recommended in those who meet the following criteria:

FDA-Approved Indications

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1. **Primary Immunodeficiencies.** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets BOTH of the following (i and ii):
     - **i.** Patient meets ONE of the following (a, b, or c):
       Note: An exception can be made for the impaired antibody response if, according to the prescriber, the delay caused by pre-vaccination and post-vaccination antibody measurement would be deleterious to the patient's health.
       - **a)** Patient has a diagnosis of congenital agammaglobulinemia, X-linked agammaglobulinemia, other agammaglobulinemia due to the absence of B-cells, Wiskott-Aldrich syndrome, ataxia telangiectasia, DiGeorge syndrome, severe combined immunodeficiency, Hyper-Immunoglobulin M (IgM) syndromes, an IgG level lower than 250 mg/dL **[documentation required]**, or a primary immune deficiency which has been confirmed by genetic or molecular testing; OR
       - **b)** Patient has a diagnosis of common variable immunodeficiency, unspecified hypogammaglobulinemia, or other immunodeficiencies with significant hypogammaglobulinemia and meets BOTH of the following (1 and 2):
         - **(1)** Patient's pretreatment IgG level is below the normal range (age-adjusted and according to the normal reference range for the reporting laboratory) **[documentation required]**; AND
         - **(2)** Patient meets ONE of the following (a or b):

a) Patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens) **[documentation required]**; OR
b) Patient has recurrent infections; OR

c) Patient has an IgG subclass deficiency **[documentation required]**, selective antibody deficiency (SAD), or another confirmed primary immunodeficiency and meets the following criteria [(1) and (2)]:
(1) Patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens) **[documentation required]**; AND
(2) Patient has recurrent infections; AND

ii. The medication is prescribed by or in consultation with one of the following physician specialists: an allergist, immunologist, otolaryngologist (ear nose and throat [ENT] physician), pulmonologist, or infectious diseases physician who treats patients with primary immune deficiencies.

B) Patient is Currently Receiving Immune Globulin. Approve if the patient has been diagnosed with a primary immunodeficiency and according to the prescriber, is continuing to receive benefit from the product **[documentation required for continued benefit]**.
Note: Examples of continued benefit with the product includes increased IgG levels or prevention and/or controlling of infections.

Dosing. Approve ONE of the following dosing regimens (A, B, C, or D):
A) An initial loading dose of 1 g/kg given intravenously one time; OR
B) 0.2 g/kg to 0.8 g/kg given intravenously once every 3 to 4 weeks; OR
C) The dose and interval between doses have been adjusted based on clinical response as determined by the prescriber; OR
D) Patient with primary immune deficiency and exposure to measles (previous exposure or risk of future measles exposure), the minimum dose has been determined by the prescriber.

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2. B-Cell Chronic Lymphocytic Leukemia for Prevention of Infections. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets BOTH of the following (i and ii):
i. Patient meets ONE of the following (a or b):
a) Patient has an immunoglobulin G (IgG) level < 600 mg/dL (6.0 g/L) **[documentation required]**; OR
b) Patient has a history of recurrent infections; AND
ii. The medication is prescribed by or in consultation with an oncologist, hematologist, or infectious diseases physician.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has a positive response to therapy according to the prescriber **[documentation required]**.
Note: Examples of a positive response to therapy include maintaining an increased IgG trough level or a decrease in the number of infections.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 0.4 g/kg given intravenously every 3 to 4 weeks; OR
B) 0.3 g/kg to 0.5 g/kg given intravenously once monthly; OR
C) The dose and interval have been adjusted to maintain a trough (pre-dose) IgG level of greater than 500 mg/dL.

3. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):
- **i.** Electrodiagnostic studies support the diagnosis of CIDP **[documentation required]**; AND
- **ii.** The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has a clinically significant improvement in neurologic symptoms, as determined by the prescriber **[documentation required]**.

Note: Examples of improvement in neurologic symptoms include improvement in disability; nerve conduction study results improved or stabilized; physical examination show improvement in neurological symptoms, strength, and sensation.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):

A) An initial loading dose of 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days; OR

B) A maintenance dose of 1 g/kg given intravenously in divided doses over 1 to 4 consecutive days given every 3 weeks; OR

C) The dose and interval are adjusted according to clinical response with a maximum dose per treatment course of 2 g/kg.

4. Dermatomyositis or Polymyositis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, and iv):
- **i.** Prior to starting any therapy for this condition, the patient meets one of the following (a or b):
  - **a)** Patient has or had an elevated creatinine kinase (CK) level, according to the prescriber **[documentation required]**; OR
  - **b)** Other measures support the diagnosis, according to the prescriber, including, but not limited to, skin manifestations, autoantibody testing, muscle biopsy results, electromyographic (EMG) findings; AND
- **ii.** Patient has tried a systemic corticosteroid **[documentation required]** OR a corticosteroid is contraindicated according to the prescriber; AND
- **iii.** Patient has tried an immunosuppressive agent **[documentation required]** OR an immunosuppressive agent is contraindicated according to the prescriber; AND
  Note: Examples of immunosuppressive agents include azathioprine, methotrexate, cyclosporine, cyclophosphamide, and mycophenolate mofetil.
- **iv.** The medication is prescribed by or in consultation with a neurologist or a rheumatologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has responded to therapy according to the prescriber **[documentation required]**.

Note: Examples of a response to therapy include improved muscle strength, improved neuromuscular symptoms, and improved functional ability.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days every 4 weeks; OR

B) 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days every 2 to 3 weeks.

5. Immune Thrombocytopenia (ITP). Approve for the duration noted if the patient meets ONE of the following (A, B, C, D, or E):

Note: The diagnosis of ITP encompasses previous nomenclature, such as idiopathic thrombocytopenia, idiopathic thrombocytopenic purpura, immune thrombocytopenic purpura.

A) Initial Therapy – Adult ≥ 18 Years of Age. Approve for 3 months if the patient meets BOTH of the following (i and ii):
- **i.** Patients meets ONE of the following (a, b, or c):
  - **a)** Patient has tried a systemic corticosteroid (e.g., prednisone); OR
  - **b)** There is an urgent need to increase the platelet count quickly; OR
  - **c)** A systemic corticosteroid is contraindicated according to the prescriber; AND
- **ii.** The medication is prescribed by or in consultation with a hematologist.

B) Initial Therapy – Patient is < 18 Years of Age. Approve for 3 months if prescribed by or in consultation with a hematologist.

C) Initial Therapy – To Increase Platelet Count Before Surgical or Dental Procedures. Approve for 1 month if prescribed by or in consultation with a hematologist.

D) Initial Therapy – Pregnant Patient. Approve for 6 months if prescribed by or in consultation with a hematologist.

E) Patient is Currently Receiving Immune Globulin OR Requires Retreatment with Immune Globulin. Approve for 1 year if the patient is responding to therapy OR if the patient has previously responded to therapy, according to the prescriber.
Note: Examples of responding to therapy include increased platelet counts, absence of significant bleeding, or preventing hemorrhage/ensuring an adequate platelet count in order for delivery in a pregnant patient.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) Up to 1 g/kg on 2 consecutive days OR up to 0.4 g/kg on 5 consecutive days (up to a total of 2 g per kg per treatment course); OR

B) The dose and interval between doses have been adjusted according to the platelet count and/or to prevent significant bleeding as determined by the prescriber.

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6. Kawasaki Disease. Approve for 3 months if prescribed by or in consultation with a pediatric cardiologist or a pediatric infectious diseases physician.

Dosing. Approve up to 2 g/kg given intravenously as a single dose or over multiple consecutive days. The dose may be repeated if needed.

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7. Multifocal Motor Neuropathy. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
- **i.** The diagnosis is supported by weakness without sensory abnormalities, upper motor neuron signs, or marked bulbar involvement and meets ONE of the following (a, b, or c):
  - **a)** The diagnosis is supported by nerve conduction studies that demonstrate motor conduction block or probable motor conduction block **[documentation required]**; OR
  - **b)** The prescriber has determined the patient has multifocal motor neuropathy without conduction block **[documentation required]**; OR
  - **c)** The diagnosis is supported by a motor nerve biopsy or by a magnetic resonance imaging (MRI) neurography **[documentation required];** AND
- **ii.** The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has improvement in neurologic symptoms as determined by the prescriber.
Note: Examples of improvement in neurologic symptoms include improvement in disability, grip strength improvement (measured with dynamometer), physical examination show improvement in neurological symptoms and strength.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) Therapy is initiated with 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days; OR
B) One of the following maintenance dosing regimen is used (i, ii, or iii):
- **i.** 0.5 g/kg to 2.4 g/kg given intravenously every month; OR
- **ii.** 1 g/kg given intravenously every 2 to 4 weeks; OR
- **iii.** 2 g/kg given intravenously every 1 to 2 months.

Other Uses with Supportive Evidence

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8. Antibody-Mediated Rejection in Transplantation. Approve for 1 year if prescribed by or in consultation with a physician affiliated with a transplant center.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) Up to 2 g/kg as an intravenous infusion (as a single dose or divided in smaller doses [e.g., 400 mg per kg daily for 5 days]); OR
B) The dosage is based on a transplant center's protocol.

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9. Autoimmune Mucocutaneous Blistering Diseases (Pemphigus Vulgaris, Pemphigus Foliaceus, Bullous Pemphigoid, Mucous Membrane Pemphigoid [Cicatricial Pemphigoid], and Epidermolysis Bullosa Acquisita). Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
- **i.** Patient meets ONE of the following (a, b, or c):
  - **a)** Patient meets BOTH of the following [(1) and (2)]:
    - **(1)** Patient has tried a systemic corticosteroid OR a corticosteroid is contraindicated according to the prescriber; AND
    - **(2)** Patient has tried an immunosuppressive agent OR an immunosuppressive agent is contraindicated according to the prescriber; OR
      Note: Examples of immunosuppressive agents include azathioprine, cyclophosphamide, dapsone, methotrexate, cyclosporine, mycophenolate mofetil, and tacrolimus.
  - **b)** Patient has rapid, debilitating, progressive disease that cannot be controlled with a systemic corticosteroid and an immunosuppressive agent; OR
  - **c)** The disease is so serious that there is inadequate time for therapy with a systemic corticosteroid and an immunosuppressive agent to have a rapid enough effect; AND
- **ii.** The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has responded to therapy according to the prescriber.
Note: Examples of response to therapy can include healing of previous lesions or fewer new lesions.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 2 g/kg per cycle given intravenously every 3 to 4 weeks. This dose is divided over 2, 3, or 5 consecutive days; OR
B) In patient with aggressive ocular disease, such as ocular cicatricial pemphigoid, 2 g/kg given intravenously may be given every 2 weeks in divided doses over 2, 3, or 5 consecutive days; OR
C) The frequency is gradually being slowly decreased as the lesions resolve and heal.

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10. Cytomegalovirus Pneumonitis or Pneumonia in a Patient with Cancer or Transplant-Related Infection. Approve for 2 months if prescribed by or in consultation with an oncologist, hematologist, or an infectious diseases physician.

Dosing. Approve 400 mg/kg given intravenously every other day for 3 to 5 doses.

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11. Desensitization Therapy Prior to and Immediately after Transplantation. Approve for 1 year if prescribed by or in consultation with a physician affiliated with a transplant center.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) Up to 2 g/kg per month administered intravenously (as a single dose or divided in smaller doses [e.g., 400 mg per kg daily for 5 days]); OR
B) The dosage is based on a transplant center's protocol.

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12. Guillain-Barré Syndrome. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 1 month (this is to provide one course of therapy) if the patient meets BOTH of the following (i and ii):
  i. Patient meets ONE of the following (a or b):
    a) The medication is initiated within 2 weeks and no longer than 4 weeks after onset of neuropathic symptoms; OR
    Note: Examples of neuropathic symptoms include weakness, inability to stand or walk without assistance, and respiratory or bulbar weakness.
    b) Patient has had a relapse (treatment related fluctuation), but had an initial response to IVIG; AND
  ii. The medication is prescribed by or in consultation with a neurologist or a specialist with experience in diagnosing and treating patients with Guillain-Barré syndrome.
B) Patient is Currently Receiving Immune Globulin. Approve for 1 month (this is to provide a second course) about 3 weeks after the first course.

Dosing. Approve 2 g/kg administered intravenously in divided doses over 2 to 5 days.

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13. Hematologic Neoplasm-Associated Hypogammaglobulinemia or Hypogammaglobulinemia after B-cell Targeted Therapies (Secondary Immunodeficiency). Approve for 6 months if the patient meets ONE of the following (A or B):
Note: Some examples of B-cell targeted therapy are chimeric antigen receptor (CAR) T-cell therapy (e.g., Kymriah [tisagenlecleucel intravenous infusion], Abecma [idecabtagene vicleucel intravenous infusion], Breyanzi [lisocabtagene maraleucel intravenous infusion], Tecartus [brexucabtagene

autoleucel intravenous infusion], Yescarta [axicabtagene ciloleucel intravenous infusion]), a rituximab product, Besponsa (inotuzumab ozogamicin intravenous infusion).
Note: Refer to B-Cell Chronic Lymphocytic Leukemia (CLL) for Prevention of Infections and Multiple Myeloma for diagnosis-specific criteria.

A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient has an immunoglobulin G (IgG) level of < 600 mg/dL (6.0 g/L) **[documentation required]** [excluding paraprotein]; AND
- **ii.** Patient has recurrent or severe infections or there is a high risk of infection according to the prescriber; AND
- **iii.** The medication is being prescribed by or in consultation with an oncologist, hematologist, infectious disease physician, or immunologist.

B) Patient is Currently Receiving Immune Globulin. Approve if the patient is having a positive response to therapy according to the prescriber **[documentation required]**.
Note: Examples of a positive response to therapy include maintaining an increased IgG trough level or a decrease in the number of infections.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):

A) 0.4 g/kg to 0.6 g/kg given intravenously once a month; OR

B) 0.2 g/kg to 0.8 g/kg given intravenously once every 3 to 4 weeks; OR

C) The dose and interval between doses have been adjusted based on clinical response as determined by the prescriber.

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14. Hematopoietic Cell Transplantation to Prevent Infection. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, iii, and iv):
- **i.** Patient has had a HCT within the previous year; AND
- **ii.** Patient has an immunoglobulin G (IgG) level < 600 mg/dL (6.0 g/L) **[documentation required]** OR the patient has multiple myeloma or malignant macroglobulinemia; AND
- **iii.** According to the prescriber, the patient has a significant risk of having frequent and/or severe infections; AND
- **iv.** The medication is prescribed by or in consultation with a hematologist, oncologist, or infectious diseases physician.

B) Patient is Currently Receiving Immune Globulin. Approve for 6 months if the patient is having a positive response to therapy according to the prescriber **[documentation required]**.
Note: Examples of a positive response to therapy include maintaining an increased IgG trough level, controlling the number of infections, or a decrease in the number of infections.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):

A) During the first 100 days after HCT, the patient meets ONE of the following (i or ii):
- **i.** Adults and adolescents: 0.5 g/kg per week given intravenously and the dose is adjusted to maintain trough (pre-dose) serum IgG greater than 400 mg/dL; OR
- **ii.** Pediatric patient with allogeneic HCT: 0.4 g/kg per month given intravenously and the dose is adjusted to keep IgG greater than 400 mg/dL; OR

B) Greater than 100 days post-HCT, the dose is 0.5 g/kg given intravenously every 3 to 4 weeks, and the dose is adjusted to keep IgG greater than 400 mg/dL; OR

C) The dosage is based on a transplant center's protocol.

15. Human Immunodeficiency Virus (HIV)- or Hepatitis C-Associated Thrombocytopenia. Approve for 1 month if the patient meets BOTH of the following (A and B):

A) Patient is receiving antiviral therapy; AND

B) The medication is prescribed by or in consultation with an infectious diseases specialist, a physician who specializes in the treatment of HIV infection, a gastroenterologist, hepatologist, or a liver transplant physician.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) Up to 2 g/kg given intravenously in divided doses over 2 to 5 days; OR

B) Up to 1 g/kg one time given intravenously up to once weekly.

16. Human Immunodeficiency Virus (HIV), to Prevent Recurrent Infections. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, and iv):

i. Patient is < 18 years of age; AND

ii. Patient is receiving combination antiretroviral therapy; AND

iii. Patient has ONE of the following (a, b, or c):

a) Hypogammaglobulinemia (i.e., IgG < 400 mg/dL [4.0 g/L]) **[documentation required]**; OR

b) Functional antibody deficiency is demonstrated by poor specific antibody titers (that is, the patient does not develop specific antibody responses against protein and polysaccharide antigens) **[documentation required]**; OR

c) Functional antibody deficiency is demonstrated by the patient having recurrent (two or more per year), serious infections (e.g., bacteremia, meningitis, pneumonia) despite administration of combination antiretroviral therapy and appropriate antimicrobial prophylaxis; AND

iv. The medication is prescribed by or in consultation with an infectious diseases specialist or an immunologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the frequency and/or severity of infections have decreased according to the prescriber **[documentation required]**.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) The dose is 0.4 g/kg given by intravenous infusion every 2 to 4 weeks; OR

B) The dose and interval are adjusted according to clinical effectiveness.
Note: Examples of adjusting according to clinical effectiveness may include the need to increase the dose or frequency based on frequency or severity of infections, hospitalizations, days of school or work missed, failure to thrive.

17. Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy. Approve for the duration noted if the patient meets ONE of the following (A or B):
Note: Examples of checkpoint inhibitors are Keytruda (pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), Yervoy (ipilimumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion), Bavencio (avelumab intravenous infusion), Imfinzi (durvalumab intravenous infusion), Libtayo (cemiplimab intravenous infusion), Jemperli (dostarlimab intravenous infusion).

A) Initial Therapy. Approve for 1 month if the patient meets ONE of the following (i, ii, or iii):

i. Patient has tried a systemic corticosteroid and has not adequately responded to therapy; OR
Note: Examples of systemic corticosteroids include prednisone, methylprednisolone.

ii. The medication is being started with a systemic corticosteroid; OR
iii. A corticosteroid is contraindicated per the prescriber.

B) Patient is Currently Receiving Immune Globulin. Approve for 6 months if the patient is having a positive response to therapy, as determined by the prescriber, and the prescriber has determined extended therapy is required.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) Up to 0.4 g/kg given intravenously daily for 5 days; OR
B) Up to 2 g/kg given intravenously over 2 to 5 days; OR
C) The dose and interval between doses have been adjusted based on clinical response as determined by the prescriber.

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18. Lambert-Eaton Myasthenic Syndrome (LEMS). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month (to allow for one course of therapy) if the patient meets ALL of the following (i, ii, and iii):
i. Patient is having refractory weakness after symptomatic treatment of LEMS with an amifampridine product (e.g., Firdapse, Ruzurgi), guanidine, or pyridostigmine; AND
ii. Patient meets ONE of the following (a or b):
a) Patient has paraneoplastic LEMS; OR
b) Patient has non-paraneoplastic LEMS AND has tried a systemic corticosteroid (e.g., prednisone) or another immunosuppressive agent (e.g., azathioprine), or has a contraindication to corticosteroids and/or immunosuppressive agents, according to the prescriber; AND
iii. The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has a response or continued effectiveness, according to the prescriber **[documentation required]**.
Note: Examples of a response to therapy include improved muscle strength or other clinical response.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) Up to 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days; OR
B) Maintenance therapy every 4 weeks with up to 2 g/kg with the dose being adjusted based on clinical symptoms.

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19. Multiple Myeloma. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
i. Patient meets ONE of the following (a or b):
a) Patient has or is at risk of severe, recurrent infections according to the prescriber; OR
b) Patient will be starting, has taken, or is currently receiving chimeric antigen receptor (CAR)-T cell therapy OR bispecific antibody therapy; AND
Note: Examples of CAR-T cell therapy includes: Abecma (idecabtagene vicleucel intravenous infusion), Carvykti (ciltacabtagene autoleucel intravenous infusion).
Note: Examples of bispecific antibody therapy includes: Elrexfio (elranatamab-bcmm subcutaneous injection), Tecvayli (teclistamab-cqyv subcutaneous injection), Talvey (talquetamab-tgvs subcutaneous injection).

ii. The medication is prescribed by or in consultation with a hematologist, oncologist, or infectious diseases specialist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year.

Dosing. Approve 0.4 g/kg to 0.5 g/kg given intravenously every 3 to 4 weeks.

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20. Multiple Sclerosis (MS), Acute Severe Exacerbation or Relapses. Approve for 1 month (this is to provide one course of therapy) if the patient meets ALL of the following (A, B, and C):

A) Patient meets ONE of the following (i or ii):

i. Patient has either not responded to OR has had a significant adverse reaction with systemic corticosteroids (e.g., methylprednisolone sodium succinate injection) OR plasma exchange; OR

Note: A trial of Acthar H.P. gel (repository corticotropin injection; adrenocorticotropic hormone, ACTH) would also count toward meeting this requirement.

ii. A systemic corticosteroid is contraindicated, according to the prescriber; AND

B) Patient meets ONE of the following (i or ii):

i. Patient is already on maintenance therapy for MS or will be starting maintenance therapy for MS; OR

Note: Maintenance therapy does NOT include IVIG. Examples of maintenance therapy for MS would include: Avonex (interferon beta-1a injection), Plegridy (peginterferon beta-1a injection), Rebif (interferon beta-1a injection), Betaseron (interferon beta-1b injection)/Extavia (interferon beta-1b injection), Copaxone (glatiramer injection)/Glatopa (glatiramer injection), Gilenya (fingolimod capsule), Lemtrada (alemtuzumab injection), Aubagio (teriflunomide tablet), Mavenclad (cladribine tablet), Mayzent (siponimod tablet), Tecfidera (dimethyl fumarate capsule), Vumerity (diroximel fumarate capsule), Zeposia (ozanimod capsule), Tysabri (natalizumab injection), Novantrone (mitoxantrone injection), Bafiertam (monomethyl fumarate capsule), Kesimpta (ofatumumab injection), Ocrevus (ocrelizumab injection), Ponvory (penesimod tablet).

ii. Patient is pregnant or patient is post-partum and the prescriber has determined maintenance therapy is not clinically appropriate; AND

C) The medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of MS.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) A single 1 g/kg given intravenously; OR

B) 0.4 g/kg per day IV infusion for 5 consecutive days.

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21. Myasthenia Gravis. Approve for the duration noted if the patient meets ONE of the following (A, B, C, or D):

A) Initial Therapy for Short-Term (Acute) Use. Approve for 5 days (to allow for one course of therapy) if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following conditions (a, b, c, or d):

a) Patient has an exacerbation of myasthenia gravis; OR

b) Patient requires stabilization of myasthenia gravis before surgery; OR

c) Patient has been started on an immunosuppressive drug and is waiting for full effect; OR

Note: Examples of immunosuppressive drugs include azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, methotrexate, or tacrolimus.

d) Patient is starting therapy with a corticosteroid and IVIG is being given to prevent or minimize exacerbations; AND

ii. The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin Short-Term (Acute) Use. Approve for 5 days (to allow for one course of therapy).

C) Initial Therapy for Maintenance. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):

i. Patient has refractory myasthenia gravis; AND

ii. Patient has tried pyridostigmine; AND

iii. Patient has tried immunosuppressive therapy with at least one of the following agents: azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, methotrexate, tacrolimus AND has had an inadequate response; AND

iv. The medication is prescribed by or in consultation with a neurologist.

D) Patient is Currently Receiving Immune Globulin for Maintenance Therapy. Approve for 1 year if the patient is responding according to the prescriber.
Note: Examples of responding to therapy includes improvement in weakness (bulbar, limb, or respiratory), improvement with ocular symptoms.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):

A) Short-term use: 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days; OR

B) Maintenance therapy: 0.4 g/kg to 1 g/kg given intravenously every 4 weeks; OR

C) The dose and interval between doses have been adjusted based on clinical response as determined by the prescriber.

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22. Passive Immunization for Measles (Post-Exposure Prophylaxis). Approve for 1 day (to allow for a single dose) if the patient meets ONE of the following (A or B):
Note: For a patient with primary immune deficiency, see criteria for PID.

A) Patient is pregnant and meets BOTH of the following (i and ii):

i. Patient has been exposed to measles; AND

ii. Patient does not have evidence of immunity to measles (i.e., the patient does not have a history of the disease or age-appropriate vaccination); OR

B) Patient meets BOTH of the following (i and ii):

i. Patient is immunocompromised; AND

ii. Patient has been exposed to measles.

Dosing. Approve the following dosing regimen: 0.4 g/kg intravenously administered one time.

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23. Post-Exposure Prophylaxis for Varicella OR Treatment or Post-Exposure Prophylaxis for Tetanus. Approve for 1 day (to allow for a single dose) if the patient meets ONE of the following (A or B):

A) For Varicella post-exposure, Varicella immune globulin is not available or cannot be administered within 10 days of exposure; OR

B) For Tetanus treatment or post-exposure, Tetanus Immune globulin is not available.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) 0.4 g/kg given intravenously one time; OR

B) 0.2 to 0.4 g/kg given intravenously one time.

24. Parvovirus B19 Infection. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 2 months if the patient meets BOTH of the following (i and ii):

i. Patient has an immunodeficiency condition; AND
Note: Examples of an immunodeficiency condition include patients with HIV infection, solid organ transplants (e.g., renal, liver), chemotherapy for hematologic malignancy.

ii. The medication is prescribed by or in consultation with an infectious diseases specialist, immunologist, hematologist, or transplant specialist.

B) Patient is Currently Receiving Immune Globulin. Approve for 6 months.

Dosing. Approve ONE of the following dosing regimens (A, B, C, or D):

A) 2 g/kg given intravenously over a period of 2 to 5 consecutive days; OR
B) 0.4 g/kg to 0.5 g/kg given intravenously daily for 5 days; OR
C) 0.4 g/kg given intravenously once every 4 weeks; OR
D) 0.2 g/kg to 0.4 g/kg given intravenously daily for 5 to 10 days.

25. Pure Red Blood Cell Aplasia (PRCA), Immunologic Subtype. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month if the patient meets ALL of the following (i, ii, and iii):

i. Patient has tried a systemic corticosteroid (e.g., prednisone); AND

ii. Patient has tried either cyclophosphamide OR cyclosporine; AND

iii. The medication is prescribed by or in consultation with an infectious diseases specialist, immunologist, hematologist, or transplant specialist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 month if the patient has responded with an increase in hemoglobin and reticulocytosis according to the prescriber.

Dosing. Approve 0.5 g/kg given intravenously for 4 weeks.

26. Stiff-Person Syndrome (Moersch-Woltman Syndrome). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following (i and ii):

i. Patient meets ONE of the following (a or b):

a) Patient has tried a benzodiazepine (e.g., diazepam) OR baclofen; OR

b) Patient has contraindications to both a benzodiazepine AND baclofen according to the prescriber; AND

ii. The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has responded to therapy according to the prescriber.
Note: Examples of response to therapy includes reduced stiffness or frequency of spasms, ability to walk unassisted.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) 2 g/kg given intravenously over a period of 2 to 5 consecutive days every month; OR
B) For maintenance therapy, the dose is adjusted to provide the minimum effective dosage of IVIG. Maximum dose is 2 g/kg given intravenously.

27. **Thrombocytopenia, Feto-neonatal Alloimmune.** Approve for 6 months if the pregnant mother or newborn patient is prescribed the medication by or in consultation with a hematologist or an obstetrician.

    Dosing. Approve ONE of the following dosing regimens (A, B, C, or D):
    A) For the mother: 1 g/kg given intravenously every week; OR
    B) For the mother: 2 g/kg given intravenously every week; OR
    C) For the mother: 1 g/kg given intravenously twice weekly; OR
    D) For the newborn: 1 g/kg to 2 g/kg given intravenously dosed per the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of immune globulin intravenous is not recommended in the following situations:

1. **Adrenoleukodystrophy.** Evidence does not support IVIG use.[18]

2. **Alzheimer's Disease (AD).** In one multicenter, double-blind, Phase III, placebo-controlled trial, 390 patients with mild to moderate AD were randomized to therapy with IVIG 400 mg/kg or 200 mg/kg, or to placebo given every 2 weeks for 18 months.[61] There was no statistically significant difference in the rate of cognitive decline when compared with placebo. Also, there was not a statistically significant change in functional ability when compared to placebo. Large placebo-controlled trials with a longer observation period are needed to establish efficacy, determine the optimal dosing regimen, and to confirm the safety of IVIG in the general AD population.[52,53]

3. **Amyotrophic Lateral Sclerosis.** There is insufficient evidence to recommend IVIG.[18]

4. **Asthma.** Global Initiative for Asthma (GINA) guidelines for asthma management and prevention do not include recommendations for use of IVIG.[54]

5. **Atopic Dermatitis.** Limited data exist to determine the utility of IVIG in the management of atopic dermatitis.[55]

6. **Autism.** Evidence does not support IVIG use.[18] Well controlled, double-blind trials are needed.

7. **Chronic Fatigue Syndrome.** Evidence does not support IVIG use.[56] One randomized, placebo-controlled trial did not find benefits in quality of life measures nor the Profile of Mood States for IVIG.[56] Although scores were improved in IVIG and placebo treatment groups, no significant between group difference was demonstrated.

8. **Complex Regional Pain Syndrome (Reflex Sympathetic Dystrophy).** There is insufficient evidence to recommend IVIG. In one single center study a single dose of 0.5 g/kg of IVIG produced a decrease in pain intensity by 50% or more compared to placebo in 3 of 12 patients.[57] In a randomized, placebo-controlled, multicenter trial, low-dose immunoglobulin treatment for 6 weeks was not effective in relieving pain in patients with moderate-to-severe complex regional pain syndrome.[58] Well-controlled large-scale trials are needed.

9. **Crohn's Disease.** There is insufficient evidence to recommend IVIG. In one single center case collection report, 19 patients with acute Crohn's disease (Crohn's Disease Activity Index [CDAI] 284.1 ± 149.8) who were resistant to steroids received IVIG daily for 7 to 10 days.[59] Four weeks after completing therapy, 14 patients were in clinical remission (CDAI < 150). Prospective, randomized, placebo-controlled trials are needed to determine if IVIG has a role in the treatment of Crohn's disease.

10. **Cystic Fibrosis.** There is insufficient evidence to recommend IVIG. In one single-center retrospective case review of 16 children with cystic fibrosis, IVIG was reportedly effective.[60] Well-designed, controlled trials are needed.[18]

11. **Diabetes Mellitus, Immunotherapy.** Evidence does not support IVIG use.[18,62,63] In one 2-year randomized controlled trial, IVIG was given every 2 months to children and adults with type 1 diabetes.[62] No beneficial effect was shown with IVIG compared with control and the authors concluded that IVIG therapy is unlikely to be a viable option for immunotherapy.

12. **Fibromyalgia Syndrome.** There is insufficient evidence to recommend IVIG. In one open-label single center study, 15 patients with fibromyalgia syndrome and distal demyelinating polyneuropathy received IVIG 400 mg/kg given daily for 5 days.[64] Pain, tenderness, and strength reportedly improved. Double-blind, placebo-controlled trials are needed to determine if IVIG is effective in fibromyalgia syndrome.

13. **In Vitro Fertilization (IVF).** There is insufficient evidence to recommend IVIG administration as part of IVF outcomes.[68]

14. **Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes (POEMS) Syndrome.** Evidence does not support IVIG use.[18]

15. **Recurrent Spontaneous Pregnancy Loss (RSPL) [Including a Patient with Antiphospholipid Antibody-Positive].** Evidence does not support IVIG use.[69-72] In one double-blind pilot study, IVIG did not improve obstetric or neonatal outcomes beyond those achieved with a heparin and low-dose aspirin regimen.[69] In another double-blind trial (n =82 of whom 47 had an index pregnancy), live birth rates did not differ significantly between IVIG-treated and placebo-treated women.[71] The American Society for Reproductive Medicine practice committee states that several trials and meta-analyses concluded that IVIG is ineffective for primary recurrent pregnancy loss and this treatment is not recommended.[72]

16. **Selective Immune Globulin A (IgA) Deficiency as the Sole Immunologic Abnormality.** Evidence does not support use of IVIG.[14,18] Selective IgA deficiency is defined as a serum IgA level less than 0.07 g/L, but normal serum IgG and IgM levels in a patient greater than 4 years of age in whom other causes of hypogammaglobulinemia have been excluded.[14] Selective IgA deficiency may co-exist in some patients with poor specific IgG antibody production, with or without IgG2 subclass deficiency.[14,18] Some of these patients with a concomitant specific antibody defect might benefit from therapy with IVIG.

17. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**B-Cell Chronic Lymphocytic Leukemia for Prevention of Infections; Hematologic Neoplasm-Associated Hypogammaglobulinemia or Hypogammaglobulinemia after B-cell Targeted Therapies (Secondary Immunodeficiency); Hematopoietic Cell Transplantation to Prevent Infection: P**atient's immunoglobulin G (IgG) level was updated to < 600 mg/dL (6.0 g/L); previously was 500 mg/dL (5.0 g/L). **Human Immunodeficiency Virus (HIV) - or Hepatitis C-Associated Thrombocytopenia.** The diagnosis Hepatitis C-Associated Thrombocytopenia was added to the policy. Criterion was updated from patient is receiving combination antiretroviral therapy to patient is receiving antiviral therapy. Criteria related to clinically significant bleeding complications according to the prescriber was removed. Criterion	10/12/2022

	regarding prescribing or consultation specialist was updated to include a gastroenterologist, a hepatologist, or a liver transplant physician. **Multiple Myeloma.** Added the wording, "or is at risk of" to the criterion related to severe recurrent infections according to the prescriber. **Passive Immunization for Varicella (Chickenpox) [Post-Exposure Prophylaxis]:** The diagnosis wording was updated to Post-Exposure Prophylaxis for Varicalla. The following criteria were removed: 1) Patient has HIV; Patient is immune compromised; Patient is pregnant; 2) Patient does not have evidence of immunity to varicella; 3) The specialist requirement. Also, Treatment or Post-Exposure Prophylaxis for Tetanus was added to the diagnosis with the following criterion: Tetanus Immune globulin is not available. Dosage of 0.2 to 0.4 g/kg intravenously one time was added. **Parvovirus B19 Infection:** Diagnosis wording was previously Pure Red Blood Cell Aplasia (PRCA) Secondary to Chronic (Persistent) Parvovirus B19 Infection. The word "chronic" immunodeficiency condition was removed from initial therapy criteria. The criterion regarding "clinically significant anemia as determined by the prescriber" and "patient is transfusion dependent" was removed. Continuation of therapy criteria related to hemoglobin and relapse were removed from the criteria. Removed "(one course) for up to two courses" from the dosage 2g/kg given intravenously over a period of 2 to 5 consecutive days. **Heart Failure, Chronic; Human Immunodeficiency Virus (HIV) Infection, Adults, for Prophylaxis of Infections; and Post-Polio Syndrome** were removed from Conditions Not Recommended for Approval	
Annual Revision	**Cytomegalovirus Pneumonitis or Pneumonia in a Patient with Cancer or Transplant-Related Infection:** Added the wording pneumonitis; the diagnosis wording was previously Cytomegalovirus Pneumonia in a Patient with Cancer or Transplant-Related Infection. **Multiple Myeloma:** The following option for approval was added in initial therapy as an alternative to infection status 1) Patient will be starting, has taken, or is currently receiving chimeric antigen receptor (CAR)-T cell therapy OR bispecific antibody therapy. Note: Examples of CAR-T cell therapy includes: Abecma (idecabtagene vicleucel intravenous infusion), Carvykti (ciltacabtagene autoleucel intravenous infusion). Note: Examples of bispecific antibody therapy includes: Elrexfio (elranatamab-bcmm subcutaneous injection), Tecvayli (teclistamab-cqyv subcutaneous injection), Talvey (talquetamab-tgvs subcutaneous injection). **Parvovirus B19 Infection:** 0.2 g/kg to 0.4 g/kg given intravenously daily for 5 to 10 days was added as an alternative dosing regimen. **Anemia, Aplastic** was removed from Condition Not Recommended for Approval.	10/25/2023
Selected Revision	**Alyglo was added to the policy** with the same criteria as all other immune globulin products. **Chronic Inflammatory Demyelinating Polyneuropahy (CIDP) or Polyradiculoneurapthy**: Updated dosing from an initial loading dose of 2 g/kg given intravenously in divided doses over 2 to 4 days consecutive days to 2 to 5 days consecutive days. Updated dosing from a maintenance dose of 1 g/kg given intravenously over one day or divided into two doses of 0.5 g/kg given on 2 consecutive days to a maintenance dose of 1 g/kg given intravenously in divided doses over 1 to 4 consecutive days.	02/07/2024
Selected Revision	**Immune Thrombocytopenia (ITP).** The duration of approval for initial therapy for adults and pediatric patients was changed from 1 year to 3 months. Criterion for patients requiring retreatment with immune globulin was added to the continuation criteria. Continuation criterion was also updated from "Patient has responded to therapy" to patient is responding to therapy OR the patient has previously responded to therapy. **The following was added to the Policy Statement:** If the client is using the IVIG MSM Policy in tandem with this UM policy, the new approval may be entered without another clinical review for a preferred product only.	04/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immune Globulin – Intravenous Utilization Management Medical Policy

- Alyglo™ (immune globulin intravenous solution-stwk – GC Biopharma)
- Asceniv™ (immune globulin intravenous solution-sira – ADMA Biologics)
- Bivigam® (immune globulin intravenous solution – AMDA Biologics)
- Flebogamma® DIF (immune globulin intravenous solution – Grifols)
- Gammagard® Liquid (immune globulin solution – Takeda)
- Gammagard® S/D < 1 mcg/mL in 5% solution (immune globulin intravenous solution – Takeda)
- Gammaked™ (immune globulin solution caprylate/chromatography purified – Kedrion)
- Gammaplex® (immune globulin intravenous solution – BPL)
- Gamunex®-C (immune globulin solution caprylate/chromatography purified – Grifols)
- Octagam® (immune globulin intravenous solution – Octapharma)
- Panzyga® (immune globulin intravenous solution-ifas – Octapharma/Pfizer)
- Privigen® (immune globulin intravenous solution – CSL Behring)

REVIEW DATE: 10/25/2023; selected revision 02/07/2024 and 4/10/2024

OVERVIEW

Immune globulin intravenous (IVIG) products are concentrated human immunoglobulins, primarily immunoglobulin G (IgG).

All of these products (except Octagam 10%) are FDA-approved for replacement therapy in patients with **primary immune deficiencies** due to defects in humoral immunity. The following indications are FDA approved:

- **B-cell chronic lymphocytic leukemia (CLL)**, for prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent infections.[6,18,21]
- **Chronic inflammatory demyelinating polyneuropathy (CIDP)**, to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.[5,7,9,12,15,67]
- **Dermatomyositis (or polymyositis)**. Octagam 10% is indicated for the treatment of dermatomyositis in adults.[11] Patients with dermatomyositis treated with Octagam were under treatment with corticosteroids and/or maximally two immune-suppressants OR patients had previous failure or intolerance with a corticosteroid and at least one additional immunosuppressive drug.[33] IVIG may be considered amongst the treatment options for patients with polymyositis not responding to first line immunosuppressive treatment.[32]
- **Idiopathic (immune) thrombocytopenic purpura (ITP)**, acute and chronic, when a rapid rise in platelet count is needed to prevent and/or control bleeding or to allow a patient with ITP to undergo surgery.[2,4,6-9,11,12,15,23-25]
- **Kawasaki disease** in pediatric patients for the prevention of coronary artery aneurysm.[6,26] The American Heart Association and the American Academy of Pediatrics recommend initial therapy with 2 g of IVIG per kg as a single intravenous (IV) dose given over 10 to 12 hours.[26] The dose can be repeated if needed.
- **Multifocal motor neuropathy** in adults as maintenance therapy to improve muscle strength and disability.[5]

- **Primary humoral immune deficiency (PID)**, for replacement therapy, including but not limited to the humoral immune defect in the following conditions: common variable immunodeficiency, X-linked agammaglobulinemia [congenital agammaglobulinemia], Wiskott-Aldrich Syndrome, and severe combined immunodeficiencies.[1-10,12,15,16,25,80] Gammagard Liquid 10%, Gammaked, and Gamunex-C may be administered via IV or subcutaneous infusion for primary immunodeficiency.[5,7,9] IVIG is also indicated for measles prophylaxis in individuals with PID who have been exposed to measles or who are at high risk of measles exposure.[3,4,7-10,12,13,17,24,45,80]

IVIG is prepared from pooled plasma collected from a large number of human donors.[1-12,15,16,25] The donors in a typical pool of plasma have a wide range of antibodies against infectious agents. These products have IgG subclasses similar to that found in normal humans. Asceniv contains not only antibodies which satisfy the requirement to treat patients with PID, it also has elevated levels of respiratory syncytial virus (RSV) antibodies.[19]

IVIG also is used for many off-label indications. Much of the evidence for clinical effectiveness of IVIG is anecdotal (i.e., case reports, open series, or cohort studies). Some conditions have been studied in controlled trials. Usually, IVIG is indicated only if standard approaches have failed, become intolerable, or are contraindicated.

- **Antibody-mediated rejection (ABMR) in transplantation:** Current strategies for treatment of antibody-mediated rejection include plasmapheresis, IVIG, and T-cell or B-cell-depleting agents.[75] Although there are no controlled trials regarding the most appropriate treatments, the benefits of immune globulin have been well described and has been used as the standard-of-care (along with plasmapheresis) in multiple studies.[18,76] Clinical practice guidelines (2009 Kidney Disease: Improving Global Outcomes) recommends a combination of corticosteroids, plasmapheresis, IVIG, anti-CD20 antibody, and lymphocyte-depleting antibody for antibody-mediated rejection.[76,77] As in desensitization therapy, much of the information for IVIG use is in patients with kidney transplants, but the same principles apply to transplantation of other organs and tissues. Immune globulin has been used in lung transplant patients to treat ABMR[20,44,78] and a scientific statement from the American Heart Association states that primary therapy for ABMR in patients with heart transplants may include IVIG, plasmapheresis, high-dose corticosteroids, and anti-lymphocyte antibodies.[36]
- **Autoimmune mucocutaneous blistering diseases (pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid [cicatricial pemphigoid], and epidermolysis bullosa acquisita):** Conventional therapy (a systemic corticosteroid and an immunosuppressive agent) is started at the same time or before IVIG. Many case reports and uncontrolled case series suggest benefit of IVIG in patients with recalcitrant disease or in those with contraindications to conventional therapy.[28-30] International expert recommendations for the management of pemphigus note that first-line treatment includes corticosteroids and anti-CD20 monoclonal antibodies. First-line corticosteroid-sparing agents include azathioprine and mycophenolate mofetil, and other corticosteroid-sparing agents include IVIG.[2]
- **Cytomegalovirus (CMV) pneumonitis or pneumonia in patients with cancer or transplant-related infection:** For CMV pneumonia, therapy generally consists of antivirals (e.g., ganciclovir, foscarnet). The National Comprehensive Cancer Network (NCCN) guidelines on prevention and treatment of cancer-related infections (version 1.2023 – June 28, 2023) lists IVIG as an adjunctive therapy for CMV pneumonitis, but notes that IVIG use as an antiviral is controversial.[31]
- **Desensitization therapy prior to and immediately after transplantation:** Most of the information on use of IVIG for desensitization is in patients with kidney transplantation but many of the same principles apply to transplantation of other organs and tissues.[34,35] Current protocols

include using low-dose IVIG with plasma exchange or high-dose IVIG with or without B-cell depletions with rituximab.[18]

- **Guillain Barré syndrome (GBS):** The American Academy of Neurology recommends IVIG in patients who require aid to walk within 2 or 4 weeks from the onset of neuropathic symptoms.[37] The effect of IVIG in GBS has only been investigated in randomized controlled trials in patients who are unable to walk at nadir (i.e., severely affected patients), not in mildly affected patients who are able to walk unaided at nadir.[38] IVIG is not indicated or proven to be effective in patients mildly affected with GBS.[32,38]
- **Hematologic neoplasm-associated hypogammaglobulinemia or hypogammaglobulinemia after B-cell targeted therapies (secondary immunodeficiency):** Clinical guidelines for immunoglobulin use by the National Health Service-England note secondary antibody deficiency can be hypogammaglobinemia associated with therapeutic monoclonals targeted at B-cells and plasma cells, non-Hodgkin's lymphoma, CLL, multiple myeloma, or other relevant B-cell malignancies.[27] NCCN guidelines regarding management of immunotherapy-related toxicities (version 2.2023 – May 9, 2023) recommends that after anti-CD19 chimeric antigen receptor (CAR)-T cell therapy, IVIG replacement should be considered for patients with serum IgG levels < 400 to 600 mg/dL and serious or recurrent infections.[73]
- **Hematopoietic cell transplantation (HCT) to prevent infections:** HCT is defined as transplantation of any blood- or marrow-derived hematopoietic stem cells, regardless of transplant type (i.e., allogeneic or autologous) or cell source (i.e., bone marrow, peripheral blood, or umbilical cord blood). With regard to IVIG, guidelines recommend IVIG for prevention or preemptive treatment of specific infections in HCT recipients.[39] In adult or adolescent HCT recipients (allogeneic or autologous), IVIG is used to prevent infections in those with severe hypogammaglobulinemia (i.e., serum IgG < 400 mg/dL) during the first 100 days after HCT. In pediatric patients, IVIG is indicated in those with an allogeneic HCT if hypogammaglobulinemia is severe during the first 100 days after HCT. For prevention of infections beyond 100 days post-HCT (allogeneic or autologous), IVIG is recommended in recipients with severe hypogammaglobulinemia (i.e., serum IgG < 400 mg/dL). Guidelines from the American Society for Blood and Marrow Transplantation make recommendations for IVIG dosing in HCT recipients to prevent infectious complications.[39] During the first 100 days after HCT, the dose in adults and adolescents is 0.5 g/kg per week. The IVIG dose should be individualized to maintain trough (pre-dose) serum IgG > 400 to 500 mg/dL. The dose in allogeneic pediatric HCT patients is 0.4 g/kg per month, adjusted to keep IgG > 400 mg/dL. Higher and more frequent dosing may be necessary in patients for prevention of early disease after HCT because the half-life of IVIG is reduced to between 1 to 10 days in this population. Dosing for > 100 days post-HCT is 0.5 g/kg given every 3 to 4 weeks. The dose is not adjusted using serum IgG level in patients with multiple myeloma or malignant macroglobulinemia. NCCN guidelines on prevention and treatment of cancer-related infections discussed similar recommendations.[31]
- **Human immunodeficiency virus (HIV)- or Hepatitis C-associated thrombocytopenia:** Secondary ITP can occur in patients with HIV infection.[23,24] It can also occur in patients with Hepatitis C. The American Society of Hematology (ASH) guidelines for ITP recommend initial treatment with corticosteroids, IVIG, or Rh0(D) immune globulin for patients with secondary ITP due to HIV. ASH also recommends IVIG for secondary ITP associated with Hepatitis C.[23,24]
- **HIV-infected infants and children to prevent recurrent infections:** IVIG is recommended to prevent serious bacterial infections in HIV-infected children who have hypogammaglobulinemia (IgG < 400 mg/dL).[40] Clinicians providing care for adolescents are advised to use the US Department of Health and Human Services Adult and Adolescent HIV-guideline for the care of post-pubertal adolescents (sexual maturity rating [SMR] four and five) and to use the pediatric guideline for guidance on the care of adolescents at SMR 3 or lower.[40]

- **Immunotherapy-related toxicities associated with checkpoint inhibitor therapy:** NCCN guidelines for the management of immunotherapy-related toxicities (version 2.2023 – May 9, 2023) recommend IVIG for the management of severe pneumonitis after 48 hours of methylprednisolone therapy, as treatment for severe myasthenia gravis, encephalitis, cardiovascular adverse events, musculoskeletal adverse events, moderate or severe GBS, transverse myelitis, bullous dermatitis, and Stevens-Johnson syndrome/toxic epidermal necrolysis.[73] The American Society of Clinical Oncology also has practice guidelines on the management of immune-related adverse events in patients treated with checkpoint inhibitor therapy.[74] These practice guidelines address the above mentioned indications along with other conditions (e.g., severe cutaneous adverse reactions, myositis, autoimmune hemolytic anemia, immune thrombocytopenia).
- **Lambert-Eaton Myasthenic Syndrome:** Limited but moderate- to high-quality evidence from randomized controlled trials have shown that 3,4-diaminopyridine or IVIG was associated with improved muscle strength score and compounded muscle action potential amplitudes. IVIG may be used as an alternative in patients who do not respond or do not tolerate other therapies.[18]
- **Multiple myeloma:** Patients with multiple myeloma are often functionally hypogammaglobulinemic with total immunoglobulin production being elevated, but the repertoire of antibody production restricted.[31] The NCCN guidelines on multiple myeloma (version 1.2024 – September 22, 2023) notes that IVIG replacement during CAR-T cell and bispecific antibody therapies are not guided by the presence of infections.[42] It also should be considered in the setting of recurrent, serious infections and/or hypogammaglobulinemia (IgG < 400 mg/dL).
- **Multiple sclerosis, acute severe exacerbation or relapses:** Medication options for relapse management include high dose corticosteroids, intramuscular adrenocorticotrophic hormone, plasmapheresis, and IVIG. IVIG is sometimes used to treat relapses that do not respond to corticosteroids.[43] During pregnancy, relapses severe enough to require treatment can be safely managed with a short-term course of corticosteroids after the first trimester. Methylprednisolone is the preferred agent because it is metabolized before crossing the placenta.[43]
- **Myasthenia gravis:** Recommendations from an international consensus guidance statement for management of adult or juvenile myasthenia gravis include the use of IVIG in some patients.[65] Symptomatic and immunosuppressive treatment of myasthenia gravis includes pyridostigmine as initial therapy in most patients. Corticosteroids or immunosuppressive therapies are used in all patients with myasthenia gravis who have not met treatment goals after an adequate trial of pyridostigmine. A nonsteroidal immunosuppressive agent (e.g., azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus) should be used alone when corticosteroids are contraindicated or refused. In patients with refractory myasthenia gravis, chronic IVIG and chronic plasma exchange (PLEX), cyclophosphamide, or rituximab may be used. PLEX and IVIG are recommended as short-term treatments in patients with myasthenia gravis with life-threatening effects such as respiratory insufficiency or dysphagia, to prepare for surgery in patients with significant bulbar dysfunction, when rapid response is needed, when other treatments are not adequate, and before starting corticosteroids if necessary to prevent or minimize exacerbations. IVIG can be considered as maintenance therapy in patients with refractory myasthenia gravis or in patients with relative contraindications to immunosuppressive agents. Refractory myasthenia gravis is defined as the post intervention status of unchanged or worse after corticosteroids and at least two other immunosuppressive agents used in adequate doses for an adequate duration, with persistent symptoms or side effects that limit functioning as defined by the patient or physician. The international consensus guidance statement for myasthenia gravis[65] recommends an initial dose of 2 g/kg given in divided doses over 2 to 5 days. For maintenance therapy, the recommended dose is 0.4 to 1 g/kg given every 4 weeks; an attempt to decrease frequency can be made over time. If additional treatment is required, the dose should be adjusted based on the response.

- **Passive immunization for measles (post-exposure prophylaxis):** When administered within 6 days of exposure, immune globulin (IG) can prevent or modify measles in patients who are nonimmune.[13] IG therapy is not indicated in persons who have received one dose of measles-containing vaccine at ≥ 12 months, unless the patient is severely immunocompromised. The Advisory Committee on Immunization Practices recommends the use of IG therapy for post-exposure prophylaxis of measles in the following patients who are at risk for severe disease and complication from measles: infants < 12 months of age, pregnant women without evidence of measles immunity, and severely immunocompromised persons.[13] For infants < 12 months of age, intramuscular IG is used; infants 6 through 11 months of age can receive measles, mumps and rubella vaccine instead of IG if given within 72 hours of exposure. IVIG is used for pregnant women and severely immunocompromised patients. ACIP recommends 400 mg/kg as an IV infusion.[13]
- **Post-exposure prophylaxis for varicella OR treatment or post-exposure prophylaxis for tetanus:** Children infected with HIV without a history of previous varicella infection OR children who have not received two doses of varicella vaccine should receive VariZIG® or, if not available, IVIG within 10 days after close contact with a person who has chickenpox or shingles.[41,46] VariZIG is indicated for post-exposure prophylaxis in certain patients without immunity to varicella and is given as soon as possible after exposure, preferable within 4 days, and as late as 10 days after exposure.[47] In situations where administration of VariZIG does not appear possible within 10 days of exposure, IVIG is considered an alternative and should be given within 10 days of exposure[48] (and ideally within 96 hours of exposure).[40] The dose is 400 mg/kg given once.[40,41,46] Per the Centers for Disease Control and Prevention, if tetanus immune globulin is not available, clinicians can use immune globulin at a dose of 200 to 400 mg/kg.[48]
- **Parvovirus B19 infection and pure red blood cell aplasia, immunologic subtype:** In immunosuppressed patients lacking neutralizing antibodies, IVIG has been useful for the treatment of persistent B19 infection.[49] The guidelines from the American Society of Transplantation Infectious Diseases Community of Practice state that IVIG is frequently used for the treatment of solid organ transplant recipients with symptomatic parvovirus B19 infection.[66] A Canadian expert panel of hematologists recommend prednisone followed by cyclophosphamide or cyclosporine as first-line therapy for immunologic type pure red blood cell aplasia.[22] The panel considers IVIG a reasonable second-line option for this serious condition. Recent reviews note that 200 to 400 mg/kg/day for 5 to 10 days is considered the recommended treatment course.[79]
- **Stiff-Person Syndrome (Moersch-Woltman Syndrome):** Per the European Federation of Neurological Societies, IVIG should be reserved for patients who have no symptomatic relief after the use of diazepam and/or baclofen and have severe disability in carrying out daily activities.[32]
- **Thrombocytopenia, feto-neonatal alloimmune:** Antenatal therapy with IVIG administered to the mother is effective in increasing fetal platelet counts in neonatal alloimmune thrombocytopenia.[50,51] First-line therapy for newborns with fetal/neonatal alloimmune thrombocytopenia is antigen-negative compatible platelets; IVIG is adjunctive therapy.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of IVIG products. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with IVIG products as well as the monitoring required for

adverse events and long-term efficacy, some approvals require IVIG products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

If the prescriber is switching between IVIG products and a case has already been approved by a clinician, a new approval may be entered without another clinical review. The new approval should only be extended for the remaining doses and duration which were granted on the original review. The indication (or diagnosis code) and dosing need to be the same as the original review. If the indication or dosing is different, a new clinical review would need to be completed. If the client is using the *Immune Globulin – Intravenous Medical Step Management Policy* in tandem with this Utilization Management policy, the new approval may be entered without another clinical review for a preferred product only.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of immune globulin intravenous products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. **Primary Immunodeficiencies.** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets BOTH of the following (i and ii):
     - **i.** Patient meets ONE of the following (a, b, or c):
       Note: An exception can be made for the impaired antibody response if, according to the prescriber, the delay caused by pre-vaccination and post-vaccination antibody measurement would be deleterious to the patient's health.
       - **a)** Patient has a diagnosis of congenital agammaglobulinemia, X-linked agammaglobulinemia, other agammaglobulinemia due to the absence of B-cells, Wiskott-Aldrich syndrome, ataxia telangiectasia, DiGeorge syndrome, severe combined immunodeficiency, Hyper-Immunoglobulin M (IgM) syndromes, an IgG level lower than 250 mg/dL, or a primary immune deficiency which has been confirmed by genetic or molecular testing; OR
       - **b)** Patient has a diagnosis of common variable immunodeficiency, unspecified hypogammaglobulinemia, or other immunodeficiencies with significant hypogammaglobulinemia and meets BOTH of the following (1 and 2):
         - **(1)** Patient's pretreatment IgG level is below the normal range (age-adjusted and according to the normal reference range for the reporting laboratory); AND
         - **(2)** Patient meets ONE of the following (a or b):
           - **a)** Patient has an impaired antibody response (i.e., failure to product antibodies to specific antigens); OR
           - **b)** Patient has recurrent infections; OR
       - **c)** Patient has an IgG subclass deficiency, selective antibody deficiency (SAD), or another confirmed primary immunodeficiency and meets the following criteria [(1) and (2)]:
         - **(1)** Patient has an impaired antibody response (i.e., failure to product antibodies to specific antigens); AND
         - **(2)** Patient has recurrent infections; AND
     - **ii.** The medication is prescribed by or in consultation with one of the following physician specialists: an allergist, immunologist, otolaryngologist (ear nose and throat [ENT] physician), pulmonologist, or infectious diseases physician who treats patients with primary immune deficiencies.

B) Patient is Currently Receiving Immune Globulin. Approve if the patient has been diagnosed with a primary immunodeficiency and according to the prescriber, is continuing to receive benefit from the product.
Note: Examples of continued benefit with the product includes increased IgG levels or prevention and/or controlling of infections.

Dosing. Approve ONE of the following dosing regimens (A, B, C, or D):
A) An initial loading dose of 1 g/kg given intravenously one time; OR
B) 0.2 g/kg to 0.8 g/kg given intravenously once every 3 to 4 weeks; OR
C) The dose and interval between doses have been adjusted based on clinical response as determined by the prescriber; OR
D) Patients with primary immune deficiency and exposure to measles (previous exposure or risk of future measles exposure), the minimum dose has been determined by the prescriber.

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2. B-Cell Chronic Lymphocytic Leukemia for Prevention of Infections. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 4 months if the patient meets BOTH of the following (i and ii):
i. Patient meets ONE of the following (a or b):
a) Patient has an immunoglobulin G (IgG) level < 600 mg/dL (6.0 g/L); OR
b) Patient has a history of recurrent infections; AND
ii. The medication is prescribed by or in consultation with an oncologist, hematologist, or infectious diseases physician.
B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has a positive response to therapy according to the prescriber.
Note: Examples of a positive response to therapy include maintaining an increased IgG trough level or a decrease in the number of infections.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 0.4 g/kg given intravenously every 3 to 4 weeks; OR
B) 0.3 g/kg to 0.5 g/kg given intravenously once monthly; OR
C) The dose and interval have been adjusted to maintain a trough (pre-dose) IgG level of greater than 500 mg/dL.

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3. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):
i. Electrodiagnostic studies support the diagnosis of CIDP; AND
ii. The medication is prescribed by or in consultation with a neurologist.
B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has a clinically significant improvement in neurologic symptoms, as determined by the prescriber.
Note: Examples of improvement in neurologic symptoms include improvement in disability; nerve conduction study results improved or stabilized; physical examination show improvement in neurological symptoms, strength, and sensation.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) An initial loading dose of 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days; OR

B) A maintenance dose of 1 g/kg given intravenously in divided doses over 1 to 4 consecutive days given every 3 weeks; OR
C) The dose and interval are adjusted according to clinical response with a maximum dose per treatment course of 2 g/kg.

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4. Dermatomyositis or Polymyositis. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, and iv):
i. Prior to starting any therapy for this condition, the patient meets ONE of the following (a or b):
a) Patient has or had an elevated creatinine kinase (CK) level, according to the prescriber; OR
b) Other measures support the diagnosis, according to the prescriber, including, but not limited to, skin manifestations, autoantibody testing, muscle biopsy results, electromyographic (EMG) findings; AND
ii. Patient has tried a systemic corticosteroid OR a corticosteroid is contraindicated according to the prescriber; AND
iii. Patient has tried an immunosuppressive agent OR an immunosuppressive agent is contraindicated according to the prescriber; AND
Note: Examples of immunosuppressive agents include azathioprine, methotrexate, cyclosporine, cyclophosphamide, and mycophenolate mofetil.
iv. The medication is prescribed by or in consultation with a neurologist or a rheumatologist.
B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has responded to therapy according to the prescriber.
Note: Examples of a response to therapy includes improved muscle strength, improved neuromuscular symptoms, and improved functional ability.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days every 4 weeks; OR
B) 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days every 2 to 3 weeks.

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5. Immune Thrombocytopenia (ITP). Approve for the duration noted if the patient meets ONE of the following (A, B, C, D, or E):
Note: The diagnosis of ITP encompasses previous nomenclature, such as idiopathic thrombocytopenia, idiopathic thrombocytopenic purpura, immune thrombocytopenic purpura.
A) Initial Therapy – Adult ≥ 18 Years of Age: Approve for 3 months if the patient meets BOTH of the following (i and ii):
i. Patient meets ONE of the following (a, b, or c):
a) Patient has tried a systemic corticosteroid (e.g., prednisone); OR
b) There is an urgent need to increase the platelet count quickly; OR
c) A systemic corticosteroid is contraindicated according to the prescriber; AND
ii. The medication is prescribed by or in consultation with a hematologist.
B) Initial Therapy – Patient is < 18 Years of Age. Approve for 3 months if prescribed by or in consultation with a hematologist.
C) Initial Therapy – To Increase Platelet Count Before Surgical or Dental Procedures. Approve for 1 month if prescribed by or in consultation with a hematologist.
D) Initial Therapy – Pregnant Patient. Approve for 6 months if prescribed by or in consultation with a hematologist.

E) Patient is Currently Receiving Immune Globulin OR Requires Retreatment with Immune Globulin. Approve for 1 year if the patient is responding to therapy OR if the patient has previously responded to therapy, according to the prescriber.
Note: Examples of responding to therapy include increased platelet counts, absence of significant bleeding, or preventing hemorrhage/ensuring an adequate platelet count in order for delivery in pregnant patients.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) Up to 1 g/kg on 2 consecutive days OR up to 0.4 g/kg on 5 consecutive days (up to a total of 2 g per kg per treatment course); OR
B) The dose and interval between doses have been adjusted according to the platelet count and/or to prevent significant bleeding as determined by the prescriber.

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6. Kawasaki Disease. Approve for 3 months if prescribed by or in consultation with a pediatric cardiologist or a pediatric infectious diseases physician.

Dosing. Approve up to 2 g/kg given intravenously as a single dose or over multiple consecutive days. The dose may be repeated if needed.

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7. Multifocal Motor Neuropathy. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
  i. The diagnosis is supported by weakness without sensory abnormalities, upper motor neuron signs, or marked bulbar involvement and meets ONE of the following (a, b, or c):
    a) The diagnosis is supported by nerve conduction studies that demonstrate motor conduction block or probable motor conduction block; OR
    b) The prescriber has determined the patient has multifocal motor neuropathy without conduction block; OR
    c) The diagnosis is supported by a motor nerve biopsy or by a magnetic resonance imaging (MRI) neurography; AND
  ii. The medication is prescribed by or in consultation with a neurologist.
B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has improvement in neurologic symptoms as determined by the prescriber.
Note: Examples of improvement in neurologic symptoms include improvement in disability, grip strength improvement (measured with dynamometer), physical examination show improvement in neurological symptoms and strength.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) Therapy is initiated with 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days; OR
B) One of the following maintenance dosing regimens is used (i, ii, or iii):
  i. 0.5 g/kg to 2.4 g/kg given intravenously every month; OR
  ii. 1 g/kg given intravenously every 2 to 4 weeks; OR
  iii. 2 g/kg given intravenously every 1 to 2 months.

Other Uses with Supportive Evidence

8. Antibody-Mediated Rejection in Transplantation. Approve for 1 year if prescribed by or in consultation with a physician affiliated with a transplant center.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) Up to 2 g/kg as an intravenous infusion (as a single dose or divided in smaller doses [e.g., 400 mg per kg daily for 5 days]); OR
B) The dosage is based on a transplant center's protocol.

9. Autoimmune Mucocutaneous Blistering Diseases (Pemphigus Vulgaris, Pemphigus Foliaceus, Bullous Pemphigoid, Mucous Membrane Pemphigoid [Cicatricial Pemphigoid], and Epidermolysis Bullosa Acquisita). Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
i. Patient meets ONE of the following (a, b, or c):
a) Patient meets BOTH of the following [(1) and (2)]:
(1) Patient has tried a systemic corticosteroid OR a corticosteroid is contraindicated according to the prescriber; AND
(2) Patient has tried an immunosuppressive agent OR an immunosuppressive agent is contraindicated according to the prescriber; OR
Note: Examples of immunosuppressive agents include azathioprine, cyclophosphamide, dapsone, methotrexate, cyclosporine, mycophenolate mofetil, and tacrolimus.
b) Patient has rapid, debilitating, progressive disease that cannot be controlled with a systemic corticosteroid and an immunosuppressive agent; OR
c) The disease is so serious that there is inadequate time for therapy with a systemic corticosteroid and an immunosuppressive agent to have a rapid enough effect; AND
ii. The medication is prescribed by or in consultation with a dermatologist.
B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has responded to therapy according to the prescriber.
Note: Examples of response to therapy can include healing of previous lesions or fewer new lesions.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 2 g/kg per cycle given intravenously every 3 to 4 weeks. This dose is divided over 2, 3, or 5 consecutive days; OR
B) In patient with aggressive ocular disease, such as ocular cicatricial pemphigoid, 2 g/kg given intravenously may be given every 2 weeks in divided doses over 2, 3, or 5 consecutive days; OR
C) The frequency is gradually being slowly decreased as the lesions resolve and heal.

10. Cytomegalovirus Pneumonitis or Pneumonia in a Patient with Cancer or Transplant-Related Infection. Approve for 2 months if prescribed by or in consultation with an oncologist, hematologist, or an infectious diseases physician.

Dosing. Approve 400 mg/kg given intravenously every other day for 3 to 5 doses.

11. Desensitization Therapy Prior to and Immediately after Transplantation. Approve for 1 year if prescribed by or in consultation with a physician affiliated with a transplant center.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) Up to 2 g/kg per month administered intravenously (as a single dose or divided in smaller doses [e.g., 400 mg per kg daily for 5 days]); OR

B) The dosage is based on a transplant center's protocol.

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12. Guillain Barré Syndrome. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month (this is to provide one course of therapy) if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following (a or b):

a) The medication is initiated within 2 weeks and no longer than 4 weeks after onset of neuropathic symptoms; OR
Note: Examples of neuropathic symptoms include weakness, inability to stand or walk without assistance, and respiratory or bulbar weakness.

b) Patient has had a relapse (treatment related fluctuation), but had an initial response to IVIG; AND

ii. The medication is prescribed by or in consultation with a neurologist or a specialist with experience in diagnosing and treating patients with Guillain Barré syndrome.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 month (this is to provide a second course) about 3 weeks after the first course.

Dosing. Approve 2 g/kg administered intravenously in divided doses over 2 to 5 days.

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13. Hematologic Neoplasm-Associated Hypogammaglobulinemia or Hypogammaglobulinemia after B-cell Targeted Therapies (Secondary Immunodeficiency [SID]). Approve for 6 months if the patient meets ONE of the following (A or B):
Note: Some examples of B-cell targeted therapy are chimeric antigen receptor (CAR)-T cell therapy (e.g., Kymriah [tisagenlecleucel intravenous infusion], Abecma [idecabtagene vicleucel intravenous infusion], Breyanzi [lisocabtagene maraleucel intravenous infusion], Tecartus [brexucabtagene autoleucel intravenous infusion], Yescarta [axicabtagene ciloleucel intravenous infusion]), a rituximab product, Besponsa (inotuzumab ozogamicin intravenous infusion).
Note: Refer to B-Cell Chronic Lymphocytic Leukemia (CLL) for Prevention of Infections and Multiple Myeloma for diagnosis-specific criteria.

A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, and iii):

i. Patient has an immunoglobulin G (IgG) level of < 600 mg/dL (6.0 g/L) [excluding paraprotein]; AND

ii. Patient has recurrent or severe infections or there is a high risk of infection according to the prescriber; AND

iii. The medication is being prescribed by or in consultation with an oncologist, hematologist, infectious disease physician, or immunologist.

B) Patient is Currently Receiving Immune Globulin. Approve if the patient is having a positive response to therapy according to the prescriber.
Note: Examples of a positive response to therapy include maintaining an increased IgG trough level or a decrease in the number of infections.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 0.4 g/kg to 0.6 g/kg given intravenously once a month; OR
B) 0.2 g/kg to 0.8 g/kg given intravenously once every 3 to 4 weeks; OR
C) The dose and interval between doses have been adjusted based on clinical response as determined by the prescriber.

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14. Hematopoietic Cell Transplantation (HCT) to Prevent Infection. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, iii, and iv):
i. Patient has had a HCT within the previous year; AND
ii. Patient has an immunoglobulin G (IgG) level < 600 mg/dL (6.0 g/L) OR the patient has multiple myeloma or malignant macroglobulinemia; AND
iii. According to the prescriber, the patient has a significant risk of having frequent and/or severe infections; AND
iv. The medication is prescribed by or in consultation with a hematologist, oncologist, or infectious diseases physician.
B) Patient is Currently Receiving Immune Globulin. Approve for 6 months if the patient is having a positive response to therapy according to the prescriber.
Note: Examples of a positive response to therapy include maintaining an increased IgG trough level, controlling the number of infections, or a decrease in the number of infections.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) During the first 100 days after HCT, the patient meets ONE of the following (i or ii):
i. Adults and adolescents: 0.5 g/kg per week given intravenously and the dose is adjusted to maintain trough (pre-dose) serum IgG greater than 400 mg/dL; OR
ii. Pediatric patient with allogeneic HCT: 0.4 g/kg per month given intravenously and the dose is adjusted to keep IgG greater than 400 mg/dL; OR
B) Greater than 100 days post-HCT, the dose is 0.5 g/kg given intravenously every 3 to 4 weeks, and the dose is adjusted to keep IgG greater than 400 mg/dL; OR
C) The dosage is based on a transplant center's protocol.

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15. Human Immunodeficiency Virus (HIV)- or Hepatitis C-Associated Thrombocytopenia. Approve for 1 month if the patient meets BOTH of the following (A and B):
A) Patient is receiving antiviral therapy; AND
B) The medication is prescribed by or in consultation with an infectious diseases specialist, a physician who specializes in the treatment of HIV infection, a gastroenterologist, hepatologist, or a liver transplant physician.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) Up to 2 g/kg given intravenously in divided doses over 2 to 5 days; OR
B) Up to 1 g/kg one time given intravenously up to once weekly.

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16. Human Immunodeficiency Virus (HIV), to Prevent Recurrent Infections. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, and iv):

i. Patient is < 18 years of age; AND
ii. Patient is receiving combination antiretroviral therapy; AND
iii. Patient has ONE of the following (a, b, or c):
a) Hypogammaglobulinemia (i.e., IgG < 400 mg/dL [4.0 g/L]); OR
b) Functional antibody deficiency is demonstrated by poor specific antibody titers (that is, the patient does not develop specific antibody responses against protein and polysaccharide antigens); OR
c) Functional antibody deficiency is demonstrated by the patient having recurrent (two or more per year), serious infections (e.g., bacteremia, meningitis, pneumonia) despite administration of combination antiretroviral therapy and appropriate antimicrobial prophylaxis; AND
iv. The medication is prescribed by or in consultation with an infectious diseases specialist or an immunologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the frequency and/or severity of infections have decreased according to the prescriber.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) The dose is 0.4 g/kg given by intravenous infusion every 2 to 4 weeks; OR
B) The dose and interval are adjusted according to clinical effectiveness.
Note: Examples of adjusting according to clinical effectiveness may include the need to increase the dose or frequency based on frequency or severity of infections, hospitalizations, days of school or work missed, failure to thrive.

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17. Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy. Approve for the duration noted if the patient meets ONE of the following (A or B):
Note: Examples of checkpoint inhibitors are Keytruda (pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), Yervoy (ipilimumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion), Bavencio (avelumab intravenous infusion), Imfinzi (durvalumab intravenous infusion), Libtayo (cemiplimab intravenous infusion), Jemperli (dostarlimab intravenous infusion).
A) Initial Therapy. Approve for 1 month if the patient meets ONE of the following (i, ii, or iii):
i. Patient has tried a systemic corticosteroid and has not adequately responded to therapy; OR
Note: Examples of systemic corticosteroids include prednisone, methylprednisolone.
ii. The medication is being started with a systemic corticosteroid; OR
iii. A corticosteroid is contraindicated per the prescriber.
B) Patient is Currently Receiving Immune Globulin. Approve for 6 months if the patient is having a positive response to therapy, as determined by the prescriber, and the prescriber has determined extended therapy is required.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) Up to 0.4 g/kg given intravenously daily for 5 days; OR
B) Up to 2 g/kg given intravenously over 2 to 5 days; OR
C) The dose and interval between doses have been adjusted based on clinical response as determined by the prescriber.

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18. Lambert-Eaton Myasthenic Syndrome (LEMS). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month (to allow for one course of therapy) if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient is having refractory weakness after symptomatic treatment of LEMS with an amifampridine product (e.g., Firdapse, Ruzurgi), guanidine, or pyridostigmine; AND
- **ii.** Patient meets ONE of the following (a or b):
  - **a)** Patient has paraneoplastic LEMS; OR
  - **b)** Patient has non-paraneoplastic LEMS AND has tried a systemic corticosteroid (e.g., prednisone) or another immunosuppressive agent (e.g., azathioprine), or has a contraindication to corticosteroids and/or immunosuppressive agents, according to the prescriber; AND
- **iii.** The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has a response or continued effectiveness, according to the prescriber.
Note: Examples of a response to therapy include improved muscle strength or other clinical response.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) Up to 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days; OR
B) Maintenance therapy every 4 weeks with up to 2 g/kg with the dose being adjusted based on clinical symptoms.

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19. Multiple Myeloma. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
- **i.** Patient meets ONE of the following (a or b):
  - **a)** Patient has or is at risk of severe, recurrent infections according to the prescriber; OR
  - **b)** Patient will be starting, has taken, or is currently receiving chimeric antigen receptor (CAR)-T cell therapy OR bispecific antibody therapy; AND
    Note: Examples of CAR-T cell therapy includes: Abecma (idecabtagene vicleucel intravenous infusion), Carvykti (ciltacabtagene autoleucel intravenous infusion).
    Note: Examples of bispecific antibody therapy includes: Elrexfio (elranatamab-bcmm subcutaneous injection), Tecvayli (teclistamab-cqyv subcutaneous injection), Talvey (talquetamab-tgvs subcutaneous injection).
- **ii.** The medication is prescribed by or in consultation with a hematologist, oncologist, or infectious diseases specialist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year.

Dosing. Approve 0.4 g/kg to 0.5 g/kg given intravenously every 3 to 4 weeks.

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20. Multiple Sclerosis (MS), Acute Severe Exacerbation or Relapses. Approve for 1 month (this is to provide one course of therapy) if the patient meets ALL of the following (A, B, and C):

A) Patient meets ONE of the following (i or ii):
- **i.** Patient has either not responded to OR has had a significant adverse reaction with systemic corticosteroids (e.g., methylprednisolone sodium succinate injection) OR plasma exchange; OR
  Note: A trial of Acthar H.P. gel [repository corticotropin injection; adrenocorticotropic hormone, ACTH] would also count toward meeting this requirement.

ii. A systemic corticosteroid is contraindicated, according to the prescriber; AND

B) Patient meets ONE of the following (i or ii):

i. Patient is already on maintenance therapy for MS or will be starting maintenance therapy for MS; OR

Note: Maintenance therapy does NOT include IVIG. Examples of maintenance therapy for MS would include: Avonex (interferon beta-1a injection), Plegridy (peginterferon beta-1a injection), Rebif (interferon beta-1a injection), Betaseron (interferon beta-1b injection)/Extavia (interferon beta-1b injection), Copaxone (glatiramer injection)/Glatopa (glatiramer injection), Gilenya (fingolimod capsule), Lemtrada (alemtuzumab injection), Aubagio (teriflunomide tablet), Mavenclad (cladribine tablet), Mayzent (siponimod tablet), Tecfidera (dimethyl fumarate capsule), Vumerity (diroximel fumarate capsule), Zeposia (ozanimod capsule), Tysabri (natalizumab injection), Novantrone (mitoxantrone injection), Bafiertam (monomethyl fumarate capsule), Kesimpta (ofatumumab injection), Ocrevus (ocrelizumab injection), Ponvory (penesimod tablet).

ii. Patient is pregnant or patient is post-partum and the prescriber has determined maintenance therapy is not clinically appropriate; AND

C) The medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of MS.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) A single 1 g/kg given intravenously; OR

B) 0.4 g/kg per day IV infusion for 5 consecutive days.

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21. Myasthenia Gravis. Approve for the duration noted if the patient meets ONE of the following (A, B, C, or D):

A) Initial Therapy for Short-Term (Acute) Use. Approve for 5 days (to allow for one course of therapy) if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following conditions (a, b, c, or d):

a) Patient has an exacerbation of myasthenia gravis; OR

b) Patient requires stabilization of myasthenia gravis before surgery; OR

c) Patient has been started on an immunosuppressive drug and is waiting for full effect; OR

Note: Examples of immunosuppressive drugs include azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, methotrexate, or tacrolimus.

d) Patient is starting therapy with a corticosteroid and IVIG is being given to prevent or minimize exacerbations; AND

ii. The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin Short-Term (Acute) Use. Approve for 5 days (to allow for one course of therapy).

C) Initial Therapy for Maintenance. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):

i. Patient has refractory myasthenia gravis; AND

ii. Patient has tried pyridostigmine; AND

iii. Patient has tried immunosuppressive therapy with at least one of the following agents: azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, methotrexate, tacrolimus AND has had an inadequate response; AND

iv. The medication is prescribed by or in consultation with a neurologist.

D) Patient is Currently Receiving Immune Globulin for Maintenance Therapy. Approve for 1 year if the patient is responding according to the prescriber.

Note: Examples of responding to therapy include improvement in weakness (bulbar, limb, or respiratory), improvement with ocular symptoms.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) Short-term use: 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days; OR
B) Maintenance therapy: 0.4 g/kg to 1 g/kg given intravenously every 4 weeks; OR
C) The dose and interval between doses have been adjusted based on clinical response as determined by the prescriber.

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22. Passive Immunization for Measles (Post-Exposure Prophylaxis). Approve for 1 day (to allow for a single dose) if the patient meets ONE of the following (A or B):
Note: For patients with primary immune deficiency, see criteria for PID.
A) Patient is pregnant and meets BOTH of the following (i and ii):
i. Patient has been exposed to measles; AND
ii. Patient does not have evidence of immunity to measles (i.e., the patient does not have a history of the disease or age-appropriate vaccination); OR
B) Patient meets BOTH of the following (i and ii):
i. Patient is immunocompromised; AND
ii. Patient has been exposed to measles.

Dosing. Approve the following dosing regimen: 0.4 g/kg intravenously administered one time.

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23. Post-Exposure Prophylaxis for Varicella OR Treatment or Post-Exposure Prophylaxis for Tetanus. Approve for 1 day (to allow for a single dose) if the patient meets ONE of the following (A or B):
A) For Varicella post-exposure, Varicella immune globulin is not available or cannot be administered within 10 days of exposure; OR
B) For Tetanus treatment or post-exposure, Tetanus Immune globulin is not available.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 0.4 g/kg given intravenously one time; OR
B) 0.2 to 0.4 g/kg given intravenously one time.

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24. Parvovirus B19 Infection. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 2 months if the patient meets BOTH of the following (i and ii):
i. Patient has an immunodeficiency condition; AND
Note: Examples of an immunodeficiency condition include patients with HIV infection, solid organ transplants (e.g., renal, liver), chemotherapy for hematologic malignancy.
ii. The medication is prescribed by or in consultation with an infectious diseases specialist, immunologist, hematologist, or transplant specialist.
B) Patient is Currently Receiving Immune Globulin. Approve for 6 months.

Dosing. Approve ONE of the following dosing regimens (A, B, C, or D):
A) 2 g/kg given intravenously over a period of 2 to 5 consecutive days; OR
B) 0.4 g/kg to 0.5 g/kg given intravenously daily for 5 days; OR

C) 0.4 g/kg given intravenously once every 4 weeks; OR
D) 0.2 g/kg to 0.4 g/kg given intravenously daily for 5 to 10 days

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25. Pure Red Blood Cell Aplasia (PRCA), Immunologic Subtype. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient has tried a systemic corticosteroid (e.g., prednisone); AND
- **ii.** Patient has tried either cyclophosphamide OR cyclosporine; AND
- **iii.** The medication is prescribed by or in consultation with an infectious diseases specialist, immunologist, hematologist, or transplant specialist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 month if the patient has responded with an increase in hemoglobin and reticulocytosis according to the prescriber.

Dosing. Approve 0.5 g/kg given intravenously for 4 weeks.

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26. Stiff-Person Syndrome (Moersch-Woltman Syndrome). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):
- **i.** Patient meets ONE of the following (a or b):
  - **a)** Patient has tried a benzodiazepine (e.g., diazepam) OR baclofen; OR
  - **b)** Patient has contraindications to both a benzodiazepine AND baclofen according to the prescriber; AND
- **ii.** The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has responded to therapy according to the prescriber.
Note: Examples of response to therapy includes reduced stiffness or frequency of spasms, ability to walk unassisted.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 2 g/kg given intravenously over a period of 2 to 5 consecutive days every month; OR
B) For maintenance therapy, the dose is adjusted to provide the minimum effective dosage of IVIG. Maximum dose is 2 g/kg given intravenously.

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27. Thrombocytopenia, Feto-neonatal Alloimmune. Approve for 6 months if the pregnant mother or newborn patient is prescribed the medication by or in consultation with a hematologist or an obstetrician.

Dosing. Approve ONE of the following dosing regimens (A, B, C, or D):
A) For the mother: 1 g/kg given intravenously every week; OR
B) For the mother: 2 g/kg given intravenously every week; OR
C) For the mother: 1 g/kg given intravenously twice weekly; OR
D) For the newborn: 1 g/kg to 2 g/kg given intravenously dosed per the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of immune globulin intravenous is not recommended in the following situations:

1. **Adrenoleukodystrophy.** Evidence does not support IVIG use.[18]

2. **Alzheimer's Disease (AD).** In one multicenter, double-blind, Phase III, placebo-controlled trial, 390 patients with mild to moderate AD were randomized to therapy with IVIG 400 mg/kg or 200 mg/kg, or to placebo given every 2 weeks for 18 months.[61] There was no statistically significant difference in the rate of cognitive decline when compared with placebo. Also, there was not a statistically significant change in functional ability when compared to placebo. Large placebo-controlled trials with a longer observation period are needed to establish efficacy, determine the optimal dosing regimen, and to confirm the safety of IVIG in the general AD population.[52,53]

3. **Amyotrophic Lateral Sclerosis.** There is insufficient evidence to recommend IVIG.[18]

4. **Asthma.** Global Initiative for Asthma (GINA) guidelines for asthma management and prevention do not include recommendations for use of IVIG.[54]

5. **Atopic Dermatitis.** Limited data exist to determine the utility of IVIG in the management of atopic dermatitis.[55]

6. **Autism.** Evidence does not support IVIG use.[18] Well controlled, double-blind trials are needed.

7. **Chronic Fatigue Syndrome.** Evidence does not support IVIG use.[56] One randomized, placebo-controlled trial did not find benefits in quality of life measures nor the Profile of Mood States for IVIG.[56] Although scores were improved in IVIG and placebo treatment groups, no significant between group difference was demonstrated.

8. **Complex Regional Pain Syndrome (Reflex Sympathetic Dystrophy).** There is insufficient evidence to recommend IVIG. In one single center study a single dose of 0.5 g/kg of IVIG produced a decrease in pain intensity by 50% or more compared to placebo in 3 of 12 patients.[57] In a randomized, placebo-controlled, multicenter trial, low-dose immunoglobulin treatment for 6 weeks was not effective in relieving pain in patients with moderate-to-severe complex regional pain syndrome.[58] Well-controlled large-scale trials are needed.

9. **Crohn's Disease.** There is insufficient evidence to recommend IVIG. In one single center case collection report, 19 patients with acute Crohn's disease (Crohn's Disease Activity Index [CDAI] 284.1 ± 149.8) who were resistant to steroids received IVIG daily for 7 to 10 days.[59] Four weeks after completing therapy, 14 patients were in clinical remission (CDAI < 150). Prospective, randomized, placebo-controlled trials are needed to determine if IVIG has a role in the treatment of Crohn's disease.

10. **Cystic Fibrosis.** There is insufficient evidence to recommend IVIG. In one single-center retrospective case review of 16 children with cystic fibrosis, IVIG was reportedly effective.[60] Well-designed, controlled trials are needed.[18]

11. **Diabetes Mellitus, Immunotherapy.** Evidence does not support IVIG use.[18,62,63] In one 2-year randomized controlled trial, IVIG was given every 2 months to children and adults with type 1 diabetes.[62] No beneficial effect was shown with IVIG compared with control and the authors concluded that IVIG therapy is unlikely to be a viable option for immunotherapy.

12. **Fibromyalgia Syndrome.** There is insufficient evidence to recommend IVIG. In one open-label single center study, 15 patients with fibromyalgia syndrome and distal demyelinating polyneuropathy

received IVIG 400 mg/kg given daily for 5 days.[64] Pain, tenderness, and strength reportedly improved. Double-blind, placebo-controlled trials are needed to determine if IVIG is effective in fibromyalgia syndrome.

13. **In Vitro Fertilization (IVF).** There is insufficient evidence to recommend IVIG administration as part of IVF outcomes.[68]

14. **Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes (POEMS) Syndrome.** Evidence does not support IVIG use.[18]

15. **Recurrent Spontaneous Pregnancy Loss (RSPL) [Including a Patient with Antiphospholipid Antibody-Positive].** Evidence does not support IVIG use.[69-72] In one double-blind pilot study, IVIG did not improve obstetric or neonatal outcomes beyond those achieved with a heparin and low-dose aspirin regimen.[69] In another double-blind trial (n =82 of whom 47 had an index pregnancy), live birth rates did not differ significantly between IVIG-treated and placebo-treated women.[71] The American Society for Reproductive Medicine practice committee states that several trials and meta-analyses concluded that IVIG is ineffective for primary recurrent pregnancy loss and this treatment is not recommended.[72]

16. **Selective Immune Globulin A (IgA) Deficiency as the Sole Immunologic Abnormality.** Evidence does not support use of IVIG.[14,18] Selective IgA deficiency is defined as a serum IgA level less than 0.07 g/L, but normal serum IgG and IgM levels in a patient greater than 4 years of age in whom other causes of hypogammaglobulinemia have been excluded.[14] Selective IgA deficiency may co-exist in some patients with poor specific IgG antibody production, with or without IgG2 subclass deficiency.[14,18] Some of these patients with a concomitant specific antibody defect might benefit from therapy with IVIG.

17. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**B-Cell Chronic Lymphocytic Leukemia for Prevention of Infections; Hematologic Neoplasm-Associated Hypogammaglobulinemia or Hypogammaglobulinemia after B-cell Targeted Therapies (Secondary Immunodeficiency); Hematopoietic Cell Transplantation to Prevent Infection: P**atient's immunoglobulin G (IgG) level was updated to < 600 mg/dL (6.0 g/L); previously was 500 mg/dL (5.0 g/L). **Human Immunodeficiency Virus (HIV) - or Hepatitis C-Associated Thrombocytopenia.** The diagnosis Hepatitis C-Associated Thrombocytopenia was added to the policy. Criterion was updated from patient is receiving combination antiretroviral therapy to patient is receiving antiviral therapy. Criteria related to clinically significant bleeding complications according to the prescriber was removed. Criterion regarding prescribing or consultation specialist was updated to include a gastroenterologist, a hepatologist, or a liver transplant physician. **Multiple Myeloma.** Added the wording, "or is at risk of" to the criterion related to severe recurrent infections according to the prescriber. **Post-Exposure Prophylaxis for Varicella:** The diagnosis wording was previously Passive Immunization for Varicella (Chickenpox) [Post-Exposure Prophylaxis]. The following criteria were removed: 1) Patient has HIV; Patient is immune compromised; Patient is pregnant; 2) Patient does not have evidence of immunity to varicella; 3) The specialist requirement. Also, Treatment or Post-Exposure Prophylaxis for Tetanus was added to the diagnosis with the following criterion: Tetanus Immune globulin is not available. Dosage of 0.2 to 0.4 g/kg intravenously one time was added. **Parvovirus B19 Infection:** Diagnosis wording was previously Pure Red Blood Cell Aplasia (PRCA) Secondary to Chronic (Persistent) Parvovirus B19 Infection. The word "chronic" immunodeficiency condition was removed from initial therapy criteria. The criterion regarding "clinically significant anemia as determined by the prescriber" and "patient is transfusion dependent" was removed. Continuation of therapy criteria related to hemoglobin and relapse were removed from the criteria. Removed "(one course) for up to two courses" from the dosage 2g/kg given intravenously over a period of 2 to 5 consecutive days. **Heart Failure, Chronic; Human Immunodeficiency Virus (HIV) Infection, Adults, for Prophylaxis of Infections; and Post-Polio Syndrome** were removed from Conditions Not Recommended for Approval	10/12/2022

Annual Revision	**Cytomegalovirus Pneumonitis or Pneumonia in a Patient with Cancer or Transplant-Related Infection:** Added the wording pneumonitis; the diagnosis wording was previously Cytomegalovirus Pneumonia in a Patient with Cancer or Transplant-Related Infection. **Multiple Myeloma:** The following option for approval was added in initial therapy as an alternative to infection status 1) Patient will be starting, has taken, or is currently receiving chimeric antigen receptor (CAR)-T cell therapy OR bispecific antibody therapy. Note: Examples of CAR-T cell therapy includes: Abecma (idecabtagene vicleucel intravenous infusion), Carvykti (ciltacabtagene autoleucel intravenous infusion). Note: Examples of bispecific antibody therapy includes: Elrexfio (elranatamab-bcmm subcutaneous injection), Tecvayli (teclistamab-cqyv subcutaneous injection), Talvey (talquetamab-tgvs subcutaneous injection). **Parvovirus B19 Infection:** 0.2 g/kg to 0.4 g/kg given intravenously daily for 5 to 10 days was added as an alternative dosing regimen. **Anemia, Aplastic** was removed from Condition Not Recommended for Approval.	10/25/2023
Selected Revision	**Alyglo was added to the policy** with the same criteria as all other immune globulin products. **Chronic Inflammatory Demyelinating Polyneuropahy (CIDP) or Polyradiculoneurapthy**: Updated dosing from an initial loading dose of 2 g/kg given intravenously in divided doses over 2 to 4 days consecutive days to 2 to 5 days consecutive days. Updated dosing from a maintenance dose of 1 g/kg given intravenously over one day or divided into two doses of 0.5 g/kg given on 2 consecutive days to a maintenance dose of 1 g/kg given intravenously in divided doses over 1 to 4 consecutive days.	02/07/2024
Selected Revision	**Immune Thrombocytopenia (ITP).** The duration of approval for initial therapy for adults and pediatric patients was changed from 1 year to 3 months. Criterion for patients requiring retreatment with immune globulin was added to the continuation criteria. Continuation criterion was also updated from "Patient has responded to therapy" to patient is responding to therapy OR the patient has previously responded to therapy. **The following was added to the Policy Statement:** If the client is using the IVIG MSM Policy in tandem with this UM policy, the new approval may be entered without another clinical review for a preferred product only.	04/10/2024

CARECONTINUUM™

MEDICAL STEP MANAGEMENT POLICY

POLICY: Immune Globulin – Subcutaneous Medical Step Management Policy

- Cutaquig® (immune globulin 16.5% subcutaneous solution – Octapharma/Pfizer)
- Cuvitru™ (immune globulin 20% subcutaneous solution – Takeda)
- Gammagard® Liquid (immune globulin 10% solution – Takeda)
- Gammaked™ (immune globulin 10% solution caprylate/chromatography purified – Kedrion)
- Gamunex®-C (immune globulin 10% solution caprylate/chromatography purified – Grifols)
- Hizentra® (immune globulin 20% subcutaneous solution – CSL Behring)
- HyQvia® (immune globulin 10% subcutaneous solution with recombinant human hyaluronidase – Takeda)
- Xembify® (immune globulin 20% subcutaneous solution – Grifols)

REVIEW DATE: 04/10/2024

OVERVIEW

Immune globulin subcutaneous (SCIG) products are concentrated human immunoglobulins, primarily immunoglobulin G (IgG), that are prepared from pooled plasma collected from a large number of human donors. SCIG products are indicated for the following uses:

- **Chronic inflammatory demyelinating polyneuropathy,** for maintenance therapy in adults.[1,4,5]
- **Primary humoral immune deficiency (PID)**, for replacement therapy, including but not limited to the humoral defect in the following conditions: common variable immunodeficiency, X-linked agammaglobulinemia (congenital agammaglobulinemia), Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.[1-8] SCIG is also indicated for measles prophylaxis in individuals with PID who have been exposed to measles or who are at high risk of measles exposure.[1,4,5,7,8]

Hizentra, Cuvitru, Xembify, and Cutaquig are indicated as a subcutaneous (SC) infusion only.[4,6-8] Gammagard Liquid, Gammaked, and Gamunex-C may be administered as a SC infusion or an intravenous (IV) infusion for PID.[1-3] HyQvia is indicated for SC infusion only, with sequential infusion of the recombinant human hyaluronidase first and followed 10 minutes later with the immune globulin infusion.[5] The recombinant human hyaluronidase acts locally to increase dispersion and absorption of the immune globulin.

POLICY STATEMENT

This Medical Step Management program has been developed to encourage the use of Preferred Products. For all medications (Preferred and Non-Preferred), the patient is required to meet the respective *Immune Globulin Subcutaneous Utilization Management Medical Policy* criteria. The program also directs the patient to try two Preferred Products prior to the approval of a Non-Preferred Product. Requests for Non-Preferred Products will also be reviewed using the exception criteria (below). All approvals are provided for the duration noted in the *Immune Globulin Subcutaneous Utilization Management Medical Policy* criteria.

Automation: None.

Preferred Products: Cutaquig, Gammagard Liquid, Gammaked, Gamunex-C, Hizentra, Xembify

Non-Preferred Products: Cuvitru, HyQvia

RECOMMENDED EXCEPTION CRITERIA

Non-Preferred Product(s)	Exception Criteria
Cuvitru	**1.** Approve if the patient meets BOTH of the following (A and B): **A)** Patient meets the standard *Immune Globulin Subcutaneous Utilization Management Medical Policy* criteria; AND **B)** Patient meets ONE of the following conditions (i, ii, or iii): **i.** Patient has tried TWO of the following products: Cutaquiq, Gammagard Liquid, Gammaked, Gamunex-C, Hizentra, Xemfiby; OR **ii.** Patient with hyperprolinemia, the patient has tried Xembify; OR **iii.** Patient with a hypersensitivity to polysorbate 80.
HyQvia	**2.** Approve if the patient meets BOTH of the following (A and B): **A)** Patient meets the standard *Immune Globulin Subcutaneous Utilization Management Medical Policy* criteria; AND **B)** Patient meets ONE of the following conditions (i or ii): **i.** Patient has tried TWO of the following products: Cutaquiq, Gammagard Liquid, Gammaked, Gamunex-C, Hizentra, Xemfiby; OR **ii.** Patient being treated for chronic inflammatory demyelinating polyneuropathy, the patient has tried Hizentra.

REFERENCES

1. Gammagard® Liquid 10% [prescribing information]. Lexington, MA: Takeda; January 2024.
2. Gammaked™ 10% solution [prescribing information]. Fort Lee, NJ: Kedrion; January 2020.
3. Gamunex®-C 10% solution [prescribing information]. Research Triangle Park, NC: Grifols; January 2020.
4. Hizentra® 20% subcutaneous solution [prescribing information]. Kankakee, IL: CSL Behring; April 2023.
5. HyQvia® 10% subcutaneous solution with recombinant human hyaluronidase [prescribing information]. Lexington, MA: Takeda; January 2024.
6. Xembify® 20% subcutaneous solution [prescribing information]. Research Triangle Park, NC: Grifols; August 2020.
7. Cuvitru™ 20% subcutaneous solution [prescribing information]. Lexington, MA: Takeda; March 2023.
8. Cutaquig® 16.5% subcutaneous solution [prescribing information]. New York, NY: Pfizer; November 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	04/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT ADVANCED CLINICAL EVALUATION MEDICAL POLICY

POLICY: Immune Globulin Subcutaneous Utilization Management Medical Policy – Advanced Clinical Evaluation

- Cutaquig® (immune globulin 16.5% subcutaneous solution – Octapharma/Pfizer)
- Cuvitru™ (immune globulin 20% subcutaneous solution – Takeda)
- Gammagard® Liquid (immune globulin 10% solution – Takeda)
- Gammaked™ (immune globulin 10% solution caprylate/chromatography purified – Kedrion)
- Gamunex®-C (immune globulin 10% solution caprylate/chromatography purified – Grifols)
- Hizentra® (immune globulin 20% subcutaneous solution – CSL Behring)
- HyQvia® (immune globulin 10% subcutaneous solution with recombinant human hyaluronidase – Takeda)
- Xembify® (immune globulin 20% subcutaneous solution – Grifols)

REVIEW DATE: 10/25/2023; selected revision 02/07/2024

OVERVIEW

Immune globulin subcutaneous (SCIG) products are concentrated human immunoglobulins, primarily immunoglobulin G (IgG), that are prepared from pooled plasma collected from a large number of human donors. SCIG products are indicated for the following uses:

- **Chronic inflammatory demyelinating polyneuropathy,** for maintenance therapy in adults.[1,4,5]
- **Primary humoral immune deficiency (PID**), for replacement therapy, including but not limited to the humoral defect in the following conditions: common variable immunodeficiency, X-linked agammaglobulinemia (congenital agammaglobulinemia), Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.[1-5,7-9] SCIG is also indicated for measles prophylaxis in individuals with PID who have been exposed to measles or who are at high risk of measles exposure.[1,4,5,8,9]

Hizentra, Cuvitru, Xembify, and Cutaquig are indicated as a subcutaneous (SC) infusion only.[4,7-9] Gammagard Liquid, Gammaked, and Gamunex-C may be administered as a SC infusion or an intravenous (IV) infusion for PID.[1-3] HyQvia is indicated for SC infusion only, with sequential infusion of the recombinant human hyaluronidase first and followed 10 minutes later with the immune globulin infusion.[5] The recombinant human hyaluronidase acts locally to increase dispersion and absorption of the immune globulin.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of SCIG products. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with SCIG as well as the monitoring required for adverse events and long-term efficacy, initial approval requires SCIG products to

be prescribed by or in consultation with a physician who specializes in the condition being treated. All reviews will be forwarded to a Physician Medical Director for evaluation.

Documentation: Documentation is required for use of SCIG as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Immune Globulin Subcutaneous Advanced Clinical Evaluation Medical Policy*, and who is requesting reauthorization, the criteria utilized do NOT require re-submission of documentation for reauthorization, except for the criterion requiring documentation of a continued benefit from Immune Globulin therapy.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Cutaquig, Cuvitru, Gammagard Liquid, Gammaked, Gamunex-C, Hizentra, HyQvia, and Xembify is recommended in those who meet the following criteria:

FDA-Approved Indications

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1. Primary Immunodeficiencies. Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following (a, b, or c):

Note: An exception can be made for the impaired antibody response if, according to the prescriber, the delay caused by pre-vaccination and post-vaccination antibody measurement would be deleterious to the patient's health.

a) Patient has a diagnosis of congenital agammaglobulinemia, X-linked agammaglobulinemia, other agammaglobulinemia due to the absence of B-cells, Wiskott-Aldrich syndrome, ataxia telangiectasia, DiGeorge syndrome, severe combined immunodeficiency, Hyper-Immunoglobulin M (IgM) syndromes, an IgG level lower than 250 mg/dL **[documentation required]**, or a primary immune deficiency which has been confirmed by genetic or molecular testing; OR

b) Patient has a diagnosis of common variable immunodeficiency, unspecified hypogammaglobulinemia, or other immunodeficiencies with significant hypogammaglobulinemia and meets the following [(1) and (2)]:

(1) Patient's pretreatment IgG level is below the normal range (age-adjusted and according to the normal reference range for the reporting laboratory) **[documentation required]**; AND

(2) Patient meets ONE of the following [(a) or (b)]:

(a) Patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens) **[documentation required]**; OR

(b) Patient has recurrent infections; OR

c) Patient has an IgG subclass deficiency **[documentation required]**, selective antibody deficiency (SAD), or another confirmed primary immunodeficiency and meets the following [(1) and (2)]:

(1) Patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens) **[documentation required]**; AND

(2) Patient has recurrent infections; AND

ii. The medication is prescribed by or in consultation with one of the following physician specialists: an allergist, immunologist, otolaryngologist (ear nose and throat [ENT] physician), pulmonologist, or an infectious diseases physician who treats patients with primary immune deficiencies.

B) Patient is Currently Receiving Immune Globulin. Approve if the patient has been diagnosed with a primary immunodeficiency and according to the prescriber the patient is continuing to receive benefit from the product **[documentation required for continued benefit]**.
Note: Examples of continued benefit with the product includes increased IgG levels or prevention and/or controlling of infections.

Dosing. Approve ONE of the following dosing regimens (A, B, C, D, E, or F):

A) Patient is transitioning from immune globulin intravenous (IVIG), and the maintenance dose (given once weekly, every 2 weeks, or more frequently than once weekly [e.g., 2 to 7 times per week]) is based on the patient's previous monthly IVIG dose; OR

B) Patient is transitioning from another immune globulin subcutaneous (SCIG) product, and the maintenance dose (given once weekly, every 2 weeks, or more frequently than once weekly) is based on the patient's previous weekly SCIG dose; OR

C) Patient is initiating SCIG therapy without previous IVIG or SCIG therapy and is receiving a loading dose (e.g., 100 mg/kg once daily for 5 consecutive days) followed by once weekly (or more frequently as necessitated by volume) maintenance dosing; OR

D) The dose and interval between doses has been adjusted based on clinical response, as determined by the prescriber; OR

E) For a patient with primary immune deficiency and exposure to measles (previous exposure or risk of future measles exposure), the minimum dose has been determined by the prescriber; OR

F) For HyQvia only: Approve if the patient meets ONE of the following (i, ii, or iii):

i. Patient is starting HyQvia and the dose and interval is being ramped-up to determine tolerability; OR
Note: The patient may be switching from IVIG or from another SCIG product OR the patient may be naïve to immune globulin therapy. See prescribing information for ramp-up schedule.

ii. Patient has already been started on HyQvia after the initial dose ramp-up and ONE of the following applies (a, b, or c):
a) The dose is 300 mg/kg to 600 mg/kg given at 3 to 4 week intervals; OR
b) The dose and frequency is the same as previously used when receiving IVIG; OR
c) The dose and interval between doses has been adjusted based on clinical response as determined by the prescriber.

iii. For a patient with primary immune deficiency and exposure to measles (previous exposure or risk of future measles exposure), the minimum dose has been determined by the prescriber.

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2. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Electrodiagnostic studies support the diagnosis of CIDP **[documentation required]**; AND

iii. The medication has been prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has a clinically significant improvement in neurological symptoms as determined by the prescriber **[documentation required]**.
Note: Examples of improvement in neurologic symptoms include improvement in disability; nerve conduction study results improved or stabilized; physical examination show improvement in neurological symptoms, strength, and sensation.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) The dose is either 0.2 g/kg or 0.4 g/kg per week administered in one or two sessions over 1 or 2 consecutive days; OR
B) The dose and interval between doses has been titrated and adjusted based on clinical response as determined by the prescriber; OR
C) For HyQvia only: Approve if the patient meets ONE of the following (i, ii, or iii):
- **i.** Patient is starting HyQvia and the dose and interval is being ramped-up to determine tolerability; OR
- **ii.** Patient has already been started on HyQvia after the initial dose ramp-up and ONE of the following applies (a, b, or c):
  - **a)** The dose and frequency is the same as the patient's previous IVIG treatment; OR
  - **b)** The dosing range is 0.4 g/kg to 2.4 g/kg, given in a frequency of 2-, 3-, or 4 week intervals; OR
  - **c)** The dose and interval between doses has been adjusted based on clinical response as determined by the prescriber; OR
- **iii.** If the dose is ≤ 0.4 g/kg HyQvia may be administered without a ramp-up.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of immune globulin subcutaneous is not recommended in the following situations:

1. **Selective Immune Globulin A (IgA) Deficiency as the Sole Immunologic Abnormality.** Evidence does not support use of immune globulin.[15,24] Selective IgA deficiency is defined as a serum IgA level less than 0.07 g/L, but normal serum IgG and immunoglobulin M (IgM) levels in a patient greater than 4 years of age in whom other causes of hypogammaglobulinemia have been excluded.[24] Selective IgA deficiency may co-exist in some patients with poor specific IgG antibody production, with or without IgG2 subclass deficiency.[15,24] Some of these patients with a concomitant specific antibody defect might benefit from therapy with SCIG.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Gammagard® Liquid 10% [prescribing information]. Lexington, MA: Takeda; January 20243.
2. Gammaked™ 10% solution [prescribing information]. Fort Lee, NJ: Kedrion; January 2020.
3. Gamunex®-C 10% solution [prescribing information]. Research Triangle Park, NC: Grifols; January 2020.
4. Hizentra® 20% subcutaneous solution [prescribing information]. Kankakee, IL: CSL Behring; April 2023.
5. HyQvia® 10% subcutaneous solution with recombinant human hyaluronidase [prescribing information]. Lexington, MA: Takeda; January 2024.
6. McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS; Centers for Disease Control and Prevention. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2013;62:1-34.
7. Xembify® 20% subcutaneous solution [prescribing information]. Research Triangle Park, NC: Grifols; August 2020.

8. Cuvitru™ 20% subcutaneous solution [prescribing information]. Lexington, MA: Takeda; March 2023.
9. Cutaquig® 16.5% subcutaneous solution [prescribing information]. New York, NY: Pfizer; November 2021.
10. Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol.* 2017;139(3S):S1-S46.
11. Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol.* 2015;136:1186-1205.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	10/12/2022
Selected Revision	HyQvia: Removal of age criteria. No dosing updates needed.	4/19/2023
Annual Revision	No criteria changes.	10/25/2023
Selected Revision	Removed drug specific criteria for HyQvia. HyQvia will use the same criteria as the other immune globulin products. **HyQvia dosing for Primary Immunodeficiencies**: The dose and interval between doses has been adjusted based on clinical response as determined by the prescribing physician was updated to prescriber. **HyQvia dosing for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy** was added.	02/07/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immune Globulin Subcutaneous Utilization Management Medical Policy

- Cutaquig® (immune globulin 16.5% subcutaneous solution – Octapharma/Pfizer)
- Cuvitru™ (immune globulin 20% subcutaneous solution – Takeda)
- Gammagard® Liquid (immune globulin 10% solution – Takeda)
- Gammaked™ (immune globulin 10% solution caprylate/chromatography purified – Kedrion)
- Gamunex®-C (immune globulin 10% solution caprylate/chromatography purified – Grifols)
- Hizentra® (immune globulin 20% subcutaneous solution – CSL Behring)
- HyQvia® (immune globulin 10% subcutaneous solution with recombinant human hyaluronidase – Takeda)
- Xembify® (immune globulin 20% subcutaneous solution – Grifols)

REVIEW DATE: 10/25/2023; selected revision 02/07/2024

OVERVIEW

Immune globulin subcutaneous (SCIG) products are concentrated human immunoglobulins, primarily immunoglobulin G (IgG), that are prepared from pooled plasma collected from a large number of human donors. SCIG products are indicated for the following uses:

- **Chronic inflammatory demyelinating polyneuropathy,** for maintenance therapy in adults.[1,4,5]
- **Primary humoral immune deficiency (PID)**, for replacement therapy, including but not limited to the humoral defect in the following conditions: common variable immunodeficiency, X-linked agammaglobulinemia (congenital agammaglobulinemia), Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.[1-5,7-9] SCIG is also indicated for measles prophylaxis in individuals with PID who have been exposed to measles or who are at high risk of measles exposure.[1,4,5,8,9]

Hizentra, Cuvitru, Xembify, and Cutaquig are indicated as a subcutaneous (SC) infusion only.[4,7-9] Gammagard Liquid, Gammaked, and Gamunex-C may be administered as a SC infusion or an intravenous (IV) infusion for PID.[1-3] HyQvia is indicated for SC infusion only, with sequential infusion of the recombinant human hyaluronidase first and followed 10 minutes later with the immune globulin infusion.[5] The recombinant human hyaluronidase acts locally to increase dispersion and absorption of the immune globulin.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of SCIG products. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with SCIG as well as the monitoring required for adverse events and long-term efficacy, initial approval requires SCIG products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Cutaquig, Cuvitru, Gammagard Liquid, Gammaked, Gamunex-C, Hizentra, HyQvia, and Xembify is recommended in those who meet the following criteria:

FDA-Approved Indications

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1. Primary Immunodeficiencies. Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following (a, b, or c):

Note: An exception can be made for the impaired antibody response if, according to the prescriber, the delay caused by pre-vaccination and post-vaccination antibody measurement would be deleterious to the patient's health.

a) Patient has a diagnosis of congenital agammaglobulinemia, X-linked agammaglobulinemia, other agammaglobulinemia due to the absence of B-cells, Wiskott-Aldrich syndrome, ataxia telangiectasia, DiGeorge syndrome, severe combined immunodeficiency, Hyper-Immunoglobulin M (IgM) syndromes, an IgG level lower than 250 mg/dL, or a primary immune deficiency which has been confirmed by genetic or molecular testing; OR

b) Patient has a diagnosis of common variable immunodeficiency, unspecified hypogammaglobulinemia, or other immunodeficiencies with significant hypogammaglobulinemia and meets the following [(1) and (2)]:

(1) Patient's pretreatment IgG level is below the normal range (age-adjusted and according to the normal reference range for the reporting laboratory); AND

(2) Patient meets ONE of the following [(a) or (b)]:

(a) Patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); OR

(b) Patient has recurrent infections; OR

c) The patient has an IgG subclass deficiency, selective antibody deficiency (SAD), or another confirmed primary immunodeficiency and meets the following [(1) and (2)]:

(1) Patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); AND

(2) Patient has recurrent infections; AND

ii. The medication is prescribed by or in consultation with one of the following physician specialists: an allergist, immunologist, otolaryngologist (ear nose and throat [ENT] physician), pulmonologist, or an infectious diseases physician who treats patients with primary immune deficiencies.

B) Patient is Currently Receiving Immune Globulin. Approve if the patient has been diagnosed with a primary immunodeficiency and according to the prescriber the patient is continuing to receive benefit from the product.

Note: Examples of continued benefit with the product includes increased IgG levels or prevention and/or controlling of infections.

Dosing. Approve ONE of the following dosing regimens (A, B, C, D, E, or F):

A) The patient is transitioning from immune globulin intravenous (IVIG), and the maintenance dose (given once weekly, every 2 weeks, or more frequently than once weekly [e.g., 2 to 7 times per week]) is based on the patient's previous monthly IVIG dose; OR

B) The patient is transitioning from another immune globulin subcutaneous (SCIG) product, and the maintenance dose (given once weekly, every 2 weeks, or more frequently than once weekly) is based on the patient's previous weekly SCIG dose; OR

C) The patient is initiating SCIG therapy without previous IVIG or SCIG therapy and is receiving a loading dose (e.g., 100 mg/kg once daily for 5 consecutive days) followed by once weekly (or more frequently as necessitated by volume) maintenance dosing; OR

D) The dose and interval between doses has been adjusted based on clinical response, as determined by the prescriber; OR

E) For a patient with primary immune deficiency and exposure to measles (previous exposure or risk of future measles exposure), the minimum dose has been determined by the prescriber; OR

F) For HyQvia only: Approve if the patient meets ONE of the following (i, ii, or iii):

- **i.** Patient is starting HyQvia and the dose and interval is being ramped-up to determine tolerability; OR
  Note: The patient may be switching from IVIG or from another SCIG product OR the patient may be naïve to immune globulin therapy. See prescribing information for ramp-up schedule.
- **ii.** Patient has already been started on HyQvia after the initial dose ramp-up and ONE of the following applies (a, b, or c):
  - **a)** The dose is 300 mg/kg to 600 mg/kg given at 3 to 4 week intervals; OR
  - **b)** The dose and frequency is the same as previously used when receiving IVIG; OR
  - **c)** The dose and interval between doses has been adjusted based on clinical response as determined by the prescriber.
- **iii.** For a patient with primary immune deficiency and exposure to measles (previous exposure or risk of future measles exposure), the minimum dose has been determined by the prescriber.

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2. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Electrodiagnostic studies support the diagnosis of CIDP; AND
- **iii.** The medication has been prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has a clinically significant improvement in neurological symptoms as determined by the prescriber.
Note: Examples of improvement in neurologic symptoms include improvement in disability; nerve conduction study results improved or stabilized; physical examination show improvement in neurological symptoms, strength, and sensation.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):

A) The dose is either 0.2 g/kg or 0.4 g/kg per week administered in one or two sessions over 1 or 2 consecutive days; OR

B) The dose and interval between doses has been titrated and adjusted based on clinical response as determined by the prescriber; OR

C) For HyQvia only: Approve if the patient meets ONE of the following (i, ii, or iii):
- **i.** Patient is starting HyQvia and the dose and interval is being ramped-up to determine tolerability; OR
- **ii.** Patient has already been started on HyQvia after the initial dose ramp-up and ONE of the following applies (a, b, or c):

a) The dose and frequency is the same as the patient's previous IVIG treatment; OR
b) The dosing range is 0.4 g/kg to 2.4 g/kg, given in a frequency of 2-. 3-, or 4-week intervals; OR
c) The dose and interval between doses has been adjusted based on clinical response as determined by the prescriber; OR

iii. If the dose is ≤ 0.4 g/kg HyQvia may be administered without a ramp-up.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of immune globulin subcutaneous is not recommended in the following situations:

1. **Selective Immune Globulin A (IgA) Deficiency as the Sole Immunologic Abnormality.** Evidence does not support use of immune globulin.[15,24] Selective IgA deficiency is defined as a serum IgA level less than 0.07 g/L, but normal serum IgG and immunoglobulin M (IgM) levels in a patient greater than 4 years of age in whom other causes of hypogammaglobulinemia have been excluded.[24] Selective IgA deficiency may co-exist in some patients with poor specific IgG antibody production, with or without IgG2 subclass deficiency.[15,24] Some of these patients with a concomitant specific antibody defect might benefit from therapy with SCIG.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	10/12/2022
Selected Revision	HyQvia: Removal of age criteria. No dosing updates needed.	4/19/2023
Annual Revision	No criteria changes.	10/25/2023
Selected Revision	Removed drug specific criteria for HyQvia. HyQvia will use the same criteria as the other immune globulin products. **HyQvia dosing for Primary Immunodeficiencies**: The dose and interval between doses has been adjusted based on clinical response as determined by the prescribing physician was updated to prescriber. **HyQvia dosing for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy** was added.	02/07/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immunologicals – Cinqair Utilization Management Medical Policy
- Cinqair® (reslizumab intravenous infusion – Teva Respiratory)

REVIEW DATE: 04/19/2024

OVERVIEW

Cinqair, an interleukin-5 antagonist monoclonal antibody, is indicated for **severe asthma** as add-on maintenance treatment of patients ≥ 18 years of age who have an eosinophilic phenotype.[1] Limitations of Use: Cinqair is not indicated for the treatment of other eosinophilic conditions or for the relief of acute bronchospasm/status asthmaticus.

Clinical Efficacy

The Cinqair pivotal studies included adult and adolescent patients with moderate to severe asthma who had baseline blood eosinophil levels ≥ 400 cells/microliter despite therapy.[2-4] In one study that did not require patients to have elevated eosinophils at baseline, clinical benefit in regard to forced expiratory volume in 1 second (FEV_1) was not statistically significant with Cinqair vs. placebo. However, a significant improvement was observed in a subgroup of patients with baseline eosinophil levels ≥ 400 cells/microliter.

Guidelines

The Global Initiative for Asthma Global Strategy for Asthma Management and Prevention (2023) proposes a step-wise approach to asthma treatment.[5] Cinqair is listed as an option for add-on therapy in patients ≥ 18 years of age with severe eosinophilic asthma (i.e., patients who continue to experience exacerbations or have poor symptom control despite treatment with a high-dose ICS/long-acting $beta_2$-agonist [LABA] and who have eosinophilic biomarkers or require therapy with maintenance oral corticosteroids). Higher blood eosinophil levels, higher number of severe exacerbations in the previous year, adult-onset asthma, nasal polyposis, maintenance oral corticosteroid requirements, and low lung function may predict a good asthma response to Cinqair.

According to the European Respiratory Society/American Thoracic Society guidelines (2014; updated in 2020), severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which remains uncontrolled despite this therapy.[6,7] Uncontrolled asthma is defined as asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids or asthma that meets one of the following four criteria:

1) Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 or Asthma Control Test < 20;
2) Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year;
3) Serious exacerbations: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year;
4) Airflow limitation: FEV_1 < 80% predicted after appropriate bronchodilator withholding.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Cinqair. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the durations noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cinqair, as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Cinqair to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indication

1. Asthma. Approve Cinqair for the duration noted if the patient meets one of the following conditions (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, iv, and v):

i. Patient is ≥ 18 years of age; AND

ii. Patient has a blood eosinophil count ≥ 400 cells per microliter within the previous 4 weeks or within 4 weeks prior to treatment with Cinqair or another monoclonal antibody therapy that may lower blood eosinophil levels; AND

Note: Examples of monoclonal antibody therapies that may lower blood eosinophil levels include Cinqair, Adbry (tralokinumab-ldrm subcutaneous injection), Dupixent (dupilumab subcutaneous injection), Fasenra (benralizumab subcutaneous injection), Nucala (mepolizumab subcutaneous injection), Tezspire (tezepelumab-ekko subcutaneous injection), and Xolair (omalizumab subcutaneous injection).

iii. Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):

a) An inhaled corticosteroid; AND

b) At least one additional asthma controller or asthma maintenance medication; AND

Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting beta$_2$-agonists, inhaled long-acting muscarinic antagonists, and monoclonal antibody therapies (e.g., Cinqair, Dupixent, Fasenra, Nucala, Tezspire, Xolair). Use of a combination inhaler containing both an inhaled corticosteroid and additional asthma controller/maintenance medication(s) would fulfill the requirement for both criteria a and b.

iv. Patient has asthma that is uncontrolled or was uncontrolled at baseline as defined by ONE of the following (a, b, c, d, or e):

Note: "Baseline" is defined as prior to receiving Cinqair or another monoclonal antibody therapy for asthma. Examples of monoclonal antibody therapies for asthma include Cinqair, Dupixent, Fasenra, Nucala, Tezspire, and Xolair.

a) Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR

b) Patient experienced one or more asthma exacerbation(s) requiring a hospitalization, an emergency department visit, or an urgent care visit in the previous year; OR

c) Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR

d) Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR
e) Patient has asthma that worsens upon tapering of oral (systemic) corticosteroid therapy; AND

v. The medication is prescribed by or in consultation with an allergist, immunologist, or pulmonologist.

B) Patient is Currently Receiving Cinqair. Approve for 1 year if the patient meets the following (i, ii, and iii):

i. Patient has already received at least 6 months of therapy with Cinqair; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Cinqair should be considered under criterion 1A (Asthma, Initial Therapy).

ii. Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination; AND

iii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Cinqair therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, emergency department, urgent care, or medical clinic visits due to asthma; and decreased requirement for oral corticosteroid therapy.

Dosing. Approve 3 mg/kg administered intravenously once every 4 weeks.

Conditions Not Recommended for Approval

Coverage of Cinqair is not recommended in the following situations:

1. **Concurrent use of Cinqair with another Monoclonal Antibody Therapy.** The efficacy and safety of Cinqair used in combination with other monoclonal antibody therapies have not been established.
Note: Monoclonal antibody therapies are Adbry® (tralokinumab-ldrm subcutaneous injection), Dupixent® (dupilumab subcutaneous injection), Fasenra® (benralizumab subcutaneous injection), Nucala® (mepolizumab subcutaneous injection), Teszpire® (tezepelumab-ekko subcutaneous injection), or Xolair® (omalizumab subcutaneous injection).

2. **Eosinophilic Esophagitis or Eosinophilic Gastroenteritis.** Cinqair is not indicated for the treatment of eosinophilic conditions other than asthma.[1] In addition to data from a small pilot study and from a small compassionate use program, one randomized, double-blind, placebo-controlled study (n =226) evaluated the efficacy of Cinqair in pediatric and adolescent patients with eosinophilic esophagitis.[8-10] In this study, patients were randomly assigned to receive Cinqair IV at varying doses for 12 weeks. At Week 15, peak esophageal eosinophil counts were reduced from baseline and all reductions with Cinqair were significant compared with placebo. Improvements in physician's global assessment scores were also observed in all groups (including placebo), but the difference between Cinqair and placebo was not statistically significant. Guidelines for the management of eosinophilic esophagitis from the American Gastroenterological Association and the Joint Task Force on Allergy Immunology Practice Parameters (2020) only recommend using anti-interleukin-5 therapies in the context of a clinical trial.[11] Additional, well-controlled trials are needed to determine the role of Cinqair in the treatment of eosinophilic esophagitis and eosinophilic gastroenteritis.

3. **Hypereosinophilic Syndrome.** Cinqair is not indicated for the treatment of eosinophilic conditions other than asthma.[1] One very small pilot study (n = 4) evaluated the safety and efficacy of Cinqair in patients with hypereosinophilic syndrome who were refractory to or intolerant of treatment with conventional therapy.[12] A single dose of Cinqair resulted in a response in two of four patients. In the

two responders, blood eosinophil counts dropped to within the normal range within 48 hours of the Cinqair infusion and this was accompanied by an improvement in clinical signs and symptoms. The World Health Organization (WHO) and international consensus classification of eosinophilic disorders update on diagnosis, risk stratification, and management (2024) notes that Cinqair has not been evaluated extensively for the treatment of hypereosinophilic syndrome.[13] At this time, the WHO considers Cinqair investigational for the treatment of hypereosinophilic syndrome. Additional, well-controlled trials are needed to determine the role of Cinqair in the treatment of hypereosinophilic syndrome.

4. **Nasal Polyps.** Cinqair is not indicated for the treatment of nasal polyps.[1] One double-blind, placebo-controlled, randomized safety and pharmacokinetic study (n = 24) evaluated the use of Cinqair in patients with nasal polyps.[14] Patients received a single infusion of either Cinqair 3 mg/kg, Cinqair 1 mg/kg, or placebo. It was reported that blood eosinophil counts and concentrations of eosinophil cation protein were reduced for up to 8 weeks following the Cinqair infusion. Nasal polyp scores improved for approximately 4 weeks in one-half of patients receiving active treatment. Additionally, a pooled subgroup analysis from the two pivotal Cinqair asthma exacerbation trials found that in patients with inadequately controlled asthma and chronic sinusitis with nasal polyps (n = 150) Cinqair demonstrated enhanced efficacy. Patients in this subgroup experienced an 83% reduction the clinical asthma exacerbation rate with Cinqair vs. placebo.[15] The magnitude of this reduction was greater than that observed with the overall study population. The Joint Task Force on Practice Parameters published guidelines for the medical management of CRSwNP in 2023.[16] Use of other anti-interleukin-5 antagonist monoclonal antibodies is recommended. However, no recommendations are provided for Cinqair.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Conditions not recommended for approval:** Criteria were updated to clarify that use of Cinqair with another monoclonal antibody therapy is specific to Fasenra, Nucala, Dupixent, Tezspire, Xolair, and Adbry.	03/22/2023
Annual Revision	**Asthma:** Removed leukotriene receptor antagonists as an example of additional asthma controller or asthma maintenance medications.	04/19/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immunologicals – Fasenra Utilization Management Medical Policy
- Fasenra® (benralizumab subcutaneous injection – AstraZeneca)

REVIEW DATE: 04/19/2024

OVERVIEW

Fasenra, an interleukin-5 receptor alpha (IL-5Rα)-directed cytolytic monoclonal antibody, is indicated for **severe asthma** as add-on maintenance treatment of patients ≥ 6 years of age who have an eosinophilic phenotype.[1] Limitations of Use: Fasenra is not indicated for the treatment of other eosinophilic conditions or for the relief of acute bronchospasm/status asthmaticus.

Clinical Efficacy

In two pivotal asthma studies, the addition of Fasenra to existing therapy significantly reduced annualized asthma exacerbation rates in patients with baseline blood eosinophil levels ≥ 300 cells/microliter.[2-4] The magnitude of the improvements observed with Fasenra in this patient population were larger than those observed in patients with lower baseline eosinophil levels (e.g., < 150 cells/microliter). Another pivotal study involved adults with severe asthma receiving high-dose inhaled corticosteroid (ICS)/long-acting beta$_2$-agonist (LABA) and chronic oral corticosteroid therapy who had a baseline blood eosinophil level ≥ 150 cells/microliter.[4]

Guidelines

The Global Initiative for Asthma Global Strategy for Asthma Management and Prevention (2023) proposes a step-wise approach to asthma treatment.[5] Fasenra is listed as an option for add-on therapy in patients ≥ 12 years of age with severe eosinophilic asthma (i.e., patients who continue to experience exacerbations or have poor symptom control despite treatment with a high-dose ICS/long-acting beta$_2$-agonist [LABA] and who have eosinophilic biomarkers or require therapy with maintenance oral corticosteroids). Of note, guidelines have not been updated since the lower age indication of Fasenra was FDA-approved. Higher blood eosinophil levels, higher number of severe exacerbations in the previous year, adult-onset asthma, nasal polyposis, maintenance oral corticosteroid requirements, and low lung function may predict a good asthma response to Fasenra.

According to the European Respiratory Society/American Thoracic Society guidelines (2014; updated in 2020), severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which remains uncontrolled despite this therapy.[6,7] Uncontrolled asthma is defined as asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids or asthma that meets one of the following four criteria:

1) Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 or Asthma Control Test < 20;
2) Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year;
3) Serious exacerbations: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year;
4) Airflow limitation: forced expiratory volume in 1 second (FEV_1) < 80% predicted after appropriate bronchodilator withholding.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Fasenra. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the durations noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Fasenra, as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Fasenra to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Fasenra is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. Asthma. Approve Fasenra for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, iv, and v):

i. Patient is ≥ 6 years of age; AND

ii. Patient has a blood eosinophil level ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with Fasenra or another monoclonal antibody therapy that may lower blood eosinophil levels; AND

Note: Examples of monoclonal antibody therapies that may lower blood eosinophil levels include Fasenra, Adbry (tralokinumab-ldrm subcutaneous injection), Cinqair (reslizumab intravenous infusion), Dupixent (dupilumab subcutaneous injection), Nucala (mepolizumab subcutaneous injection), Tezspire (tezepelumab-ekko subcutaneous injection), and Xolair (omalizumab subcutaneous injection).

iii. Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):

a) An inhaled corticosteroid; AND

b) At least one additional asthma controller or asthma maintenance medication; AND

Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting $beta_2$-agonists, inhaled long-acting muscarinic antagonists, and monoclonal antibody therapies for asthma (e.g., Cinqair, Dupixent, Fasenra, Nucala, Tezspire, Xolair). Use of a combination inhaler containing both an inhaled corticosteroid and additional asthma controller/maintenance medication(s) would fulfill the requirement for both criteria a and b.

iv. Patient has asthma that is uncontrolled or was uncontrolled at baseline as defined by ONE of the following (a, b, c, d, or e):

Note: "Baseline" is defined as prior to receiving Fasenra or another monoclonal antibody therapy for asthma. Examples of monoclonal antibody therapies for asthma include Fasenra, Cinqair, Dupixent, Nucala, Tezspire, and Xolair.

a) Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR

b) Patient experienced one or more asthma exacerbation(s) requiring a hospitalization, an emergency department visit, or an urgent care visit in the previous year; OR

c) Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR
d) Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR
e) Patient has asthma that worsens upon tapering of oral (systemic) corticosteroid therapy; AND

v. The medication is prescribed by or in consultation with an allergist, immunologist, or pulmonologist.

B) Patient is Currently Receiving Fasenra. Approve for 1 year if the patient meets the following (i, ii, and iii):

i. Patient has already received at least 6 months of therapy with Fasenra; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Fasenra should be considered under criterion 1A (Asthma, Initial Therapy).

ii. Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination inhaler; AND

iii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Fasenra therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, emergency department, urgent care, or medical clinic visits due to asthma; and decreased requirement for oral corticosteroid therapy.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) If the patient weighs < 35 kg, approve the following dosing regimens (i or ii):
i. 10 mg administered subcutaneously once every 4 weeks for the first 3 doses; OR
ii. 10 mg administered subcutaneously once every 8 weeks; OR

B) If the patient weighs ≥ 35 kg, approve the following dosing regimens (i or ii):
i. 30 mg administered subcutaneously once every 4 weeks for the first 3 doses; OR
ii. 30 mg administered subcutaneously once every 8 weeks.

Conditions Not Recommended for Approval

Coverage of Fasenra is not recommended in the following situations:

1. **Chronic Obstructive Pulmonary Disease (COPD).** Fasenra is not indicated for the treatment of COPD.[1] One double-blind, placebo-controlled, Phase IIa study (n = 101) evaluated the efficacy and safety of Fasenra in patients 40 to 80 years of age with eosinophilia and moderate to severe COPD.[8] The annualized rate of acute COPD exacerbations was not reduced with Fasenra compared with placebo. Lung function was also not significantly improved with Fasenra vs. placebo. Numerically greater (although non-significant) improvements in exacerbations and lung function were observed with Fasenra vs. placebo in patients with baseline blood eosinophil levels of 200 cells/microliter or more. Two double-blind, placebo-controlled, Phase III studies (GALATHEA and TERRANOVA) also evaluated Fasenra in patients with moderate to very severe COPD (n = 1,120 and n = 1,545 patients, respectively, with eosinophils ≥ 220 cells/mm^3).[9] Following, 56 weeks of therapy, the annualized COPD exacerbation rates were not statistically significantly reduced with Fasenra vs. placebo in either study. Current COPD guidelines from the Global Initiative for Chronic Lung Disease (2024) note the negative data with Fasenra and state that further studies are needed.[10]

2. **Concurrent use of Fasenra with another Monoclonal Antibody Therapy.** The efficacy and safety of Fasenra used in combination with other monoclonal antibody therapies have not been established.
Note:: Monoclonal antibody therapies are Adbry® (tralokinumab-ldrm subcutaneous injection), Cinqair® (reslizumab intravenous infusion), Dupixent® (dupilumab subcutaneous injection), Nucala®

(mepolizumab subcutaneous injection), Teszpire® (tezepelumab-ekko subcutaneous injection), or Xolair® (omalizumab subcutaneous injection).

3. **Hypereosinophilic Syndrome.** Fasenra is not indicated for the treatment of eosinophilic conditions other than asthma.[1] A small, randomized, double-blind, placebo-controlled, Phase II trial (n = 20) evaluated the efficacy of Fasenra in patients who had platelet-derived growth factor receptor alpha (PDGFRA)-negative hypereosinophilic syndrome with an absolute eosinophil count of 1,000 cells/mm^3.[11] At Week 12, 90% of patients receiving Fasenra (n = 9/10) vs. 30% of patients receiving placebo (n = 3/10) achieved a 50% or greater reduction in the absolute eosinophil count (P = 0.02). Following the randomized phase, all patients received open-label Fasenra 30 mg every 4 weeks. During this time, 74% of patients (n = 14/19) had sustained clinical and hematologic responses for 48 weeks. The World Health Organization (WHO) and international consensus classification of eosinophilic disorders update on diagnosis, risk stratification, and management (2024) acknowledges that Fasenra has been studied in patients with hypereosinophilic syndrome.[12] A Phase III study of Fasenra in this patient population is currently underway, with primary completion anticipated in May 2024. At this time, the WHO notes that Fasenra remains investigational. Available data with Fasenra is discussed, but this therapy continues to be considered investigational.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Conditions not recommended for approval:** Criteria were updated to clarify that use of Fasenra with another monoclonal antibody therapy is specific to Cinqair, Nucala, Dupixent, Tezspire, Xolair, and Adbry.	03/22/2023
Annual Revision	**Asthma:** The age of approval was reduced from ≥ 12 years of age to ≥ 6 years of age. Removed leukotriene receptor antagonists as an example of additional asthma controller or asthma maintenance medications. The Dosing criteria were updated to add 10 mg administered subcutaneously (SC) once every 4 weeks for the first three doses or 10 mg administered SC once every 8 weeks for a patient who weighs < 35 kg. The dosing criteria previously in the policy will still apply to a patient who weighs ≥ 35 kg.	04/19/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immunologicals – Nucala Utilization Management Medical Policy
- Nucala® (mepolizumab subcutaneous injection – GlaxoSmithKline)

REVIEW DATE: 04/19/2024

OVERVIEW

Nucala, an interleukin (IL)-5 antagonist monoclonal antibody, is indicated for the following uses:[1]

- **Asthma**, as add-on maintenance treatment of patients ≥ 6 years of age with severe disease with an eosinophilic phenotype. Limitations of Use: Nucala is not indicated for the relief of acute bronchospasm or status asthmaticus.
- **Chronic rhinosinusitis with nasal polyps** (CRSwNP), as an add-on maintenance treatment in patients ≥ 18 years of age with an inadequate response to nasal corticosteroids.
- **Eosinophilic granulomatosis with polyangiitis** (EGPA) [formerly known as Churg-Strauss Syndrome] in adult patients.
- **Hypereosinophilic syndrome** (HES), in patients ≥ 12 years of age who have had HES for ≥ 6 months without an identifiable non-hematologic secondary cause.

Clinical Efficacy

Asthma

In the pivotal asthma studies of Nucala, patients were generally required to have elevated eosinophils at baseline (e.g., peripheral blood eosinophil count ≥ 150 cells/microliter at screening or ≥ 300 cells/microliter at some time during the previous year). Across the studies, efficacy was assessed as early as 24 weeks.[1-4]

Chronic Rhinosinusitis with Nasal Polyps

In one pivotal study involving adult patients with chronic rhinosinusitis with nasal polyposis, the primary efficacy endpoints were assessed at 52 weeks.[1,5] However, improvements in nasal polyp size and symptoms compared with placebo were observed much earlier on in the course of treatment (i.e., between 9 and 24 weeks).

Eosinophilic Granulomatosis with Polyangiitis

One study evaluated the efficacy of Nucala in patients ≥ 18 years of age with relapsing or refractory EGPA who had received ≥ 4 weeks of a stable oral corticosteroid dose (i.e., prednisolone, prednisone).[6] Patients were also required to have a baseline relative eosinophil level of 10% or an absolute eosinophil level > 1,000 cells per microliter; however, the baseline mean absolute eosinophil level was approximately 175 cells per microliter across both treatment groups. While remission benefit of Nucala was demonstrated in the overall patient population, the magnitude of improvements observed with Nucala were larger in patients with baseline eosinophil levels ≥ 150 cells per microliter than in patients with lower baseline levels.

Hypereosinophilic Syndrome

One study evaluated the efficacy of Nucala in patients ≥ 12 years of age with hypereosinophilic syndrome for ≥ 6 months.[7] Patients with non-hematologic secondary hypereosinophilic syndrome and those with FIP1L1-PDGFRα kinase-positive hypereosinophilic syndrome were excluded. All patients had a baseline blood eosinophil count ≥ 1,000 cells per microliter. Additionally, all patients had been on stable therapy for their hypereosinophilic syndrome (e.g., oral corticosteroids, immunosuppressive agents, or cytotoxic therapy) for 4 weeks or more prior to randomization. Efficacy was assessed following 32 weeks of therapy.

Guidelines

Asthma Guidelines

The Global Initiative for Asthma Global Strategy for Asthma Management and Prevention (2023) proposes a step-wise approach to asthma treatment.[8] Nucala is listed as an option for add-on therapy in patients ≥ 6 years of age with severe eosinophilic asthma (i.e., patients who continue to experience exacerbations or have poor symptom control despite treatment with a high-dose ICS/long-acting beta$_2$-agonist [LABA] and who have eosinophilic biomarkers or require therapy with maintenance oral corticosteroids). Higher blood eosinophil levels, higher number of severe exacerbations in the previous year, adult-onset asthma, nasal polyposis, maintenance oral corticosteroid requirements, and low lung function may predict a good asthma response to Nucala.

According to the European Respiratory Society/American Thoracic Society guidelines (2014; updated in 2020), severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which remains uncontrolled despite this therapy.[9,10] Uncontrolled asthma is defined as asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids or asthma that meets one of the following four criteria:

1) Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 or Asthma Control Test < 20;
2) Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year;
3) Serious exacerbations: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year;
4) Airflow limitation: forced expiratory volume in 1 second (FEV_1) < 80% predicted after appropriate bronchodilator withholding.

Chronic Rhinosinusitis with Nasal Polyps Guidelines

The Joint Task Force on Practice Parameters (JTFPP) published a focused guideline update for the medical management of CRSwNP (2023), which updated recommendations regarding intranasal corticosteroids and biologic therapies.[11] Intranasal corticosteroids are recommended for the treatment of CRSwNP. Use of biologics (e.g., Nucala) is also recommended. However, in patients who derived a sufficient benefit from other therapies such as intranasal corticosteroids, surgery, or aspirin therapy after desensitization, biologics may not be preferred. Conversely, biologics may be preferred over other medical treatment options in patients who continue to have a high burden of disease despite receiving at least 4 weeks of treatment with an intranasal corticosteroid.

The diagnosis of CRSwNP was not addressed in this focused guideline update. Previous guidelines have noted that the presence of two or more signs and symptoms of chronic rhinosinusitis (e.g., rhinorrhea, postnasal drainage, anosmia, nasal congestion, facial pain, headache, fever, cough, and purulent discharge) that persist for an extended period of time makes the diagnosis of chronic rhinosinusitis likely.[12-15] However, this requires confirmation of sinonasal inflammation, which can either be done via direct visualization or computed tomography (CT) scan. Oral corticosteroids and surgical intervention were not specifically addressed in this update. Prior guidelines recommend short courses of oral corticosteroid as needed and consideration of surgical removal as an adjunct to medical therapy in patients with CRSwNP that is not responsive or is poorly responsive to medical therapy.[12,13,15]

Eosinophilic Granulomatosis with Polyangiitis Guidelines
The American College of Rheumatology (ACR)/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated (ANCA) Vasculitis (2021) includes recommendations regarding the management of EGPA.[16] For patients with active, non-severe EGPA, combination therapy with Nucala and corticosteroids is recommended over other traditional treatments such as methotrexate, azathioprine, or mycophenolate mofetil in the setting of remission induction. Non-severe EGPA is defined as vasculitis in the absence of life- or organ-threatening manifestations. In general, the clinical profile includes rhinosinusitis, asthma, mild systemic symptoms, uncomplicated cutaneous disease, and mild inflammatory arthritis. Nucala, in combination with corticosteroids, is also a recommended therapy for patients who have relapsed and are experiencing non-severe disease manifestations (i.e., asthma and/or sinonasal disease) while receiving either low-dose corticosteroids alone, methotrexate, azathioprine, or mycophenolate mofetil. For patients with severe EGPA, cyclophosphamide or rituximab is preferred over Nucala for remission induction. The European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of ANCA-associated vasculitis (2022) also address the use of Nucala for the treatment of EGPA.[17] Similar to the ACR guidelines, EULAR recommends Nucala for induction of remission in patients with relapsing or refractory EGPA without active organ- or life-threatening disease. It is also recommended for maintenance of remission in these patients. Additionally, it is also among the many recommended treatment options for the maintenance of remission of EGPA after induction of remission for organ-threatening or life-threatening disease.

Hypereosinophilia Guidelines
The World Health Organization (WHO) and international consensus classification of eosinophilic disorders update on diagnosis, risk stratification, and management (2024) notes that corticosteroids remain first-line therapy for the treatment of HES.[18] Nucala, hydroxyurea, pegylated-interferon, imatinib, and hematopoietic stem cell transplantation are listed as second-line treatment options.

POLICY STATEMENT
Prior Authorization is recommended for medical benefit coverage of Nucala. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the durations noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nucala, as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Nucala to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Nucala is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1) **Asthma.** Approve Nucala for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, iv, and v):
     - **i.** Patient is ≥ 6 years of age; AND
     - **ii.** Patient has a blood eosinophil level ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with Nucala or another monoclonal antibody therapy that may lower blood eosinophil levels; AND
       Note: Examples of monoclonal antibody therapies that may lower blood eosinophil levels include Nucala, Adbry (tralokinumab-ldrm subcutaneous injection), Cinqair (reslizumab intravenous infusion), Dupixent (dupilumab subcutaneous injection), Fasenra (benralizumab subcutaneous injection), Tezspire (tezepelumab-ekko subcutaneous injection), and Xolair (omalizumab subcutaneous injection).
     - **iii.** Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):
       - **a)** An inhaled corticosteroid; AND
       - **b)** At least one additional asthma controller or asthma maintenance medication; AND

       Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting beta$_2$-agonists, inhaled long-acting muscarinic antagonists, and monoclonal antibody therapies for asthma (e.g., Cinqair, Dupixent, Fasenra, Nucala, Tezspire, Xolair). Use of a combination inhaler containing both an inhaled corticosteroid and additional asthma controller/maintenance medication(s) would fulfill the requirement for both criteria a and b.
     - **iv.** Patient has asthma that is uncontrolled or was uncontrolled at baseline as defined by ONE of the following (a, b, c, d, or e):
       Note: "Baseline" is defined as prior to receiving Nucala or another monoclonal antibody therapy for asthma. Examples of monoclonal antibody therapies for asthma include Nucala, Cinqair, Dupixent, Fasenra, Tezspire, and Xolair.
       - **a)** Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR
       - **b)** Patient experienced one or more asthma exacerbation(s) requiring a hospitalization, an emergency department visit, or an urgent care visit in the previous year; OR
       - **c)** Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR
       - **d)** Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR
       - **e)** Patient has asthma that worsens upon tapering of oral (systemic) corticosteroid therapy; AND
     - **v.** The medication is prescribed by or in consultation with an allergist, immunologist, or pulmonologist.
   - **B)** Patient is Currently Receiving Nucala. Approve for 1 year if the patient meets the following (i, ii, and iii):
     - **i.** Patient has already received at least 6 months of therapy with Nucala; AND
       Note: A patient who has received < 6 months of therapy or who is restarting therapy with Nucala should be considered under criterion 1A (Asthma, Initial Therapy).
     - **ii.** Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination inhaler; AND
     - **iii.** Patient has responded to therapy as determined by the prescriber.
       Note: Examples of a response to Nucala therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, emergency department, urgent care,

or medical clinic visits due to asthma; and decreased requirement for oral corticosteroid therapy.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) If the patient is ≥ 12 years of age, approve 100 mg administered subcutaneously once every 4 weeks; OR

B) If the patient is 6 to 11 years of age, approve 40 mg administered subcutaneously once every 4 weeks.

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2) Chronic Rhinosinusitis with Nasal Polyps. Approve Nucala for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, iv, v, and vi):

i) Patient is ≥ 18 years of age; AND

ii) Patient has chronic rhinosinusitis with nasal polyps as evidenced by direct examination, endoscopy, or sinus computed tomography (CT) scan; AND

iii) Patient has experienced two or more of the following symptoms for at least 6 months: nasal congestion, nasal obstruction, nasal discharge, and/or reduction/loss of smell; AND

iv) Patient meets BOTH of the following (a and b):

a) Patient has received at least 4 weeks of therapy with an intranasal corticosteroid; AND

b) Patient will continue to receive therapy with an intranasal corticosteroid concomitantly with Nucala; AND

v) Patient meets ONE of the following (a, b, or c):

a) Patient has received at least one course of treatment with a systemic corticosteroid for 5 days or more within the previous 2 years; OR

b) Patient has a contraindication to systemic corticosteroid therapy; OR

c) Patient has had prior surgery for nasal polyps; AND

vi) Nucala is prescribed by or in consultation with an allergist, immunologist, or an otolaryngologist (ear, nose and throat [ENT] physician specialist).

B) Patient is Currently Receiving Nucala. Approve for 1 year if the patient meets the following (i, ii, and iii):

i) Patient has already received at least 6 months of therapy with Nucala; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Nucala should be considered under criterion 4A [Nasal Polyps, Initial Therapy]).

ii) Patient continues to receive therapy with an intranasal corticosteroid; AND

iii) Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Nucala therapy are reduced nasal polyp size, improved nasal congestion, reduced sinus opacification, decreased sino-nasal symptoms, improved sense of smell.

Dosing. Approve 100 mg administered subcutaneously once every 4 weeks.

3) Eosinophilic Granulomatosis with Polyangiitis (EGPA) [formerly known as Churg-Strauss Syndrome]. Approve Nucala for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, and v):

i. Patient is ≥ 18 years of age; AND;

ii. Patient has active, non-severe disease; AND

Note: Non-severe disease is defined as vasculitis without life- or organ-threatening manifestations. Examples of symptoms in patients with non-severe disease include rhinosinusitis, asthma, mild systemic symptoms, uncomplicated cutaneous disease, mild inflammatory arthritis.

iii. Patient has/had a blood eosinophil level ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with any monoclonal antibody therapy that may lower blood eosinophil levels; AND

Note: Examples of monoclonal antibody therapies that may lower blood eosinophil levels include Nucala, Adbry (tralokinumab-ldrm subcutaneous injection), Cinqair (reslizumab intravenous infusion), Dupixent (dupilumab subcutaneous injection), Fasenra (benralizumab subcutaneous injection), Tezspire (tezepelumab-ekko subcutaneous injection), and Xolair (omalizumab subcutaneous injection).

iv. Patient has tried therapy with a corticosteroid (e.g., prednisone) for a minimum of 4 weeks; AND

v. The medication is prescribed by or in consultation with an allergist, immunologist, pulmonologist, or rheumatologist.

B) Patient is Currently Receiving Nucala. Approve for 1 year if the patient meets the following (i and ii):

i. Patient has already received at least 6 months of therapy with Nucala; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with Nucala should be considered under criterion 2A (Eosinophilic Granulomatosis with Polyangiitis, Initial Therapy).

ii. Patient has responded to therapy as determined by the prescriber.

Note: Examples of a response to Nucala therapy are reduced rate of relapse, corticosteroid dose reduction, and reduced eosinophil levels.

Dosing. Approve 300 mg administered subcutaneously once every 4 weeks.

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4) Hypereosinophilic Syndrome. Approve Nucala for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 8 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):

i. Patient is ≥ 12 years of age; AND

ii. Patient has had hypereosinophilic syndrome for ≥ 6 months; AND

iii. Patient has FIP1L1-PDGFRα-negative disease; AND

iv. Patient does NOT have an identifiable non-hematologic secondary cause of hypereosinophilic syndrome according to the prescriber; AND

Note: Examples of secondary causes of hypereosinophilic syndrome include drug hypersensitivity, parasitic helminth infection, human immunodeficiency virus infection, non-hematologic malignancy.

v. Patient has/had a blood eosinophil level ≥ 1,000 cells per microliter prior to treatment with any monoclonal antibody therapy that may lower blood eosinophil levels; AND
Note: Examples of monoclonal antibody therapies that may lower blood eosinophil levels include Nucala, Adbry (tralokinumab-ldrm subcutaneous injection), Cinqair (reslizumab intravenous infusion), Dupixent (dupilumab subcutaneous injection), Fasenra (benralizumab subcutaneous injection), Tezspire (tezepelumab-ekko subcutaneous injection), and Xolair (omalizumab subcutaneous injection).

vi. Patient has tried at least one other treatment for hypereosinophilic syndrome for a minimum of 4 weeks; AND
Note: Example of treatments for hypereosinophilic syndrome include systemic corticosteroids, hydroxyurea, cyclosporine, imatinib, or pegylated-interferon.

vii. Nucala is prescribed by or in consultation with an allergist, immunologist, pulmonologist, or rheumatologist.

B) Patient is Currently Receiving Nucala. Approve for 1 year if the patient meets the following (i and ii):

i. Patient has already received at least 8 months of therapy with Nucala; AND
Note: A patient who has received < 8 months of therapy or who is restarting therapy with Nucala should be considered under criterion 3A (Hypereosinophilic Syndrome, Initial Therapy).

ii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Nucala therapy are decreased number of flares, improved fatigue, reduced corticosteroid requirements, and decreased eosinophil levels.

Dosing. Approve 300 mg administered subcutaneously once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nucala is not recommended in the following situations:

1. **Atopic Dermatitis.** Nucala is not indicated for the treatment of atopic dermatitis.[1] In one small study, intravenous (IV) mepolizumab significantly reduced peripheral blood eosinophil counts in patients with moderate to severe atopic dermatitis.[19,20] However, mepolizumab IV therapy did not result in clinical success as assessed by Physician's Global Assessment of Improvement scores compared with placebo. Other clinical outcomes were also not significantly improved with mepolizumab IV. Another small study evaluated subcutaneous Nucala in patients with moderate to severe atopic dermatitis.[21] Following 16 weeks of therapy, Nucala did not demonstrate efficacy, with 11% (n = 2/11) of patients meeting the primary endpoint of treatment success with Nucala vs. 0 with placebo. Further research is warranted to determine if Nucala has a place in therapy in the treatment of these conditions.

2. **Chronic Obstructive Pulmonary Disease (COPD).** Nucala is not indicated for the treatment of COPD.[1] Two Phase III studies, METREX (n = 836) and METREO (n = 675) evaluated Nucala in patients with COPD who had a history of moderate or severe exacerbations despite treatment with inhaled triple therapy (inhaled corticosteroid/long-acting muscarinic antagonist/long-acting beta$_2$-agonist).[22] METREX included patients regardless of eosinophil counts, but did include a subgroup of patients who were considered to have an eosinophilic phenotype (eosinophil count ≥ 150 cells/microliter) [n = 462]. METREO only included patients with an eosinophilic phenotype (defined as an eosinophil count ≥ 150 cells/microliter at screening or ≥ 300 cells/microliter within the previous year). Overall, lower COPD exacerbation rates were observed with Nucala vs. placebo; however, none of these reductions were statistically significant in either the METREX overall modified intent to treat

(mITT) population or the METREO mITT population (which included all eosinophilic phenotype patients). In the subgroup of patients in the METREX study with an eosinophilic phenotype, the COPD exacerbation rates were statistically lower with Nucala vs. placebo, as was the difference in the time to first exacerbation. In July 2018, the FDA's Pulmonary Allergy Drugs Advisory Committee voted against approval of Nucala as an add-on treatment to inhaled corticosteroid-based maintenance treatments to reduce flare-ups in patients with COPD.[23] The Committee had concerns about the defining criteria for the eosinophilic phenotype of COPD as well as the lack of data on patient asthma history. Subsequently, in September 2018, the FDA rejected the approval of Nucala for COPD citing the need for additional clinical data. Current COPD guidelines from the Global Initiative for Chronic Lung Disease (2024) note the mixed data with Nucala.[24] The guidelines state that further studies are needed to determine if Nucala may have a role in a highly selected subgroup of patients with eosinophilic COPD.

3. **Concurrent use of Nucala with another Monoclonal Antibody Therapy.** The efficacy and safety of Nucala used in combination with other monoclonal antibody therapies have not been established. Note: Monoclonal antibody therapies are Adbry® (tralokinumab-ldrm subcutaneous injection), Cinqair® (reslizumab intravenous injection), Dupixent® (dupilumab subcutaneous injection), Fasenra® (benralizumab subcutaneous injection), Teszpire® (tezepelumab-ekko subcutaneous injection), or Xolair® (omalizumab subcutaneous injection).

4. **Eosinophilic Esophagitis, Eosinophilic Gastroenteritis, or Eosinophilic Colitis.** Nucala is not indicated for the treatment of eosinophilic esophagitis, eosinophilic gastroenteritis or eosinophilic colitis.[1] A few small studies reported IV mepolizumab to be efficacious in these conditions.[25-27] Of note, Nucala is not approved for IV administration.[1] One randomized, double-blind trial (n = 66) evaluated the efficacy of Nucala in patients with EoE.[28] Following 3 months of therapy, there was no statistically significant improvement in dysphagia symptoms with Nucala vs. placebo, as measured by the EoE Symptom Activity Index (EEsAI) [primary endpoint]. The EEsAI was also not significantly different between the two treatment groups at 6 months of treatment. However, significantly more patients achieved a histologic response (i.e., < 15 eosinophils/high-power field) with Nucala compared with placebo. Guidelines for the management of eosinophilic esophagitis from the American Gastroenterological Association (AGA) and the Joint Task Force on Allergy-Immunology Practice Parameters (2020) only recommend using anti-interleukin-5 therapies in the context of a clinical trial.[29] Further research is warranted to determine if Nucala has a place in therapy in the treatment of these conditions.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual Revision	**Conditions not recommended for approval:** Criteria were updated to clarify that use of Nucala with another monoclonal antibody therapy is specific to Cinqair, Fasenra, Dupixent, Tezspire, Xolair, and Adbry.	03/22/2023
Selected Revision	**Chronic Rhinosinusitis with Nasal Polyps:** Approval condition updated from "Nasal Polyps" to "Chronic Rhinosinusitis with Nasal Polyps". Duration of the intranasal corticosteroid requirement was changed from 3 months to 4 weeks.	02/14/2024
Annual Revision	**Asthma:** Removed leukotriene receptor antagonists as an example of additional asthma controller or asthma maintenance medications.	04/19/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immunologicals – Tezspire Utilization Management Medical Policy
- Tezspire® (tezepelumab-ekko subcutaneous injection – AstraZeneca/Amgen)

REVIEW DATE: 02/14/2024

OVERVIEW

Tezspire, a thymic stromal lymphopoietin (TSLP) blocker, is indicated as add-on maintenance treatment of patients ≥ 12 years of age with **severe asthma**.[1]

Clinical Efficacy

Tezspire has been studied in patients ≥ 12 years of age with severe asthma.[2] The patients enrolled in the Phase III pivotal Tezspire trial had experienced two or more asthma exacerbations in the previous year, despite treatment with a medium- or high-dose inhaled corticosteroid (ICS) and one additional controller medication (e.g., long-acting beta$_2$-agonist [LABA], leukotriene antagonist).[2,3] In one study, 6 months of these previous therapies were required for enrollment, while in another, 12 months of ICS therapy with at least 3 months of additional controller therapy was required. In these trials, asthma exacerbation data was evaluated following 52 weeks of treatment. However, improvements in lung function parameters and symptom scores were reported as early as the first post-baseline assessment (i.e., 2 weeks of therapy).

Guidelines

The Global Initiative for Asthma Global Strategy for Asthma Management and Prevention (2023) proposes a stepwise approach to asthma treatment.[4] The majority of patients can be managed with an ICS with or without a LABA and/or additional controller. Tezspire is listed as an option for add-on therapy in patients ≥ 12 years of age with difficult-to-treat, severe asthma. Higher blood eosinophil levels and higher fractional exhaled nitric oxide may predict a good asthma response to Tezspire.

According to the European Respiratory Society/American Thoracic Society guidelines (2014; updated in 2020), severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which remains uncontrolled despite this therapy.[5,6] Uncontrolled asthma is defined as asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids or asthma that meets one of the following four criteria:

1) Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 or Asthma Control Test < 20;
2) Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year;
3) Serious exacerbations: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year;
4) Airflow limitation: forced expiratory volume in 1 second (FEV_1) < 80% predicted after appropriate bronchodilator withholding.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Tezspire. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tezspire as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Tezspire to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tezspire is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. Asthma. Approve Tezspire for the duration noted if the patient meets one of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, and iv):

i. Patient is ≥ 12 years of age; AND

ii. Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):

a) An inhaled corticosteroid; AND

b) At least one additional asthma controller or asthma maintenance medication; AND
Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting beta$_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, and monoclonal antibody therapies for asthma (e.g., Tezspire, Cinqair [reslizumab intravenous infusion], Fasenra [benralizumab subcutaneous injection], Nucala [mepolizumab subcutaneous injection]), Dupixent [dupilumab subcutaneous injection], Xolair [omalizumab subcutaneous injection]). Use of a combination inhaler containing both an inhaled corticosteroid and additional asthma controller/maintenance medication(s) would fulfill the requirement for both criteria a and b.

iii. Patient has asthma that is uncontrolled or was uncontrolled at baseline as defined by ONE of the following (a, b, c, d, or e):
Note: "Baseline" is defined as prior to receiving Tezspire or another monoclonal antibody therapy for asthma. Examples of monoclonal antibody therapies for asthma include Cinqair, Dupixent, Fasenra, Nucala, Tezspire, and Xolair.

a) Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR

b) Patient experienced one or more asthma exacerbation(s) requiring a hospitalization, an emergency department visit, or an urgent care visit in the previous year; OR

c) Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR

d) Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR

e) Patient has asthma that worsens upon tapering of oral (systemic) corticosteroid therapy; AND

iv. The medication is prescribed by or in consultation with an allergist, immunologist, or pulmonologist.

B) Patient is Currently Receiving Tezspire. Approve for 1 year if the patient meets the following (i, ii, and iii):
- **i.** Patient has already received at least 6 months of therapy with Tezspire; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with Tezspire should be considered under criterion 1A (Asthma, Initial Therapy).
- **ii.** Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination inhaler; AND
- **iii.** Patient has responded to therapy as determined by the prescriber.
  Note: Examples of a response to Tezspire therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, emergency department, urgent care, or medical clinic visits due to asthma; improved lung function parameters; and/or a decreased requirement for oral corticosteroid therapy.

Dosing. Approve 210 mg given subcutaneously once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tezspire is not recommended in the following situations:

1. **Atopic Dermatitis.** Tezspire is not indicated for the treatment of atopic dermatitis.[1] One Phase IIa study, ALLEVIAD (published) [n = 113] evaluated the efficacy of Tezspire in combination with topical corticosteroids (TCS) vs. placebo in adults with moderate to severe atopic dermatitis.[7] At Week 12, a larger proportion of patients in the Tezspire + TCS group achieved a 50% reduction in the Eczema Area and Severity Index (primary efficacy endpoint) compared with placebo + TCS. However, this treatment difference was not statistically significant. Another Phase II, dose-ranging study in patients with atopic dermatitis was terminated prior to completion.[8]

2. **Chronic Obstructive Pulmonary Disease (COPD).** Tezspire is not indicated for the treatment of COPD.[1] One Phase II, randomized, double-blind, placebo-controlled trial, COURSE, is currently underway evaluating the efficacy of Tezspire in patients with moderate- to very severe-COPD who are continuing to experience exacerbations despite triple inhaled maintenance therapy (i.e., ICS/LABA/long-acting muscarinic antagonist).[8] Results are not yet available.

3. **Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP).** Tezspire is not indicated for the treatment of CRSwNP.[1] One Phase III, randomized, double-blind, placebo-controlled trial, WAYPOINT, is currently underway evaluating the efficacy of Tezspire in adults with severe CRSwNP.[8] Results are not yet available. A post-hoc analysis of one of the Tezspire pivotal asthma studies, showed an improvement in sino-nasal symptoms with Tezspire in patients with concomitant asthma and CRSwNP.[9,] These results supported the need for the Phase III study to confirm any benefits.

4. **Chronic Spontaneous Urticaria**. Tezspire is not indicated for the treatment of chronic spontaneous urticaria.[1] One Phase II, randomized, double-blind, placebo-controlled trial, INCEPTION, evaluated the efficacy of Tezspire in patients with chronic spontaneous urticaria.[8] Results are not yet available.

5. **Concurrent use of Tezspire with another Monoclonal Antibody Therapy.** The efficacy and safety of Tezspire used in combination with other monoclonal antibody therapies have not been established.
   Note: Monoclonal antibody therapies are Adbry® (tralokinumab-ldrm subcutaneous [SC] injection), Cinqair® (reslizumab intravenous injection), Dupixent® (dupilumab SC injection), Fasenra®

(benralizumab SC injection), Nucala® (mepolizumab SC injection), or Xolair® (omalizumab SC injection).

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Conditions not recommended for approval:** For "Concurrent use of Tezspire with another Monoclonal Antibody Therapy", the condition was updated to specify that "other monoclonal antibody therapy" is defined as "Cinqair, Dupixent, Fasenra, Nucala, Xolair, and Adbry". There were no other changes to the criteria.	02/08/2023
Annual Revision	No criteria changes.	02/14/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immunologicals – Xolair Utilization Management Medical Policy
- Xolair® (omalizumab subcutaneous injection – Genentech/Novartis)

REVIEW DATE: 03/07/2024

OVERVIEW

Xolair, an anti-immunoglobulin (Ig)E monoclonal antibody, is indicated for the following uses:[1]

- **Asthma,** in patients ≥ 6 years of age with moderate to severe persistent disease who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids (ICSs). Xolair has been shown to decrease the incidence of asthma exacerbations in these patients. Limitations of Use: Xolair is not indicated for the relief of acute bronchospasm or status asthmaticus. It is also not indicated for the treatment of other allergic conditions.
- **Chronic idiopathic urticaria**, in patients ≥ 12 years of age who remain symptomatic despite H1 antihistamine treatment. Limitation of Use: Xolair is not indicated for the treatment of other forms of urticaria.
- **Chronic rhinosinusitis with nasal polyps** (CRSwNP), as add-on maintenance treatment in patients ≥ 18 years of age with an inadequate response to nasal corticosteroids.
- **IgE-mediated food allergy**, in patients ≥ 1 year of age, for the reduction of allergic reactions (Type I), including anaphylaxis, that may occur with accidental exposure to one or more foods. Xolair is to be used in conjunction with food allergen avoidance. Limitation of Use: Xolair is not indicated for the emergency treatment of allergic reactions, including anaphylaxis.

Dosing of Xolair for the treatment of asthma or nasal polyps is based on body weight and the serum total IgE level measured before the start of treatment.[1] Dosing for these indications is only provided for patients with a pretreatment serum IgE level ≥ 30 IU/mL. Dosing of Xolair in patients with chronic idiopathic urticaria is not dependent on serum IgE level or body weight.

Clinical Efficacy

Timing of efficacy assessments varied by indication across the numerous pivotal studies in which Xolair demonstrated benefit. In the majority of the asthma trials, efficacy with Xolair was assessed as early as 16 weeks.[1-11] In chronic idiopathic urticaria, one of the studies included a 12-week double-blind treatment period, while the other was longer with 24 weeks of double-blind treatment.[12,13] Across both studies evaluating Xolair in nasal polyps, efficacy was evaluated at Week 24.[14] Patients continued treatment with intranasal corticosteroids throughout the study. In the pivotal study of Xolair for food allergy, patients were required to have a positive skin prick test response to a food and to have a positive IgE test to food.[15] Patients were provided with an epinephrine auto-injector throughout the study.

Guidelines

Asthma Guidelines

The Global Initiative for Asthma Global Strategy for Asthma Management and Prevention (2023) proposes a step-wise approach to asthma treatment.[16] Xolair is listed as an option for add-on therapy in patients ≥ 6 years of age with difficult-to-treat, severe eosinophilic asthma (i.e., patients with symptoms and/or exacerbations despite medium- or high-dose ICS/long-acting beta2-agonist [LABA] or who require maintenance oral corticosteroid). Allergy-driven symptoms and childhood-onset asthma may predict a good asthma response to Xolair.

According to the European Respiratory Society/American Thoracic Society guidelines (2014; updated in 2020), severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which remains uncontrolled despite this therapy.[17,18] Uncontrolled asthma is defined as asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids or asthma that meets one of the following four criteria:

1) Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 or Asthma Control Test < 20;
2) Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year;
3) Serious exacerbations: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year;
4) Airflow limitation: forced expiratory volume in 1 second (FEV_1) < 80% predicted after appropriate bronchodilator withholding.

Chronic Urticaria Guidelines

Guidelines for the definition, classification, diagnosis, and management of urticaria have been published by the European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/Asia Pacific Association of Allergy, Asthma and Clinical Immunology (2022).[19] The American Academy of Dermatology was involved in the development of these guidelines and endorses their recommendations. Chronic spontaneous urticaria is defined as the appearance of wheals, angioedema, or both for > 6 weeks due to known or unknown causes. Signs and symptoms may be present daily/almost daily or have an intermittent recurrent course. Second generation H1-antihistamines taken regularly are the recommended first-line treatment for all types of urticaria following elimination of possible underlying causes. If standard doses do not eliminate urticaria signs and symptoms, the dose of the antihistamine should be increased up to 4-fold. If symptoms persist following 2 to 4 weeks of antihistamine therapy, the addition of Xolair may be considered. For patients with refractory chronic urticaria, the addition of Xolair may be considered. Short courses of rescue systemic corticosteroids are recommended for treatment of patients with acute exacerbations of chronic urticaria. However, guidelines recommend against the long-term use of systemic steroids.

Chronic Rhinosinusitis with Nasal Polyps Guidelines

The Joint Task Force on Practice Parameters (JTFPP) published a focused guideline update for the medical management of CRSwNP (2023), which updated recommendations regarding intranasal corticosteroids and biologic therapies.[20] Intranasal corticosteroids are recommended for the treatment of CRSwNP. Use of biologics (e.g., Xolair) are also recommended. However, in patients who derived a sufficient benefit from other therapies such as intranasal corticosteroids, surgery, or aspirin therapy after desensitization, biologics may not be preferred. Conversely, biologics may be preferred over other medical treatment options in patients who continue to have a high burden of disease despite receiving at least 4 weeks of treatment with an intranasal corticosteroid.

The diagnosis of CRSwNP was not addressed in this focused guideline update. Previous guidelines have noted that the presence of two or more signs and symptoms of chronic rhinosinusitis (e.g., rhinorrhea, postnasal drainage, anosmia, nasal congestion, facial pain, headache, fever, cough, and purulent discharge) that persist for an extended period of time makes the diagnosis of chronic rhinosinusitis likely.[21-24] However, this requires confirmation of sinonasal inflammation, which can either be done via direct visualization or computed tomography (CT) scan. Oral corticosteroids and surgical intervention were not specifically addressed in this update. Prior guidelines recommend short courses of oral corticosteroid as needed and consideration of surgical removal as an adjunct to medical therapy in patients with CRSwNP that is not responsive or is poorly responsive to medical therapy.[21,22,24]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Xolair. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the durations noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Xolair, as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Xolair to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xolair is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1) Asthma. Approve Xolair for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets ALL of the following (i, ii, iii, iv, v, and vi):

i. Patient is ≥ 6 years of age; AND

ii. Patient has a baseline immunoglobulin E (IgE) level ≥ 30 IU/mL; AND
Note: "Baseline" is defined as prior to receiving any treatment with Xolair or another monoclonal antibody therapy that may lower IgE levels (e.g., Dupixent [dupilumab subcutaneous injection], Tezspire [tezepelumab-ekko subcutaneous injection]).

iii. Patient has a baseline positive skin test or *in vitro* test (i.e., a blood test) for allergen-specific immunoglobulin E (IgE) for one or more perennial aeroallergens and/or for one or more seasonal aeroallergens; AND
Note: "Baseline" is defined as prior to receiving any Xolair or another monoclonal antibody therapy that may interfere with allergen testing (e.g., Dupixent and Tezspire). Examples of perennial aeroallergens are house dust mite, animal dander, cockroach, feathers, and mold spores. Examples of seasonal aeroallergens are grass, pollen, and weeds.

iv. Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):

a) An inhaled corticosteroid; AND

b) At least one additional asthma controller or asthma maintenance medication; AND

Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting beta$_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, and monoclonal antibody therapies for asthma (e.g., Xolair, Cinqair [reslizumab intravenous infusion], Dupixent, Fasenra [benralizumab subcutaneous injection], Nucala [mepolizumab subcutaneous injection], and Tezspire). Use of a combination inhaler containing both an inhaled corticosteroid and additional asthma controller/maintenance medication(s) would fulfil the requirement for both criteria a and b.

v. Patient has asthma that is uncontrolled or was uncontrolled at baseline as defined by ONE of the following (a, b, c, d, or e):
Note: "Baseline" is defined as prior to receiving Xolair or another monoclonal antibody therapy for asthma. Examples of monoclonal antibody therapies for asthma include Cinqair, Dupixent, Fasenra, Nucala, Tezspire, and Xolair.
- **a)** Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR
- **b)** Patient experienced one or more asthma exacerbation(s) requiring a hospitalization, an emergency department visit, or an urgent care visit in the previous year; OR
- **c)** Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR
- **d)** Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR
- **e)** Patient has asthma that worsens upon tapering of oral corticosteroid therapy; AND

vi. The medication is prescribed by or in consultation with an allergist, immunologist, or pulmonologist.

B) Patient is Currently Receiving Xolair. Approve Xolair for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has already received at least 4 months of therapy with Xolair; AND
Note: A patient who has received < 4 months of therapy or who is restarting therapy with Xolair should be considered under criterion 1A (Asthma, Initial Therapy).

ii. Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination inhaler; AND

iii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Xolair therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, emergency department/urgent care, or medical clinic visits due to asthma; decreased reliever/rescue medication use; and improved lung function parameters.

Dosing. Approve up to a maximum dose of 375 mg administered subcutaneously not more frequently than once every 2 weeks.

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2) Chronic Idiopathic Urticaria (Chronic Spontaneous Urticaria). Approve Xolair for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 12 years of age; AND

ii. Patient has/had urticaria for > 6 weeks (prior to treatment with Xolair), with symptoms present > 3 days per week despite daily non-sedating H_1 antihistamine therapy with doses that have been titrated up to a maximum of four times the standard FDA-approved dose; AND
Note: Examples of non-sedating H_1 antihistamine therapy are cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine.

iii. The medication is prescribed by or in consultation with an allergist, immunologist, or dermatologist.

B) Patient is Currently Receiving Xolair. Approve Xolair for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has already received at least 4 months of therapy with Xolair; AND
Note: A patient who has received < 4 months of therapy or who is restarting therapy with Xolair should be considered under criterion 2A (Chronic Idiopathic Urticaria, Initial Therapy).

ii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Xolair therapy are decreased severity of itching, decreased number and/or size of hives.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) 150 mg administered subcutaneously once every 4 weeks; OR

B) 300 mg administered subcutaneously once every 4 weeks.

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3) Chronic Rhinosinusitis with Nasal Polyps. Approve Xolair for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):

i. Patient is ≥ 18 years of age; AND

ii. Patient has chronic rhinosinusitis with nasal polyps as evidenced by direct examination, endoscopy, or sinus computed tomography (CT) scan; AND

iii. Patient has experienced two or more of the following symptoms for at least 6 months: nasal congestion, nasal obstruction, nasal discharge, and/or reduction/loss of smell; AND

iv. Patient has a baseline immunoglobulin E (IgE) level ≥ 30 IU/mL; AND
Note: "Baseline" is defined as prior to receiving any treatment with Xolair or another monoclonal antibody therapy that may lower IgE levels (e.g., Dupixent [dupilumab subcutaneous injection], Tezspire [tezepelumab-ekko subcutaneous injection]).

v. Patient meets BOTH of the following (a and b):

a) Patient has received at least 4 weeks of therapy with an intranasal corticosteroid; AND

b) Patient will continue to receive therapy with an intranasal corticosteroid concomitantly with Xolair; AND

vi. Patient meets ONE of the following (a, b, or c):

a) Patient has received at least one course of treatment with a systemic corticosteroid for 5 days or more within the previous 2 years; OR

b) Patient has a contraindication to systemic corticosteroid therapy; OR

c) Patient has had prior surgery for nasal polyps; AND

vii. The medication is prescribed by or in consultation with an allergist, immunologist, or an otolaryngologist (ear, nose, and throat [ENT] physician specialist).

B) Patient is currently receiving Xolair. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has already received at least 6 months of therapy with Xolair; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Xolair should be considered under criterion 3A (Nasal Polyps, Initial Therapy).

ii. Patient continues to receive therapy with an intranasal corticosteroid; AND

iii. Patient has responded to Xolair therapy as determined by the prescriber.

Note: Examples of a response to Xolair therapy are reduced nasal polyp size, improved nasal congestion, reduced sinus opacification, decreased sino-nasal symptoms, and/or improved sense of smell.

Dosing. Approve up to a maximum dose of 600 mg administered subcutaneously not more frequently than once every 2 weeks.

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4) Immunoglobulin (Ig)E-Mediated Food Allergy. Approve Xolair for 1 year if the patient meets ALL of the following (A, B, C, D, E, F, and G):

A) Patient is ≥ 1 year of age; AND

B) Patient has a baseline immunoglobulin (Ig)E level ≥ 30 IU/mL; AND
Note: "Baseline" is defined as prior to receiving any treatment with Xolair or another monoclonal antibody therapy that may lower IgE levels (e.g., Dupixent [dupilumab subcutaneous injection], Tezspire [tezepelumab-ekko subcutaneous injection]).

C) Patient meets BOTH of the following (i and ii):
- **i.** Patient has a positive skin prick test (SPT) response to one or more foods; AND
- **ii.** Patient has a positive *in vitro* test (i.e., a blood test) for IgE to one or more foods; AND

D) According to the prescriber, the patient has a history of an allergic reaction to a food that met each of the following (i, ii, and iii):
- **i.** Patient demonstrated signs and symptoms of a significant systemic allergic reaction; AND
  Note: Signs and symptoms of a significant systemic allergic reaction include hives, swelling, wheezing, hypotension, and gastrointestinal symptoms.
- **ii.** This reaction occurred within a short period of time following a known ingestion of the food; AND
- **iii.** The prescriber deemed this reaction significant enough to require a prescription for an epinephrine auto-injector; AND
  Note: Examples of epinephrine auto-injectors include EpiPen, EpiPen Jr., Auvi-Q, and generic epinephrine auto-injectors.

E) Patient has been prescribed an epinephrine auto-injector; AND
Note: Examples of epinephrine auto-injectors include EpiPen, EpiPen Jr., Auvi-Q, and generic epinephrine auto-injectors.

F) According the prescriber, Xolair will be used in conjunction with a food allergen-avoidant diet; AND

G) The medication is prescribed by or in consultation with an allergist or immunologist.

Dosing. Approve up to a maximum dose of 600 mg administered subcutaneously not more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xolair is not recommended in the following situations:

1. **Atopic Dermatitis.** One single-center, double-blind, placebo-controlled trial, Atopic Dermatitis Anti-IgE Pediatric Trial (ADAPT) evaluated the efficacy of Xolair in patients 4 to 19 years of age with severe atopic dermatitis (n = 62).[25] After 24 weeks of therapy, the difference in the objective Scoring Atopic Dermatitis [SCORAD] index with Xolair vs. placebo was -6.9 (P = 0.01). This was statistically significant; however, the clinical significance is unknown. Quality of life measurements were also improved with Xolair. Smaller studies have not shown benefit and case studies have yielded mixed

results.[25-27] Additional larger, well-designed clinical trials are needed to determine if Xolair has a role in the treatment of atopic dermatitis. Atopic dermatitis guidelines from the American Academy Dermatology (2023) note that there are insufficient data to make a recommendation regarding the use of Xolair.[28]

2. **Concurrent use of Xolair with another Monoclonal Antibody Therapy.** The efficacy and safety of Xolair used in combination with other monoclonal antibody therapies have not been established. There are very limited case reports describing the combined use of Nucala and Xolair for severe asthma as well as off-label indications.[29-32] One limited case series also reported the use of Xolair and Dupixent in patients with asthma or chronic idiopathic urticaria.[33] Further investigation is warranted.
   Note: Monoclonal antibody therapies are Adbry® (tralokinumab-ldrm subcutaneous injection), Cinqair® (reslizumab intravenous infusion), Dupixent® (dupilumab subcutaneous injection), Fasenra® (benralizumab subcutaneous injection), Nucala® (mepolizumab subcutaneous injection), or Teszpire® (tezepelumab-ekko subcutaneous injection).

3. **Eosinophilic Gastroenteritis, Eosinophilic Esophagitis, or Eosinophilic Colitis.** There are limited and conflicting data from very small studies and case series on the use of Xolair for the treatment of eosinophilic gastrointestinal conditions.[34-37] Guidelines for the management of eosinophilic esophagitis from the American Gastroenterological Association and the Joint Task Force on Allergy-Immunology Practice Parameters (2020) recommend against the use of Xolair in patients with this condition.[38]

4. **Latex Allergy in Health Care Workers with Occupational Latex Allergy.** A small European study assessed the effects of Xolair treatment in health care workers (n = 18) with occupational latex allergy.[39] Xolair use in these patients resulted in a reduction in mean conjunctival challenge test scores as compared with placebo-treated patients after 16-weeks of therapy. Also, three patients who did not respond to Xolair treatment during the double-blind phase responded during the 16-week open-label phase. Thus, the overall ocular response rate for all patients in the open-label phase was 93.8% (n = 15/16). Also 11 of 15 patients in the open-label phase had a negative response to a latex glove challenge test (4 patients had a mild response). Well-controlled trials are needed.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Conditions Not Recommended for Approval:** Criteria were updated to clarify that use of Xolair with another monoclonal antibody therapy is specific to Cinqair, Fasenra, Nucala, Dupixent, Tezspire, and Adbry.	03/22/2023
Selected Revision	**Chronic Rhinosinusitis with Nasal Polyps:** Approval condition updated from "Nasal Polyps" to "Chronic Rhinosinusitis with Nasal Polyps". Duration of the intranasal corticosteroid requirement was changed from 3 months to 4 weeks.	02/14/2024
Early Annual Revision	**IgE-Mediated Food Allergy:** New approval criteria for this indication were added. **Conditions Not Recommended for Approval:** "Peanut and Other Food Allergies" was removed as a Condition Not Recommended for Approval.	03/06/2024 and 03/07/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Inflammatory Conditions – Cimzia Utilization Management Medical Policy
- Cimzia® (certolizumab pegol subcutaneous injection [lyophilized powder or solution] – UCB)

REVIEW DATE: 03/27/2024

OVERVIEW

Cimzia, a tumor necrosis factor inhibitor (TNFi), is indicated for the following uses:[1]
- **Ankylosing spondylitis**, for the treatment of adults with active disease.
- **Crohn's disease**, for reducing signs and symptoms and maintaining clinical responses in adults with moderate to severe active disease who have had an inadequate response to conventional therapy.
- **Non-radiographic axial spondyloarthritis**, in patients with objective signs of inflammation.
- **Plaque psoriasis**, for the treatment of adults with moderately to severely active disease who are candidates for systemic therapy or phototherapy.
- **Psoriatic arthritis**, for the treatment of adult patients with active disease.
- **Rheumatoid arthritis**, for the treatment of adults with moderately to severely active disease.

Cimzia may be used as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).

Dosing Information

Approved induction dosing is 400 mg given subcutaneously at Weeks 0, 2, and 4. For psoriasis, maintenance dosing is 400 mg given every 2 weeks. For other indications, maintenance dosing is generally given as 400 mg subcutaneously per 28-day period. This dose may be administered as a single 200 mg injection given once every 2 weeks or as two 200 mg doses (400 mg dose) given once every 4 weeks. Of note, if a patient who has rheumatoid arthritis is in remission, guidelines from the American College of Rheumatology (ACR) [2021] mention tapering (reducing the dose or dosing frequency) as an option for patients with rheumatoid arthritis who have been at target (low disease activity or remission) for at least 6 months prior to tapering.[6]

Guidelines

TNFis feature prominently in guidelines for treatment of inflammatory conditions.
- **Axial Spondyloarthritis and Spondyloarthritis:** Guidelines for ankylosing spondylitis and non-radiographic axial spondyloarthritis are published by the ACR/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[2] TNFis are recommended for the initial biologic. In those who are secondary nonresponders to a TNFi, a second TNFi is recommended over switching out of the class.
- **Crohn's Disease:** The American College of Gastroenterology has guidelines for Crohn's disease (2018).[3] TNFis are listed as an option for disease that is resistant to corticosteroids, severely active disease, perianal fistulizing disease, and maintenance of remission. In post-operative Crohn's disease, a TNFi should be started within 4 weeks of surgery to prevent recurrence. Guidelines from the American Gastroenterological Association (2021) include TNFis among the therapies for moderate to severe Crohn's disease, for induction and maintenance of remission.[7]

- **Plaque Psoriasis:** Guidelines from the American Academy of Dermatologists and National Psoriasis Foundation (2019) recommend TNFis as a monotherapy treatment option for adults with moderate to severe disease.[4] Based on extrapolation of data, Cimzia is likely to have class characteristics similar to the other TNFis.
- **Psoriatic Arthritis:** Guidelines from ACR (2018) generally recommend treatment with a TNFi over other therapies as initial treatment for patients who are treatment-naïve.[5]
- **Rheumatoid Arthritis:** Guidelines from ACR (2021) recommend addition of a biologic or a targeted synthetic disease modifying anti-rheumatic drug (DMARD) for a patient taking the maximum tolerated dose of methotrexate who is not at target.[6]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Cimzia. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of a patient treated with Cimzia as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Cimzia to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cimzia is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Ankylosing Spondylitis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving Cimzia. Approve for 1 year if the patient meets BOTH of the following (i and ii):
     - **i.** Patient has been established on therapy for at least 6 months; AND
       Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).
     - **ii.** Patient meets at least ONE of the following (a or b):
       - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
         Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

Dosing. Approve ONE of the following regimens (A, B, or C):

A) For Initial Therapy, approve 400 mg as a subcutaneous injection followed by additional similar doses at 2 and 4 weeks after the first injection, then ONE of the following (i or ii):
- **i.** 400 mg administered subcutaneously not more frequently than once every 4 weeks; OR
- **ii.** 200 mg administered subcutaneously no more frequently than once every 2 weeks; OR

B) For Initial or Continuation, approve 400 mg administered subcutaneously not more frequently than once every 4 weeks; OR

C) For Initial or Continuation, approve 200 mg administered subcutaneously not more frequently than once every 2 weeks.

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2. Crohn's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient meets ONE of the following (a, b, c, or d):
  - **a)** Patient has tried or is currently taking corticosteroids, or corticosteroids are contraindicated in this patient; OR
  - **b)** Patient has tried one other conventional systemic therapy for Crohn's disease; OR
    Note: Examples of systemic therapies for Crohn's disease include azathioprine, 6-mercaptopurine, and methotrexate. An exception to the requirement for a trial of or contraindication to steroids or a trial of one other conventional systemic agent can be made if the patient has already tried at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for Crohn's disease. A trial of mesalamine does not count as a systemic agent for Crohn's disease.
  - **c)** Patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas; OR
  - **d)** Patient had ileocolonic resection (to reduce the chance of Crohn's disease recurrence); AND
- **iii.** The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving Cimzia. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on therapy for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).
- **ii.** Patient meets at least ONE of the following (a or b):
  - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
    Note: Examples of objective measures include fecal markers (e.g., fecal lactoferrin, fecal calprotectin), serum markers (e.g., C-reactive protein), imaging studies (magnetic resonance enterography [MRE], computed tomography enterography [CTE]), endoscopic assessment, and/or reduced dose of corticosteroids.
  - **b)** Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or blood in stool.

Dosing. Approve ONE of the following regimens (A, B, or C):

A) For Initial Therapy, approve 400 mg as a subcutaneous injection followed by additional similar doses at 2 and 4 weeks after the first injection, then ONE of the following (i or ii):
- **i.** 400 mg administered subcutaneously not more frequently than once every 4 weeks; OR
- **ii.** 200 mg administered subcutaneously not more frequently than once every 2 weeks; OR

B) For Initial or Continuation, approve 400 mg administered subcutaneously not more frequently than once every 4 weeks; OR

C) For Initial or Continuation, approve 200 mg administered subcutaneously not more frequently than once every 2 weeks.

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3. Non-Radiographic Axial Spondyloarthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
- **i.** Patient has objective signs of inflammation, defined as at least ONE of the following (a or b):
  - **a)** C-reactive protein (CRP) elevated beyond the upper limit of normal for the reporting laboratory; OR
  - **b)** Sacroiliitis reported on magnetic resonance imaging (MRI); AND
- **ii.** The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Cimzia. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on the requested drug for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).
- **ii.** Patient meets at least ONE of the following (a or b):
  - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
    Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).
  - **b)** Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

Dosing. Approve ONE of the following regimens (A, B, or C):

A) For Initial Therapy, approve 400 mg as a subcutaneous injection followed by additional similar doses at 2 and 4 weeks after the first injection, then ONE of the following (i or ii):
- **i.** 400 mg administered subcutaneously not more frequently than once every 4 weeks; OR
- **ii.** 200 mg administered subcutaneously not more frequently than once every 2 weeks; OR

B) For Initial or Continuation, approve 400 mg administered subcutaneously not more frequently than once every 4 weeks; OR

C) For Initial or Continuation, approve 200 mg administered subcutaneously not more frequently than once every 2 weeks.

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4. Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient meets ONE of the following conditions (a or b):
  - **a)** Patient has tried at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR
    Note: Examples of traditional systemic agents for psoriasis include methotrexate, cyclosporine, acitretin tablets, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis.
  - **b)** Patient has a contraindication to methotrexate, as determined by the prescriber; AND
- **iii.** The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Cimzia. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient has been established on the requested drug for at least 3 months; AND
  Note: A patient who has received < 3 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).
- **ii.** Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating the requested drug) in at least one of the following: estimated body surface area affected by psoriasis, erythema, induration/thickness, and/or scale of areas affected by psoriasis; AND
- **iii.** Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, itching, and/or burning.

Dosing. Approve ONE of the following (A or B):

A) For Initial or Continuation, approve 400 mg administered subcutaneously not more frequently than once every 2 weeks; OR

B) For Initial or Continuation, approve 200 mg administered subcutaneously not more frequently than once every 2 weeks.

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5. Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving Cimzia. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on the requested drug for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).
- **ii.** Patient meets at least ONE of the following (a or b):
  - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
    Note: Examples of standardized measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds

Enthesitis Score (LEI), Spondyloarthritis Consortuium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

Dosing. Approve ONE of the following regimens (A, B, or C):

A) For Initial Therapy, approve 400 mg as a subcutaneous injection followed by additional similar doses at 2 and 4 weeks after the first injection, then ONE of the following (i or ii):
- **i.** 400 mg administered subcutaneously not more frequently than once every 4 weeks; OR
- **ii.** 200 mg administered subcutaneously not more frequently than once every 2 weeks; OR

B) For Initial or Continuation, approve 400 mg administered subcutaneously not more frequently than once every 4 weeks; OR

C) For Initial or Continuation, approve 200 mg administered subcutaneously not more frequently than once every 2 weeks.

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6. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
- **i.** Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND
  Note: Examples of conventional synthetic DMARDs include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already had a 3-month trial of at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic for rheumatoid arthritis is not required to "step back" and try a conventional synthetic DMARD.
- **ii.** The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Cimzia. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on the requested drug for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).
- **ii.** Patient meets at least ONE of the following (a or b):
  - **a)** Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
    Note: Examples of standardized and validated measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).
  - **b)** Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

Dosing. Approve ONE of the following regimens (A, B, or C):

A) For Initial Therapy, approve 400 mg as a subcutaneous injection followed by additional similar doses at 2 and 4 weeks after the first injection, then ONE of the following (i or ii):
- **i.** 400 mg administered subcutaneously not more frequently than once every 4 weeks; OR
- **ii.** 200 mg administered subcutaneously not more frequently than once every 2 weeks; OR

B) For Initial or Continuation, approve 400 mg administered subcutaneously not more frequently than once every 4 weeks; OR

C) For Initial or Continuation, approve 200 mg administered subcutaneously not more frequently than once every 2 weeks.

Other Uses with Supportive Evidence

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7. Spondyloarthritis, Other Subtypes. Approve for the duration noted if the patient meets ONE of the following conditions (A or B):
Note: Examples of other subtypes of spondyloarthritis include undifferentiated arthritis and reactive arthritis (Reiter's disease). For ankylosing spondylitis, psoriatic arthritis, or non-radiographic axial spondyloarthritis, refer to the respective criteria under FDA-approved indications.

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient has arthritis primarily in the knees, ankles, elbows, wrists, hands, and/or feet; AND
- **ii.** Patient has tried at least ONE conventional synthetic disease-modifying antirheumatic drug (DMARD); AND
  Note: Examples include methotrexate, leflunomide, and sulfasalazine.
- **iii.** The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Cimzia. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on the requested drug for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).
- **ii.** Patients meets at least ONE of the following (a or b):
  - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
    Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS) and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).
  - **b)** Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

Dosing. Approve ONE of the following regimens (A, B, or C):

A) For Initial Therapy, approve 400 mg as a subcutaneous injection followed by additional similar doses at 2 and 4 weeks after the first injection, then ONE of the following (i or ii):
- **i.** 400 mg administered subcutaneously not more frequently than once every 4 weeks; OR
- **ii.** 200 mg administered subcutaneously not more frequently than once every 2 weeks; OR

B) For Initial or Continuation, approve 400 mg administered subcutaneously not more frequently than once every 4 weeks; OR

C) For Initial or Continuation, approve 200 mg administered subcutaneously not more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cimzia is not recommended in the following situations:

1. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Cimzia should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see Appendix for examples). Combination therapy is generally not recommended due to a potentially higher rate of AEs with combinations and lack of data supportive of additional efficacy.
   Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Cimzia.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/05/2023
Annual Revision	**Plaque Psoriasis:** For a patient currently taking Cimzia, the timeframe for established on therapy was changed from 90 days to 3 months.	03/27/2024

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Zymfentra® (infliximab-dyyb SC injection)	Inhibition of TNF	CD, UC
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA, PMR
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17RA	PsO
Bimzelx® (bimekizumab-bkzx SC injection)	Inhibition of IL-17A and IL-17F	PsO
Cosentyx® (secukinumab SC injection, secukinumab IV infusion)	Inhibition of IL-17A	SC formulation: AS, ERA, nr-axSpA, PsO, PsA
		IV formulation: AS, nr-axSpA, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Omvoh® (mirikizumab-mrkz SC injection, mirikizumab-mrkz IV infusion)	Inhibition of IL-23	UC
Skyrizi® (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion)	Inhibition of IL-23	SC formulation: CD, PSA, PsO
		IV formulation: CD
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion, vedolizimab SC injection)	Integrin receptor antagonist	SC formulation: UC
		IV formulation: CD, UC
Oral Therapies/Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Cibinqo™ (abrocitinib tablets)	Inhibition of JAK pathways	AD
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	AD, AS, nr-axSpA, RA, PsA, UC
Sotyktu™ (deucravacitinib tablets)	Inhibition of TYK2	PsO
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC
Velsipity® (etrasimod tablets)	Sphingosine 1 phosphate receptor modulator	UC
Zeposia® (ozanimod tablets)	Sphingosine 1 phosphate receptor modulator	UC

* Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; PMR – Polymyalgia rheumatic; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Inflammatory Conditions – Cosentyx Intravenous Utilization Management Medical Policy
- Cosentyx® (secukinumab intravenous infusion – Novartis)

REVIEW DATE: 11/01/2023

OVERVIEW

Cosentyx intravenous, an interleukin (IL)-17A antagonist, is indicated in the following conditions:[1]
- **Psoriatic arthritis**, in adults with active disease.
- **Ankylosing spondylitis**, in adults with active disease.
- **Non-radiographic axial spondyloarthritis**, in adults with active disease and objective signs of inflammation.

In the pivotal trial for non-radiographic axial spondyloarthritis, patients were required to have objective signs of inflammation, indicated by elevated C-reactive protein and/or sacroiliitis on magnetic resonance imaging.

Dosing Information

For approved uses, Cosentyx intravenous may be given with or without a single 6 mg/kg loading dose. The maintenance dose is 1.75 mg/kg given intravenously once every 4 weeks.

Guidelines

The intravenous formulation of Cosentyx has not been addressed in any guidelines. However, Il-17 blockers, including the subcutaneous formulation of Cosentyx, are mentioned in guidelines for treatment of inflammatory conditions.
- **Ankylosing Spondylitis and Non-Radiographic Axial Apondyloarthritis:** Guidelines for ankylosing spondylitis and non-radiographic axial spondyloarthritis are published by the ACR/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[2] Following primary nonresponse to a TNFi, either Cosentyx or Taltz® (ixekizumab injection) is recommended; however, if the patient is a secondary nonresponder, a second TNFi is recommended over switching out of the class. In patients with a contraindication to a TNFi, use of an IL-17 blocker is recommended over traditional oral agents such as methotrexate or sulfasalazine.
- **Psoriatic Arthritis:** Guidelines from the American College of Rheumatology (ACR)/National Psoriasis Foundation (2018) generally recommend TNFis as the first-line treatment strategy over other biologics (e.g., IL-17 blockers) with differing mechanisms of action.[3]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Cosentyx intravenous. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cosentyx intravenous as well as the monitoring

required for adverse events and long-term efficacy, initial approval requires Cosentyx intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cosentyx intravenous is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. Ankylosing Spondylitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Cosentyx Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on Cosentyx intravenous or subcutaneous for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with Cosentyx intravenous or subcutaneous is reviewed under criterion A (Initial Therapy).
- **ii.** Patient meets at least ONE of the following (a or b):
  - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Cosentyx intravenous or subcutaneous); OR
    Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).
  - **b)** Compared with baseline (prior to initiating Cosentyx intravenous or subcutaneous), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

Dosing. Approve the following dosing regimens (A or B):

A) A single 6 mg/kg intravenous loading dose followed by 1.75 mg/kg (up to a maximum of 300 mg per dose) given once every 4 weeks thereafter, up to a maximum of 300 mg per dose; OR

B) 1.75 mg/kg (up to a maximum of 300 mg per dose) given intravenously once every 4 weeks.

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2. Non-Radiographic Axial Spondyloarthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has objective signs of inflammation, defined as at least ONE of the following (a or b):
  - **a)** C-reactive protein elevated beyond the upper limit of normal for the reporting laboratory; OR

b) Sacroiliitis reported on magnetic resonance imaging; AND

iii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Cosentyx Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on Cosentyx intravenous or subcutaneous for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with Cosentyx intravenous or subcutaneous is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Cosentyx intravenous or subcutaneous); OR

Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating Cosentyx intravenous or subcutaneous), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

Dosing. Approve the following dosing regimens (A or B):

A) A single 6 mg/kg intravenous loading dose followed by 1.75 mg/kg (up to a maximum of 300 mg per dose) given once every 4 weeks thereafter, up to a maximum of 300 mg per dose; OR

B) 1.75 mg/kg (up to a maximum of 300 mg per dose) given intravenously once every 4 weeks.

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3. Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets both of the following (i and ii):

i. Patient is ≥ 18 years of age; AND

ii. The medication is prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving Cosentyx Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on Cosentyx intravenous or subcutaneous for at least 6 months; AND

Note: A patient who has received < 6 months of therapy with Cosentyx intravenous or subcutaneous or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Cosentyx intravenous or subcutaneous); OR

Note: Examples of standardized measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating Cosentyx intravenous or subcutaneous), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

Dosing. Approve the following dosing regimens (A or B):

A) A single 6 mg/kg intravenous loading dose followed by 1.75 mg/kg (up to a maximum of 300 mg per dose) given once every 4 weeks thereafter, up to a maximum of 300 mg per dose; OR

B) 1.75 mg/kg (up to a maximum of 300 mg per dose) given intravenously once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cosentyx intravenous is not recommended in the following situations:

1. **Concurrent Use with other Biologics or Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs).** Cosentyx intravenous should not be administered in combination with another biologic or targeted synthetic DMARD used for an inflammatory condition (See Appendix for examples). Combination therapy is generally not recommended due to the potential for a higher rate of adverse effects with combination therapies and lack of evidence for additive efficacy.
   Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Cosentyx intravenous.

2. **Crohn's Disease.** Exacerbations of Crohn's disease, in some cases serious, occurred in clinical trials in patients treated with Cosentyx.[1] In a Phase II published study in patients with Crohn's disease (n = 59), an intravenous formulation of Cosentyx did not reduce the Crohn's disease activity index by ≥ 50 points compared with placebo and the study was terminated prematurely.[4]

3. **Enthesitis-Related Arthritis.** Cosentyx subcutaneous is indicated and has approved dosing regimens for treatment of enthesitis-related arthritis.[1]

4. **Plaque Psoriasis.** Cosentyx subcutaneous is indicated and has approved dosing regimens for treatment of plaque psoriasis.[1]

5. **Rheumatoid Arthritis.** In a published, double-dummy Phase III study, Cosentyx was less effective than current treatments in patients with rheumatoid arthritis who were previously treated with a tumor necrosis factor inhibitor (TNFi).[5] Patients were randomized to one of four treatment groups: 1) induction with an intravenous formulation of Cosentyx (10 mg/kg) followed by Cosentyx 150 mg subcutaneously given once every 4 weeks (Q4W) [n = 137]; 2) secukinumab intravenous induction (10 mg/kg) followed by Cosentyx 75 mg subcutaneously Q4W (n = 138). At Week 24, ACR 20 response was significantly better with Cosentyx 150 mg subcutaneous (31%) and Orencia intravenous (43%) vs. placebo (18%). ACR 20 response with Cosentyx 75 mg was 28%, which was not significantly better than the placebo group. ACR 50/70 responses were 17%/10% with Cosentyx 150 mg and 12%/5% with Cosentyx 75 mg which was not significantly different from that of placebo (9%/5%). The group treated with Orencia intravenous had significantly improved ACR 50/70 responses at Week 24 (28%/12%). Using as observed data, ACR 20/50/70 responses at Week 52 were 63%/46%/19% with Cosentyx 150 mg, 57%/26%/7% with Cosentyx 75 mg, and 75%/52%/23% with Orencia intravenous. There is a published Phase II dose-ranging study (n = 237) evaluating Cosentyx in rheumatoid arthritis.[6-8] The ACR 20 response at Week 16 (using last observation carried forward analysis) was 34%, 46.9%, 46.5%, 53.7% for the 25, 75, 150, and 300 mg doses vs. 36% for placebo; however, this

did not achieve statistical significance. After Week 16, patients who responded to Cosentyx had sustained response through Week 52, with patients on the 150 mg dose having the greatest improvement over time (55% and 40% of patients with ACR 50 and ACR 70 responses, respectively, at Week 52). In another Phase II study, Cosentyx did not achieve higher ACR 20 response rates at Week 12 vs. placebo.[9] There was an open-label treatment period where ACR responses were generally maintained through Week 52. Some patients were treated with an intravenous formulation of secukinumab and generally responded similarly to those treated with Cosentyx subcutaneous. In another Phase II study, an intravenous formulation of secukinumab demonstrated limited efficacy in biologic-naïve patients with rheumatoid arthritis associated with the HLA-DRB1 allele.[10]

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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1. Cosentyx® [prescribing information]. East Hanover, NJ: Novartis; October 2023.
2. Ward MM, Deodhar A, Gensler LS, et al. 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol*. 2019;(10):1599-1613.
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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	11/01/2023

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Zymfentra® (infliximab-dyyb SC injection)	Inhibition of TNF	CD, UC
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA, PMR
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17RA	PsO
Bimzelx® (bimekizumab-bkzx SC injection)	Inhibition of IL-17A and IL-17F	PsO
Cosentyx® (secukinumab SC injection, secukinumab IV infusion)	Inhibition of IL-17A	SC formulation: AS, ERA, nr-axSpA, PsO, PsA
		IV formulation: AS, nr-axSpA, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion)	Inhibition of IL-23	SC formulation: CD, PSA, PsO
		IV formulation: CD
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion, vedolizimab SC injection)	Integrin receptor antagonist	SC formulation: UC
		IV formulation: CD, UC
Oral Therapies/Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Cibinqo™ (abrocitinib tablets)	Inhibition of JAK pathways	AD
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	AD, AS, nr-axSpA, RA, PsA, UC
Sotyktu™ (deucravacitinib tablets)	Inhibition of TYK2	PsO
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; PMR – Polymyalgia rheumatic; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Inflammatory Conditions – Entyvio Intravenous Utilization Management Medical Policy
- Entyvio® (vedolizumab intravenous infusion – Takeda)

REVIEW DATE: 04/24/2024

OVERVIEW

Entyvio intravenous (IV), an integrin receptor antagonist, is indicated for the following uses:[1]
- **Crohn's disease**, in adults with moderately to severely active disease.
- **Ulcerative colitis**, in adults with moderately to severely active disease.

Therapy begins with Entyvio 300 mg IV at Week 0 and Week 2. At Week 6, or at any scheduled Entyvio IV infusion in patients with a clinical response or remission, therapy can be switched to Entyvio SC. The recommended dose of Entyvio SC is 108 mg SC once every 2 weeks. In the pivotal studies evaluating Entyvio, all patients had previously tried corticosteroids and/or conventional agents for Crohn's disease and ulcerative colitis.

Guidelines

Guidelines for the treatment of inflammatory conditions recommend use of Entyvio.
- **Crohn's Disease:** The American College of Gastroenterology (ACG) has updated guidelines (2018) for Crohn's disease.[2] Entyvio is among the recommendations for treatment of patients with moderate to severe disease or moderate to high risk disease (for induction of remission as well as maintenance of this remission). Guidelines from the American Gastroenterological Association (AGA) [2021] include Entyvio among the therapies for moderate to severe Crohn's disease, for induction and maintenance of remission.[5]
- **Ulcerative Colitis:** Updated ACG guidelines for ulcerative colitis (2019) note that the following agents can be used for induction of remission in moderately to severely active disease: Uceris® (budesonide extended-release tablets); oral or intravenous systemic corticosteroids, Entyvio, Xeljanz® (tofacitinib tablets), or tumor necrosis factor inhibitors.[3] Current guidelines for ulcerative colitis from the AGA (2020) include Entyvio among the therapies recommended for moderate to severe disease.[6]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Entyvio intravenous. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Entyvio intravenous as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Entyvio intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Entyvio intravenous is recommended in those who meet one of the following:

FDA-Approved Indications

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1. Crohn's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):
- **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** Patient meets ONE of the following (a, b, c, or d):
    - **a)** Patient has tried or is currently taking systemic corticosteroids, or corticosteroids are contraindicated in this patient; OR
    - **b)** Patient has tried one conventional systemic therapy for Crohn's disease; OR
      Note: Examples of conventional systemic therapy for Crohn's disease include azathioprine, 6-mercaptopurine, or methotrexate. An exception to the requirement for a trial of or contraindication to steroids or a trial of one other conventional systemic agent can be made if the patient has already tried at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for Crohn's disease. These patients who have already received a biologic are not required to "step back" and try another agent. A trial of mesalamine does not count as a systemic therapy for Crohn's disease.
    - **c)** Patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas; OR
    - **d)** Patient had ileocolonic resection (to reduce the chance of Crohn's disease recurrence); AND
  - **iii.** The medication is prescribed by or in consultation with a gastroenterologist.
- **B)** Patient is Currently Receiving Entyvio Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):
  - **i.** Patient has been established on the requested drug for at least 6 months; AND
    Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).
  - **ii.** Patient meets at least ONE of the following (a or b):
    - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
      Note: Examples of objective measures include fecal markers (e.g., fecal lactoferrin, fecal calprotectin), serum markers (e.g., C-reactive protein), imaging studies (magnetic resonance enterography [MRE], computed tomography enterography [CTE]), endoscopic assessment, and/or reduced dose of corticosteroids.
    - **b)** Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or blood in stool.

Dosing. Approve the following dosage regimen (A and B):
- **A)** The dose is 300 mg as an intravenous infusion at Weeks 0, 2, and 6; AND
- **B)** Subsequent doses are separated by at least 8 weeks.

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2. Ulcerative Colitis. Approve for the duration noted if the patient meets ONE of the following (A or B):
- **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** Patient meets ONE of the following (a or b):

a) Patient has had a trial of ONE systemic therapy; OR
Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone or methylprednisolone. A trial of a mesalamine product does not count as a systemic therapy for ulcerative colitis. A trial of a biologic also counts as a trial of one systemic agent for ulcerative colitis. Refer to Appendix for examples of biologics used for ulcerative colitis.

b) Patient meets BOTH of the following [(1) and (2)]:

(1) Patient has pouchitis; AND

(2) Patient has tried an antibiotic, probiotic, corticosteroid enema, or mesalamine enema; AND
Note: Examples of antibiotics include metronidazole and ciprofloxacin. Examples of corticosteroid enemas include hydrocortisone enema.

iii. The medication is prescribed by or in consultation with a gastroenterologist.

2. Patient is Currently Receiving Entyvio Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on Entyvio intravenous or subcutaneous for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Entyvio intravenous or subcutaneous is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of assessment for inflammatory response include fecal markers (e.g., fecal calprotectin), serum markers (e.g., C-reactive protein), endoscopic assessment, and/or reduced dose of corticosteroids.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or decreased rectal bleeding.

Dosing. Approve the following dosage regimen (A and B):

A) The dose is 300 mg as an intravenous infusion at Weeks 0, 2, and 6; AND

B) Subsequent doses are separated by at least 8 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Entyvio intravenous is not recommended in the following situations:

1. **Concurrent Use with Other Biologics or with Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs) used for an Inflammatory Condition.** Entyvio should not be used in combination with tumor necrosis factor inhibitors or with Tysabri due to increased risk of infections.[1] There is also an increased risk of progressive multifocal leukoencephalopathy if used in combination with Tysabri. Combination therapy with other biologics or with targeted synthetic DMARDs used to treat inflammatory conditions (see Appendix for examples) is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of data supportive of additive efficacy.
Note: This does NOT exclude the use of conventional immunosuppressants (e.g., 6-mercaptopurine, azathioprine) in combination with Entyvio.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Entyvio intravenous infusion [prescribing information]. Deerfield, IL: Takeda; April 2024.
2. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG clinical guideline: management of Crohn's disease in adults. *Am J Gastroenterol.* 2018;113(4):481-517.
3. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384-413.
4. Bressler B, Marshall JK, Bernstein CN, et al. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. *Gastroenterology*. 2015;148(5):1035-1058.
5. Feuerstein JD, Ho EY, Shmidt E, et al. AGA clinical practice guidelines on the medical management of moderate to severe luminal and perianal fistulizing Crohn's disease. *Gastroenterology*. 2021;160(7):2496-2508.
6. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology*. 2020;158(5):1450-1461.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	06/28/2023
Early Annual Revision	**Ulcerative Colitis:** For a patient currently taking, it was clarified this applies to the intravenous or subcutaneous formulation. A note was added to clarify that a mesalamine product does not count as a systemic therapy for ulcerative colitis.	10/11/2023
Early Annual Revision	**Crohn's Disease:** For a patient currently taking, it was clarified this applies to the intravenous or subcutaneous formulation.	04/24/2024

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Zymfentra® (infliximab-dyyb SC injection)	Inhibition of TNF	CD, UC
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA, PMR
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17RA	PsO
Bimzelx® (bimekizumab-bkzx SC injection)	Inhibition of IL-17A and IL-17F	PsO
Cosentyx® (secukinumab SC injection, secukinumab IV infusion)	Inhibition of IL-17A	SC formulation: AS, ERA, nr-axSpA, PsO, PsA
		IV formulation: AS, nr-axSpA, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion)	Inhibition of IL-23	SC formulation: CD, PSA, PsO
		IV formulation: CD
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion, vedolizimab SC injection)	Integrin receptor antagonist	SC formulation: CD, UC
		IV formulation: CD, UC
Oral Therapies/Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Cibinqo™ (abrocitinib tablets)	Inhibition of JAK pathways	AD
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	AD, AS, nr-axSpA, RA, PsA, UC
Sotyktu™ (deucravacitinib tablets)	Inhibition of TYK2	PsO
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; PMR – Polymyalgia rheumatic; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Inflammatory Conditions – Ilaris Utilization Management Medical Policy
- Ilaris® (canakinumab subcutaneous injection – Novartis)

REVIEW DATE: 02/14/2024; selected revision 04/24/2024

OVERVIEW

Ilaris, an interleukin-1β (IL-1β) blocker, is indicated for the following uses:[1]

- **Periodic Fever Syndromes:**
  - **Cryopyrin-associated periodic syndromes** (CAPS), including familial cold auto-inflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS), for treatment of patients ≥ 4 years of age.
  - **Familial Mediterranean fever** (FMF), in adult and pediatric patients.
  - **Hyperimmunoglobulin D syndrome** (HIDS)/**mevalonate kinase deficiency** (MKD), in adult and pediatric patients.
  - **Tumor necrosis factor receptor associated periodic syndrome** (TRAPS), in adult and pediatric patients.
- **Active Still's disease**, including active **adult-onset Still's disease** (AOSD) and **systemic juvenile idiopathic arthritis** (SJIA), in patients ≥ 2 years of age.
- **Gout flares** in adults in whom nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

In the pivotal trial for periodic fevers (TRAPS, HIDS/MKD, and FMF), patients were required to be at least 2 years of age with a disease flare, defined as a C-reactive protein level ≥ 10 mg/L.[1] Prior to starting Ilaris, a minimum level of disease activity at baseline was required for FMF (at least one flare per month despite colchicine), HIDS/MKD (≥ three febrile acute flares within the previous 6 month period), and TRAPS (≥ six flares per year). In this study, patients were assessed for a response following 4 months of treatment with Ilaris.

Guidelines

Ilaris is used for a variety of periodic fever syndromes and inflammatory conditions. The European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACG) [2021] provide treatment guidelines for interleukin-1 (IL-1) mediated autoinflammatory diseases and indicate IL-blocking therapy has become the preferred treatment and a therapeutic trial with IL-1 blocking treatment may be started when strong clinical suspicion of a diagnosis of CAPS, TRAPS, MKD, or DIRA is entertained.[2] The guidelines also provide additional diagnosis specific treatment recommendations:

- **CAPS:** IL-1 blockers are recommended as standard of care across the spectrum of disease for improved symptom control and reduced systemic and tissue/organ inflammation. The dose and/or frequency of administration should be adjusted to control disease activity, normalize markers of systemic inflammation, and appropriate weight gain and development in the growing patient.
- **TRAPS:** IL-1 blockers are more effective than traditional disease-modifying antirheumatic drugs (DMARDs) and other biologic DMARDs in achieving disease remission and preventing long-term complications.
- **MKD/HIDS**: In patients without chronic inflammation, on demand IL-1 blockage should be attempted at the onset of flares. In children, IL-1 blocking therapy is generally required.

FMF
Guidelines for familial Mediterranean fever from the EULAR (2016) note that treatment goals are to prevent the clinical attacks and to suppress chronic subclinical inflammation.[3] IL-1 blockade is an option for patients with protracted febrile myalgia. In patients who develop amyloidosis, the maximal tolerated dose of colchicine and biologics (especially IL-1 blockade) are recommended.

Gout
Guidelines for the management of gout flares from the ACR (2020) recommend colchicine, NSAIDs, or glucocorticoids (oral, intraarticular, or intramuscular) as appropriate first-line therapy.[4] If a patient is unable to tolerate or has contraindications to any of the first line conventional alternatives, IL-1 inhibitors are conditionally recommended.

SJIA
There are standardized treatment plans published for use of Ilaris.[5,6] At Month 3, patients with unchanged or worsening disease or patients whose steroid dose is > 50% of the starting dose should have an increase in prednisone plus either addition of methotrexate or change to Actemra. Guidelines from the ACR for the management of SJIA (2021) mention Ilaris as a treatment alternative, depending upon the manifestations of SJIA being treated.[7] While there are a number of other effective options for treating synovitis in patients with active SJIA, effective options for treatment of macrophage activation syndrome are much more limited and include Kineret® (anakinra subcutaneous injection), calcineurin inhibitors, and systemic corticosteroids (no preferential sequencing noted). Although use of Ilaris is uncertain in some situations, macrophage activation syndrome is a potentially life-threatening situation with limited treatment options.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Ilaris. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ilaris, as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Ilaris to be prescribed by or in consultation with a physician who specializes in the condition being treated.

All reviews for use of Ilaris for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ilaris is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Cryopyrin-Associated Periodic Syndromes (CAPS).** Approve for the duration noted if the patient meets ONE of the following (A or B):

Note: This includes familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal onset multisystem inflammatory disease (NOMID) formerly known as chronic infantile neurological cutaneous and articular syndrome (CINCA).

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
- **i.** Patient is ≥ 4 years of age; AND
- **ii.** The medication is prescribed by or in consultation with a rheumatologist, geneticist, allergist/immunologist, or dermatologist.

B) Patient is Currently Receiving Ilaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on this medication for at least 6 months; AND
  Note: For a patient who has not received 6 months of therapy or who is restarting therapy with this medication, refer to Initial Therapy criteria above.
- **ii.** Patient meets at least ONE of the following (a or b):
  - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
    Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, and/or stabilization of serum creatinine.
  - **b)** Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom.
    Note: Examples of improvement in symptoms include fewer cold-induced attacks; less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

Dosing. Approve one of the following dosing regimens (A or B):

A) Patient is ≥ 15 kg and ≤ 40 kg: Approve up to 3 mg/kg per dose administered subcutaneously no more frequently than once every 8 weeks; OR

B) Patient is > 40 kg: Approve up to 150 mg per dose administered subcutaneously no more frequently than once every 8 weeks.

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2. Familial Mediterranean Fever (FMF). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, and v):
- **i.** Patient is ≥ 2 years of age; AND
- **ii.** Patient has tried colchicine, unless contraindicated; AND
- **iii.** Patient will be taking Ilaris in combination with colchicine, unless colchicine is contraindicated or not tolerated; AND
- **iv.** Prior to starting Ilaris, the patient meets BOTH of the following (a and b):
  - **a)** C-reactive protein level is ≥ 10 mg/L OR elevated to at least two times the upper limit of normal for the reporting laboratory; AND
  - **b)** Patient has a history of at least one flare per month despite use of colchicine, OR was hospitalized for a severe flare; AND
- **v.** The medication is prescribed by or in consultation with a rheumatologist, nephrologist, geneticist, gastroenterologist, oncologist, or hematologist.

B) Patient is Currently Receiving Ilaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on this medication for at least 6 months; AND
Note: For a patient who has not received 6 months of therapy or who is restarting therapy with this medication, refer to Initial Therapy criteria above.

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include decreased frequency of attacks, resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, and/or stabilization of serum creatinine.

C) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom.
Note: Examples of improvement in symptoms include decreased pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

Dosing. Approve one of the following dosing regimens (A or B):

A) Patient is ≤ 40 kg: Approve up to 4 mg/kg per dose administered subcutaneously no more frequently than once every 4 weeks; OR

B) Patient is > 40 kg: Approve up to 300 mg per dose administered subcutaneously no more frequently than once every 4 weeks.

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3. Gout, Acute Flare. Approve for 6 months if the patient meets ALL of the following (A, B, C and D):

A) Patient is ≥ 18 years of age; AND

B) Patient meets ONE of the following (i or ii):

i. Patient meets BOTH of the following (a and b):

a) Patient has an intolerance, contraindication, or lack of response to nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of acute gout flares; AND

b) Patient has an intolerance, contraindication, or lack of response to colchicine for the treatment of acute gout flares; OR

ii. Patient meets BOTH of the following (a and b):

a) Patient has been previously treated with corticosteroids (oral or injectable) for an acute gout flare; AND

b) According to the prescriber, patient is unable to be retreated with a repeat course of corticosteroids (oral or injectable) for acute gout flares; AND

C) According to the prescriber, patient is receiving or will be taking concomitant urate lowering medication for the prevention of gout unless contraindicated; AND
Note: Examples of uric acid lowering drugs include allopurinol, febuxostat, or probenecid.

D) Ilaris is prescribed by or in consultation with a rheumatologist.

Dosing. Approve up to 150 mg administered subcutaneously no more frequently than once every 12 weeks.

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4. Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 2 years of age; AND

ii. Prior to starting Ilaris, the patient meets BOTH of the following (a and b):

a) C-reactive protein level is ≥ 10 mg/L OR elevated to at least two times the upper limit of normal for the reporting laboratory; AND
b) Patient has a history of at least three febrile acute flares within the previous 6-month period OR was hospitalized for a severe flare; AND

iii. The medication is prescribed by or in consultation with a rheumatologist, nephrologist, geneticist, oncologist, or hematologist.

B) Patient is Currently Receiving Ilaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on this medication for at least 6 months; AND
Note: For a patient who has not received 6 months of therapy or who is restarting therapy with this medication, refer to Initial Therapy criteria above.

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include decreased frequency of attacks, resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, and/or stabilization of serum creatinine.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom.
Note: Examples of improvement in symptoms include decreased pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

Dosing. Approve one of the following dosing regimens (A or B):

A) Patient is ≤ 40 kg: Approve up to 4 mg/kg per dose administered subcutaneously no more frequently than once every 4 weeks; OR

B) Patient is > 40 kg: Approve up to 300 mg per dose administered subcutaneously no more frequently than once every 4 weeks.

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5. Stills Disease, Adult Onset. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months (which is adequate for three doses) if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND
Note: If the patient is < 18 years of age, refer to criteria for systemic juvenile idiopathic arthritis.

ii. Patient meets ONE of the following (a or b):

a) Patient has tried at least ONE other biologic; OR
Note: Examples of biologics for Still's disease include a tocilizumab product (Actemra intravenous infusion, biosimilars; Actemra subcutaneous injection), Kineret (anakinra subcutaneous injection).

b) Patient was started on Ilaris while in the hospital; AND

iii. Ilaris is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Ilaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on this medication for at least 6 months; AND
Note: For a patient who has not received 6 months of therapy or who is restarting therapy with this medication, refer to Initial Therapy criteria above.

ii. Patient meets at least ONE of the following (a or b):
- **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
  Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.
- **b)** Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom.
  Note: Examples of improvement in symptoms include less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

Dosing. Approve up to 4 mg/kg to a maximum of 300 mg per dose administered subcutaneously no more frequently than once every 4 weeks.

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6. Systemic Juvenile Idiopathic Arthritis (SJIA). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months (which is adequate for three doses) if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient is ≥ 2 years of age; AND
- **ii.** Patient meets ONE of the following (a or b):
  - **a)** Patient has tried at least ONE other biologic; OR
    Note: Examples of biologics for SJIA include a tocilizumab product (Actemra intravenous infusion, biosimilar; Actemra subcutaneous injection), Kineret (anakinra subcutaneous injection).
  - **b)** Patient was started on Ilaris while in the hospital; AND
- **iii.** Ilaris is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Ilaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on this medication for at least 6 months; AND
  Note: For a patient who has not received 6 months of therapy or who is restarting therapy with this medication, refer to Initial Therapy criteria above.
- **ii.** Patient meets at least ONE of the following (a or b):
  - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
    Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.
  - **b)** Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom.
    Note: Examples of improvement in symptoms include less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

Dosing. Approve up to 4 mg/kg to a maximum of 300 mg per dose administered subcutaneously no more frequently than once every 4 weeks.

7. **Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient is ≥ 2 years of age; AND
     - **ii.** Prior to starting Ilaris, the patient meets BOTH of the following (a and b):
       - **a)** C-reactive protein level is ≥ 10 mg/L OR elevated to at least two times the upper limit of normal for the reporting laboratory; AND
       - **b)** Patient has a history of at least six flares per year OR was hospitalized for a severe flare; AND
     - **iii.** The medication is prescribed by or in consultation with a rheumatologist, geneticist, nephrologist, oncologist, or hematologist.
   - **B)** Patient is Currently Receiving Ilaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):
     - **i.** Patient has been established on this medication for at least 6 months; AND
       Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).
     - **ii.** Patient meets at least ONE of the following (a or b):
       - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
         Note: Examples of objective measures include decreased frequency of attacks, resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, and/or stabilization of serum creatinine.
       - **b)** Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom.
         Note: Examples of improvement in symptoms include less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

   Dosing. Approve one of the following dosing regimens (A or B):
   - **A)** Patient is ≤ 40 kg: Approve up to 4 mg/kg per dose administered subcutaneously no more frequently than once every 4 weeks; OR
   - **B)** Patient is > 40 kg: Approve up to 300 mg per dose administered subcutaneously no more frequently than once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ilaris is not recommended in the following situations:

1. **Concurrent Biologic Therapy.** Ilaris has not been evaluated and should not be administered in combination with another biologic agent for an inflammatory condition (see Appendix for examples).[1] An increased incidence of serious infections has been associated with another IL-1 blocker, Kineret, when given in combination with tumor necrosis factor inhibitor in patients with rheumatoid arthritis. Concomitant administration of Ilaris and other agents that block IL-1 or its receptors is not recommended.

2. **COVID-19 (Coronavirus Disease 2019).** Forward all requests to the Medical Director.
   Note: This includes requests for cytokine release syndrome associated with COVID-19.

3. **Rheumatoid Arthritis.** Efficacy is not established. In a 12-week, Phase II, placebo-controlled, double-blind study, 277 patients who had failed methotrexate were randomized to Ilaris or placebo.[8]

Although the ACR 50 at Week 12 was higher for Ilaris 150 mg (given every 4 weeks) compared with placebo (26.5% vs. 11.4%, respectively; P = not significant), there was not a statistically significant difference in ACR 50 for the other Ilaris treatment groups (Ilaris 300 mg every 2 weeks; Ilaris 600 mg loading dose followed by 300 mg every 2 weeks).

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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8. Alten R, Gomez-Reino J, Durez P, et al. Efficacy and safety of the human anti-IL-1β monoclonal antibody canakinumab in rheumatoid arthritis: results of a 12-week, Phase II, dose-finding study. *BMC Musculoskelet Disord.* 2011;12:153.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	01/25/2023
Selected Revision	**Gout, Acute Flare:** New condition of approval added.	09/06/2023
Annual Revision	No criteria changes.	02/14/2024
Selected Revision	**Still's Disease, Adult Onset:** The requirement for previous therapy was changed to one biologic (previously was two biologics). Exceptions that apply to a patient who is not required to try two biologics were removed (no longer needed). An exception was added for a patient who was started on Ilaris in the hospital who is not required to try another biologic prior to Ilaris. **Systemic Juvenile Idiopathic Arthritis:** The requirement for previous therapy was changed to one biologic (previously was two biologics). Exceptions that apply to a patient who is not required to try two biologics were removed (no longer needed). An exception was added for a patient who was started on Ilaris in the hospital who is not required to try another biologic prior to Ilaris.	04/24/2024

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Zymfentra® (infliximab-dyyb SC injection)	Inhibition of TNF	CD, UC
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA, PMR
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17RA	PsO
Bimzelx® (bimekizumab-bkzx SC injection)	Inhibition of IL-17A and IL-17F	PsO
Cosentyx® (secukinumab SC injection, secukinumab IV infusion)	Inhibition of IL-17A	SC formulation: AS, ERA, nr-axSpA, PsO, PsA
Skyrizi® (risankizumab-rzaa SC injection)	Inhibition of IL-23	IV formulation: AS, nr-axSpA, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Inflammatory Conditions – Ilumya Utilization Management Medical Policy
- Ilumya® (tildrakizumab-asmn subcutaneous injection – Sun)

REVIEW DATE: 05/10/2023; selected revision 03/27/2024

OVERVIEW

Ilumya, an interleukin (IL)-23 blocker, is indicated for the treatment of adults with moderate to severe **plaque psoriasis** who are candidates for systemic therapy or phototherapy. It is administered subcutaneously at Weeks 0 and 4 and then once every 12 weeks thereafter. Ilumya should be administered by a healthcare professional. Safety and efficacy have not been established in patients < 18 years of age.

Guidelines

Joint guidelines from the American Academy of Dermatology and National Psoriasis Medical Board (2019) have been published for management of psoriasis with biologics.[2] These guidelines list Ilumya as a monotherapy treatment option for patients with moderate to severe plaque psoriasis. Guidelines from the European Dermatology Forum (2015) recommend biologics (i.e., etanercept, adalimumab, infliximab, Stelara® [ustekinumab subcutaneous injection]) as second-line therapy for induction and long-term treatment if phototherapy and conventional systemic agents have failed, are contraindicated, or are not tolerated.[3]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Ilumya. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ilumya, as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Ilumya to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ilumya is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Plaque Psoriasis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets ALL of the following criteria (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient meets ONE of the following (a or b):

a) Patient has tried at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR
Note: Examples of one traditional systemic agent include methotrexate, cyclosporine, acitretin tablets, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for plaque psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis.

b) Patient has a contraindication to methotrexate, as determined by the prescriber; AND

iii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Ilumya. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has been established on therapy for at least 3 months; AND
Note: A patient who has received < 3 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating the requested drug) in at least one of the following: estimated body surface area, erythema, induration/thickness, and/or scale of areas affected by psoriasis; AND

iii. Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, itching, and/or burning.

Dosing. Approve the following dosing (A and B):

A) The dose is 100 mg given as a subcutaneous injection; AND

B) Doses are administered at Weeks 0 and 4, then not more frequently than once every 12 weeks thereafter.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ilumya is not recommended in the following situations:

1. **Concurrent Use with other Biologics or with Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs).** Data are lacking evaluating concomitant use of Ilumya with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of adverse effects and lack controlled trial data in support of additive efficacy.[4]
Note: This does NOT exclude the use of methotrexate (a traditional systemic agent used to treat psoriasis) in combination with Ilumya.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	05/11/2022
Annual Revision	No criteria changes.	05/10/2023
Selected Revision	**Plaque Psoriasis:** For a patient currently taking Ilumya, the timeframe for established on therapy was changed from 90 days to 3 months.	03/27/2024

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PsA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx® (secukinumab SC injection)	Inhibition of IL-17A	AS, ERA, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection)	Inhibition of IL-23	PsA, PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Oral Therapies/Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Cibinqo™ (abrocitinib tablets)	Inhibition of JAK pathways	AD
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	AD, AS, RA, PsA, UC
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Inflammatory Conditions – Infliximab Intravenous Products Utilization Management Medical Policy
- Avsola™ (infliximab-axxq intravenous infusion – Amgen)
- Inflectra® (infliximab-dyyb intravenous infusion – Hospira/Pfizer)
- Infliximab intravenous infusion – Janssen/Johnson & Johnson
- Remicade® (infliximab intravenous infusion – Janssen/Johnson & Johnson)
- Renflexis® (infliximab-abda intravenous infusion – Samsung Bioepis/Organon)

REVIEW DATE: 11/15/2023; selected revision 03/27/2024

OVERVIEW

Infliximab products are tumor necrosis factor inhibitors (TNFis) approved for the following indications:[1-3]
- **Ankylosing spondylitis**, for reducing signs and symptoms of active disease.
- **Crohn's disease**, for the following uses:
  - Reducing the signs and symptoms and inducing and maintaining clinical remission in patients ≥ 6 years of age with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy; AND
  - Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adults with fistulizing Crohn's disease.
- **Plaque psoriasis**, for treatment of adults with chronic severe (i.e., extensive and/or disabling) disease who are candidates for systemic therapy and when other systemic therapies are less appropriate.
- **Psoriatic arthritis**, for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage and improving physical function.
- **Rheumatoid arthritis**, in combination with methotrexate for reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in patients with moderately to severely active disease.
- **Ulcerative colitis**, for the following uses:
  - Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adults with moderately to severely active disease who have had an inadequate response to conventional therapy; AND
  - Reducing signs and symptoms and inducing and maintaining clinical remission in patients ≥ 6 years of age with moderately to severely active disease who have had an inadequate response to conventional therapy.

Avsola, Inflectra, and Renflexis were approved as biosimilar to Remicade, indicating no clinically meaningful differences in safety and effectiveness and the same mechanism of action, route of administration, dosage form, and strength as Remicade.[2-3] However, minor differences in clinically inactive components are allowed. At this time, only biosimilarity has been demonstrated (not interchangeability).

Guidelines

TNFis feature prominently in guidelines for treatment of many inflammatory conditions.
- **Ankylosing Spondylitis and Non-Radiographic Spondyloarthritis:** Guidelines for ankylosing spondylitis and non-radiographic axial spondyloarthritis are published by the American College of Rheumatology (ACR)/Spondylitis Association of America/Spondyloarthritis Research and

Treatment Network (2019).[4] Following primary nonresponse to a TNFi, an interleukin (IL)-17 blocker is recommended; however, if the patient is a secondary nonresponder, a second TNFi is recommended over switching out of the class. In patients with a contraindication to a TNFi, use of an IL-17 blocker is recommended over traditional oral agents such as methotrexate or sulfasalazine.

- **Crohn's Disease:** The American College of Gastroenterology (ACG) has guidelines for Crohn's disease (2018).[5] TNFis are listed as an option for disease that is resistant to corticosteroids, severely active disease, perianal fistulizing disease, and maintenance of remission. In post-operative Crohn's disease, a TNFi should be started within 4 weeks of surgery to prevent recurrence. Guidelines from the American Gastroenterological Association (AGA) [2021] include infliximab among the therapies for moderate to severe Crohn's disease, for induction and maintenance of remission.[6]
- **Plaque Psoriasis:** Guidelines from the American Academy of Dermatologists (AAD) and National Psoriasis Foundation (NPF) [2019] recommend infliximab as a monotherapy treatment option for adults with moderate to severe disease.[7]
- **Psoriatic Arthritis:** Guidelines from ACR (2019) recommend TNFis over other biologics for use in treatment-naïve patients with psoriatic arthritis, and in those who were previously treated with an oral therapy.[8]
- **Rheumatoid Arthritis:** Guidelines from ACR (2021) recommend addition of a biologic or a targeted synthetic disease modifying anti-rheumatic drug (DMARD) for a patient taking the maximum tolerated dose of methotrexate who is not at target.[9]
- **Ulcerative Colitis:** Updated ACG guidelines for ulcerative colitis (2019) note that the following agents can be used for induction of remission in moderately to severely active disease: budesonide extended-release tablets; oral or intravenous systemic corticosteroids, Entyvio® (vedolizumab intravenous infusion), Xeljanz®/XR (tofacitanib tablets/extended-release tablets), or TNFis.[10] In addition to the approved indication, clinical guidelines for the management of pouchitis, published in 2009 indicate that first-line therapy for pouchitis is antibiotic therapy (e.g. metronidazole, ciprofloxacin).[11] Other treatment options include maintenance probiotics, oral or topical budesonide, anti-inflammatory drugs (e.g., mesalamine), or immunosuppressive drugs (e.g., infliximab). Guidelines from the AGA (2020) recommend infliximab for moderate to severe ulcerative colitis.[12]
- **Behcet's Disease:** The European League Against Rheumatism (EULAR) recommendations (2018) include TNFis for initial or recurrent sight-threatening uveitis.[13] For patients refractory to first-line treatments (e.g., corticosteroids), TNFis are among the treatment options for mucocutaneous manifestations, venous thrombosis, severe or refractory gastrointestinal disease, and recurrent/chronic joint involvement. Recommendations for the use of TNFis in ocular inflammatory disorders from the American Academy of Ophthalmology (AAO) [2014] note that TNFis may be used first-line in patients with ophthalmic manifestations of Behcet's disease and for acute exacerbations of pre-existing Behcet's disease.[14]
- **Graft-Versus-Host Disease:** Guidelines from the National Comprehensive Cancer network (NCCN) [version 3.2023 – October 9, 2023] list infliximab among the agents used for steroid-refractory disease.[15]
- **Hidradenitis Suppurativa:** Guidelines from the US and Canadian Hidradenitis Suppurativa Foundations make recommendations for topical, intralesional, and systemic medical management of disease.[16] For acute lesions of all stages, antiseptic washes, short-term oral steroids, and interlesional steroids are among the recommendations. Systemic antibiotics have been a mainstay of treatment. Infliximab is a recommended therapy for moderate to severe disease.
- **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitors:** NCCN has guidelines (version 3.2023 – October 11, 2023) for Management of Immunotherapy-Related Toxicities.[17] Infliximab is recommended among the alternatives to manage steroid-refractory

inflammatory arthritis, vision changes, myocarditis, pericarditis, acute kidney injury (e.g., azotemia, creatinine elevation, inability to maintain acid/base or electrolyte balance, urine output change), pneumonitis, myalgia, or myositis, and diarrhea/colitis. Additionally, the guidelines also note that infliximab should not be used to treat hepatitis associated with an immunotherapy-related toxicity.

- **Indeterminate Colitis:** Infliximab has been effective in some patients with refractory indeterminate colitis (retrospective reviews).[18,19] When patients who are refractory to standard therapy can be definitively classified as having ulcerative colitis, colectomy is considered an effective long-term surgical treatment. Patient's with Crohn's disease, however, have a high risk of complications after ileal pouch-anal anastomosis and are treated more aggressively with medical interventions since surgical options cannot offer the same likelihood of success as in ulcerative colitis.
- **Juvenile Idiopathic Arthritis (JIA):** There are guidelines from ACR and the Arthritis Foundation for the treatment of JIA (2021) which address oligoarthritis and temporomandibular joint (TMJ) arthritis.[20] For oligoarthritis, a biologic is recommended following a trial of a conventional synthetic DMARD. In patients with TMJ arthritis, scheduled nonsteroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular glucocorticoids are recommended first-line. A biologic is a therapeutic option if there is an inadequate response or intolerance. Additionally, rapid escalation to a biologic ± conventional synthetic DMARD (methotrexate preferred) is often appropriate given the impact and destructive nature of TMJ arthritis. In these guidelines, there is not a preferred biologic that should be initiated for JIA. The ACR/Arthritis Foundation Guideline for the treatment of JIA (2019) provides updated recommendations for juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[21] Infliximab is among the TNFis recommended as subsequent therapy following treatment with a conventional synthetic DMARD such as methotrexate. TNF antagonists such as infliximab may also be used as second- or third-line treatment for systemic JIA.[22]
- **Ocular Inflammatory Disorders:** Recommendations for the use of TNFis in ocular inflammatory disorders from the AAO (2014) note that infliximab may be used as second-line corticosteroid-sparing therapy for chronic and severe scleritis.[14] Infliximab may be used in patients with uveitis due to various causes (e.g., spondyloarthropathy-associated or human leukocyte antigen [HLA]-B27-associated uveitis, juvenile idiopathic arthritis-associated uveitis, and other posterior uveitides and panuveitis syndromes). Infliximab should be considered second-line in vision-threatening JIA-associated uveitis when methotrexate has failed or is not tolerated (strong recommendation) and vision-threatening chronic uveitis from seronegative spondyloarthropathy (strong recommendation). Infliximab may also be considered in other patients who have vision-threatening or corticosteroid-dependent disease who have failed first-line therapies. The recommendations point out that studies evaluating infliximab in uveitis included patients with birdshot chorioretinitis (BSCR), a bilateral posterior uveitis generally treated with systemic immunomodulation; these patients showed a good response to infliximab.
- **Pyoderma Gangrenosum:** Although guidelines are not current, multiple topical and systemic therapies have been used for pyoderma gangrenosum. Oral prednisone is the most common initial immunosuppressant medication.[23] Other systemic therapies include cyclosporine, methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, and TNFis (i.e., infliximab, etanercept, and adalimumab products). In case reports, TNFis have been effective.
- **Sarcoidosis:** The European Respiratory Society Task Force has guidelines for treatment of pulmonary, cutaneous, cardiac, and neurologic sarcoidosis.[24] Infliximab is a recommended therapy after continued disease or relapse while taking systemic corticosteroids and immunosuppressants (e.g., methotrexate, azathioprine, leflunomide, mycophenolate mofetil, hydroxychloroquine).

- **Still's Disease:** Still's disease presents in adults with features similar to those of systemic onset JIA.[25,26] In case series, infliximab has been effective in patients with Still's disease that was refractory to therapy with corticosteroids, methotrexate, azathioprine, and cyclophosphamide.[27]

Dosing Information

The recommended dose of infliximab intravenous is weight-based and varies slightly by indication.[1-3] Dosing increase, interval shortening, or changing to another therapy is generally recommended for attenuation of response. Thus, published recommendations note that the dose and interval of infliximab may be adjusted, as needed, in patients who initially respond but then lose that response.[2] Additionally, data are emerging concerning tapering of infliximab dosage in patients with inflammatory conditions who are in remission or have low disease activity. When the dose of any RA therapy is tapered, it is recommended that there be a comprehensive plan to monitor disease activity and address possible flares.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of infliximab products. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of a patient treated with infliximab products as well as the monitoring required for adverse events and long-term efficacy, initial approval requires infliximab products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of infliximab intravenous products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Ankylosing Spondylitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR
Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing

Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then no more frequently than once every 6 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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2. Crohn's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, and iii):

i. Patient is ≥ 6 years of age; AND

ii. Patient meets ONE of the following (a, b, c, or d):

a) Patient has tried or is currently taking corticosteroids, or corticosteroids are contraindicated in this patient; OR
Note: Examples of corticosteroids are prednisone and methylprednisolone.

b) Patient has tried one other conventional systemic therapy for Crohn's disease; OR
Note: Examples of conventional systemic therapies for Crohn's disease include azathioprine, 6-mercaptopurine, or methotrexate. An exception to the requirement for a trial of or contraindication to steroids or a trial of one other conventional systemic agent can be made if the patient has already tried at least one biologic other than the requested medication A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for Crohn's disease. A trial of mesalamine does not count as a systemic therapy for Crohn's disease.

c) Patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas; OR

d) Patient had ileocolonic resection (to reduce the chance of Crohn's disease recurrence); AND

iii. The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR
Note: Examples of objective measures include fecal markers (e.g., fecal lactoferrin, fecal calprotectin), serum markers (e.g., C-reactive protein), imaging studies (magnetic resonance enterography [MRE], computed tomography enterography [CTE]), endoscopic assessment, and/or reduced dose of corticosteroids.

b) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or blood in stool.

Dosing. Approve the following regimens (A or B):
A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.
B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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3. Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 3 months if the patient meets the following (i, ii, and iii):
i. Patient is ≥ 18 years of age; AND
ii. Patient meets ONE of the following (a or b):
a) Patient has tried at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR
Note: Examples include methotrexate, cyclosporine, acitretin (Soriatane®, generics), or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient already had a 3-month trial or previous intolerance to at least one biologic other than the requested medication. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis.
b) Patient has a contraindication to methotrexate, as determined by the prescriber; AND
iii. The medication is prescribed by or in consultation with a dermatologist.
B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
i. Patient has been established on therapy for at least 3 months; AND
Note: A patient who has received < 3 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).
ii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating an infliximab product) in at least one of the following: estimated body surface area affected, erythema, induration/thickness, and/or scale of areas affected by psoriasis; AND
iii. Compared with baseline (prior to receiving an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain, itching, and/or burning.

Dosing. Approve the following regimens (A or B):
A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.
B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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4. Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist or a dermatologist.
B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR
Note: Examples of objective measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; or decreased soft tissue swelling in joints or tendon sheaths.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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5. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND
Note: Examples include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient already had a 3-month trial of at least one biologic other than the requested medication. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic is not required to "step back" and try a conventional synthetic DMARD.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
Note: Examples of objective measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate or

C-reactive protein, Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; or decreased soft tissue swelling in joints or tendon sheaths.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 3 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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6. Ulcerative Colitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, and iii):

i. Patient is ≥ 6 years of age; AND

ii. Patient meets ONE of the following (a or b):

a) Patient had a trial of one systemic agent or was intolerant to one of these agents for ulcerative colitis; OR

Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone or methylprednisolone. A trial of a mesalamine product does not count as a systemic therapy for ulcerative colitis. A previous trial of one biologic other than the requested medication also counts as a trial of one systemic agent for ulcerative colitis. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for ulcerative colitis.

b) Patient meets BOTH of the following [(1) and (2)]:

(1) Patient has pouchitis; AND

(2) Patient has tried therapy with an antibiotic, probiotic, corticosteroid enema, or Rowasa® (mesalamine enema); AND

Note: Examples of antibiotics include metronidazole and ciprofloxacin. Examples of corticosteroid enemas include hydrocortisone enema (Cortenema, generics).

iii. The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR

Note: Examples of objective measures include fecal markers (e.g., fecal calprotectin), serum markers (e.g., C-reactive protein), endoscopic assessment, and/or reduced dose of corticosteroids.

b) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or rectal bleeding.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.
B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

Other Uses with Supportive Evidence

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7. Behcet's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):
i. Patient meets ONE of the following (a or b):
a) Patient has tried at least ONE conventional therapy; OR
Note: Examples include systemic corticosteroids (e.g., methylprednisolone), immunosuppressants (azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus, Leukeran® [chlorambucil tablet], cyclophosphamide, interferon alfa). An exception to the requirement for a trial of one conventional therapy can be made if the patient has already had a trial of at least one tumor necrosis factor inhibitor (e.g., an adalimumab product, an etanercept product). A patient who has already tried one biologic other than the requested drug for Behcet's disease is not required to "step back" and try a conventional therapy. A biosimilar of the requested biologic does not count.
b) Patient has ophthalmic manifestations of Behcet's disease; AND
ii. The medication is prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist.
A) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
i. Patient has been established on therapy for at least 3 months; AND
Note: A patient who has received < 3 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).
ii. When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); AND
Note: Examples of objective measures are dependent upon organ involvement but may include best-corrected visual acuity (if ophthalmic manifestations); serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate); or ulcer depth, number, and/or lesion size.
iii. Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain or improved visual acuity (if ophthalmic manifestations).

Dosing. Approve the following regimens (A or B):
A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, then no more frequently than once every 6 weeks thereafter.
B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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8. Graft-Versus-Host Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 1 month if the patient meets BOTH of the following (i and ii):

i. Patient has tried at least one conventional systemic treatment for graft-versus-host disease; AND
Note: Examples of conventional treatments include corticosteroids (e.g., methylprednisolone), antithymocyte globulin, cyclosporine, tacrolimus, and mycophenolate mofetil.
ii. The medication is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center; OR

B) Patient is Currently Receiving an Infliximab Product. Approve for 3 months if the patient meets BOTH of the following (i and ii):
i. Patient has been established on an infliximab product for at least 1 month; AND
Note: A patient who has received < 1 month of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).
ii. Patient meets at least one of the following (a or b):
a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR
Note: An example of objective measures is normalization of liver function tests, red blood cell count, or platelet count, or resolution of fever or rash.
b) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as improvement in skin, oral mucosal, ocular, or gastrointestinal symptoms (e.g., nausea, vomiting, anorexia).

Dosing. Approve the following regimens (A and B):
A) The dose is up to 10 mg/kg given intravenously; AND
B) Doses are administered no more frequently than once weekly.

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9. Hidradenitis Suppurativa. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):
i. Patient has tried one other therapy; AND
Note: Examples include intralesional or oral corticosteroids (e.g., triamcinolone, prednisone), systemic antibiotics (e.g., clindamycin, dicloxacillin, erythromycin), and isotretinoin.
ii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
i. Patient has been established on therapy for at least 3 months; AND
Note: A patient who has received < 3 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).
ii. When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); AND
Note: Examples of objective measures include Hurley staging, Sartorius score, Physician Global Assessment, and Hidradenitis Suppurativa Severity Index.
iii. Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain or drainage of lesions, nodules, or cysts.

Dosing. Approve the following regimens (A and B):
A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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10. Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, and iv):

i. Patient developed an immunotherapy-related toxicity other than hepatitis; AND
Note: For example, gastrointestinal system toxicity (e.g., colitis), ocular toxicity (e.g., uveitis/iritis, episcleritis, and blepharitis). myocarditis, pericarditis, inflammatory arthritis, acute kidney injury (e.g., azotemia, creatinine elevation, inability to maintain acid/base or electrolyte balance, urine output change), pneumonitis, myalgia, or myositis.

ii. Patient developed this immune-related toxicity while receiving a checkpoint inhibitor; AND
Note: Examples of checkpoint inhibitors include Keytruda (pembrolizumab intravenous [IV] infusion), Opdivo (nivolumab IV infusion), Yervoy (ipilimumab IV infusion), Tecentriq (atezolizumab IV infusion), Bavencio (avelumab IV infusion), or Imfinzi (durvalumab IV infusion).

iii. Patient has tried one systemic corticosteroid; AND
Note: Examples include methylprednisone and prednisone.

iv. The medication is prescribed by or in consultation with an oncologist, gastroenterologist, rheumatologist, or ophthalmologist; OR

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR
Note: Examples of objective measures are dependent upon organ involvement but may include clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), fecal markers (e.g., fecal calprotectin), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness or swelling (if joint symptoms), stool frequency and/or rectal bleeding (if gastrointestinal symptoms), and/or improved function or activities of daily living.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 10 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, then no more frequently than once every 4 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

11. Indeterminate Colitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

Note: Indeterminate colitis is defined as colitis that cannot be classified with certainty as either ulcerative colitis or Crohn's disease.

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, and v):
- **i.** Patient is ≥ 6 years of age; AND
- **ii.** Patient has tried one systemic corticosteroid; AND
  Note: Examples include prednisone and methylprednisolone.
- **iii.** Patient has tried mesalamine; AND
- **iv.** Patient has tried either azathioprine or 6-mercaptopurine; AND
- **v.** The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **ii.** Patient has been established on therapy for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).
- **iii.** Patient meets at least one of the following (a or b):
  - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR
    Note: Examples of objective measures include fecal markers (e.g., fecal calprotectin), serum markers (e.g., C-reactive protein), endoscopic assessment, and/or reduced dose of corticosteroids.
  - **b)** Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or rectal bleeding.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

12. Juvenile Idiopathic Arthritis (JIA). Approve for the duration noted if the patient meets ONE of the following (A or B):

Note: This includes JIA regardless of type of onset, including a patient with juvenile spondyloarthropathy/active sacroiliac arthritis. JIA is also referred to as Juvenile Rheumatoid Arthritis.

A) Initial Therapy. Approve for 6 months if the patient meets the following (i and ii):
- **i.** Patient meets ONE of the following (a or b):
  - **a)** Patient has tried one other systemic medication for this condition; OR
    Note: Examples of other medications for JIA include methotrexate, sulfasalazine, or leflunomide, a nonsteroidal anti-inflammatory drug (NSAID) [e.g., ibuprofen, naproxen]. A previous trial of one biologic other than the requested medication also counts as a trial of one medication. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for JIA.
  - **b)** Patient has aggressive disease, as determined by the prescriber; AND
- **ii.** The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on therapy for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).
- **ii.** Patient meets at least one of the following (a or b):
  - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR
    Note: Examples of objective measures include Physician Global Assessment (MD global), Parent/Patient Global Assessment of Overall Well-Being (PGA), Parent/Patient Global Assessment of Disease Activity (PDA), Juvenile Arthritis Disease Activity Score (JDAS), Clinical Juvenile Arthritis Disease Activity Score (cJDAS), Juvenile Spondyloarthritis Disease Activity Index (JSpADA), serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.
  - **b)** Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue, or improved function or activities of daily living.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 6 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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13. Pyoderma Gangrenosum. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets BOTH of the following (i and ii):
- **i.** Patient meets ONE of the following conditions (a or b):
  - **a)** Patient has tried one systemic corticosteroid; OR
    Note: Examples include prednisone and methylprednisolone.
  - **b)** Patient has tried one other immunosuppressant for at least 2 months or was intolerant to one of these medications; AND
    Note: Examples include mycophenolate mofetil and cyclosporine.
- **ii.** The medication is prescribed by or in consultation with a dermatologist; OR

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient has been established on therapy for at least 4 months; AND
  Note: A patient who has received < 4 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).
- **ii.** Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating an infliximab product) in at least one of the following: size, depth, and/or number of lesions; AND
- **iii.** Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain and/or tenderness of affected lesions.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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14. Sarcoidosis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient has tried at least one corticosteroid; AND
Note: Examples include prednisone and methylprednisolone.

ii. Patient has tried at least one immunosuppressive medication; AND
Note: Examples include methotrexate, azathioprine, leflunomide, mycophenolate mofetil, hydroxychloroquine, or chloroquine.

iii. The medication is prescribed by or in consultation with a pulmonologist, ophthalmologist, cardiologist, neurologist, or dermatologist; OR

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has been established on therapy for at least 3 months; AND
Note: A patient who has received < 3 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); AND
Note: Examples of objective measures are dependent upon organ involvement but may include lung function (e.g., predicted forced vital capacity and/or 6-minute walk distance); serum markers (e.g., C-reactive protein, liver enzymes, N-terminal pro-brain natriuretic peptide [NT-proBNP]); improvement in rash or skin manifestations, neurologic symptoms, or rhythm control; or imaging (e.g., if indicated, chest radiograph, magnetic resonance imaging [MRI], or echocardiography).

iii. Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased cough, fatigue, pain, palpitations, neurologic symptoms, and/or shortness of breath.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, then no more frequently than once every 6 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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15. Scleritis or Sterile Corneal Ulceration. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried one other therapy for this condition; AND
Note: Examples include oral non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin; oral, topical (ophthalmic) or intravenous corticosteroids (such as prednisone, prednisolone, methylprednisolone); methotrexate; cyclosporine; or other immunosuppressants.

ii. The medication is prescribed by or in consultation with an ophthalmologist; OR

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR
Note: Examples of objective measures are serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased eye pain, redness, light sensitivity, tearing, and/or improvement in visual acuity.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 10 mg/kg as an intravenous infusion administered at baseline and followed by up to three additional similar doses (for example, up to three additional doses given 2, 6, and 8 weeks after the initial infusion).

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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16. Spondyloarthritis, Other Subtypes Approve for the duration noted if the patient meets ONE of the following (A or B):
Note: Examples of other subtypes include undifferentiated arthritis, non-radiographic axial spondylitis, Reactive Arthritis [Reiter's disease]. For ankylosing spondylitis or psoriatic arthritis, refer to the respective criteria under FDA-approved indications.

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following (a or b):

a) Patient has arthritis primarily in the knees, ankles, elbows, wrists, hands, and/or feet AND has tried at least ONE conventional synthetic disease-modifying antirheumatic drug (DMARD); OR
Note: Examples include methotrexate, leflunomide, and sulfasalazine.

b) Patient has axial spondyloarthritis with objective signs of inflammation, defined as at least one of the following [(1) or (2)]:

(1) C-reactive protein elevated beyond the upper limit of normal for the reporting laboratory; OR

(2) Sacroiliitis reported on magnetic resonance imaging; AND

ii. The medication is prescribed by or in consultation with a rheumatologist; OR

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR

Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS) and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then no more frequently than once every 6 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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17. Still's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient has tried one corticosteroid; AND
Note: Examples include prednisone and methylprednisolone.

ii. Patient has tried one conventional synthetic disease-modifying antirheumatic drug (DMARD) given for at least 2 months or was intolerant; AND
Note: An example is methotrexate. A previous trial of one biologic other than the requested drug (e.g., Actemra [tocilizumab intravenous injection, tocilizumab subcutaneous injection], Arcalyst [rilonacept subcutaneous injection], Ilaris [canakinumab subcutaneous injection]) also counts towards this requirement for previous therapy for Still's disease. A biosimilar of the requested biologic does not count.

iii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on an this medication for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR
Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 6 mg/kg as an intravenous fusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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18. Uveitis. Approve for the duration noted if the patient meets ONE of the following (A or B):
Note: This includes other posterior uveitides and panuveitis syndromes.

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried one of the following therapies: periocular, intraocular, or systemic corticosteroids, or immunosuppressives; AND
Note: Examples of corticosteroids include prednisolone, triamcinolone, betamethasone, methylprednisolone, prednisone. Examples of immunosuppressives include methotrexate, mycophenolate mofetil, and cyclosporine. An exception to the requirement for a trial of one of these therapies can be made if the patient has already had a trial of an etanercept product or an adalimumab product for uveitis. A patient who has already tried one biologic other than the requested medication also counts. A biosimilar of the requested biologic does not count.

ii. The medication is prescribed by or in consultation with an ophthalmologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR
Note: Examples of objective measures include best-corrected visual acuity, assessment of chorioretinal and/or inflammatory retinal vascular lesions, or anterior chamber cell grade or vitreous haze grade.

b) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased eye pain, redness, light sensitivity, and/or blurred vision; or improvement in visual acuity.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 10 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, then no more frequently than once every 4 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of infliximab intravenous products is not recommended in the following situations:

1. Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD). Data are lacking evaluating concomitant use of an infliximab product in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see APPENDIX for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of AEs and lack controlled trial data in support of additive efficacy.
Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with an infliximab product.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Ankylosing Spondylitis:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Crohn's Disease:** Initial approval duration was changed to 6 months (previously was 3 months). Note was clarified to state that a previous trial of a biologic applies to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. A note was added to clarify that a trial of mesalamine does not count as a systemic agent for Crohn's disease. For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Plaque Psoriasis:** Note was clarified to state that a previous trial of a biologic applies to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 90 days. Requirements were added that for a patient who is currently receiving an infliximab product, the patient must have at least one objective and at least one subjective response to therapy. Previously, response was more general and according to the prescriber. **Psoriatic Arthritis:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Rheumatoid Arthritis:** Initial approval duration was changed to 6 months (previously was 3 months). Note was clarified to state that a previous trial of a biologic applies to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Ulcerative Colitis:** Initial approval duration was changed to 6 months (previously was 3 months). Note was clarified to state that a previous trial of a biologic applies to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Behcet's Disease:** Note was clarified to state that a previous trial of a biologic applies to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 90 days. Requirements were added that for a patient who is currently receiving an infliximab product, the patient must have at least one objective and at least one subjective response to therapy. Previously, response was more general and according to the prescriber.	10/26/2022

	Graft-Versus-Host Disease: For a patient currently receiving, it was clarified that this applies to a patient who is receiving an infliximab product for ≥ 1 month. Requirements were added for a patient who is currently receiving, that there has been at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Hidradenitis Suppurativa:** For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an adalimumab product for ≥ 90 days. Requirements were added that for a patient who is currently receiving an infliximab product, the patient must have at least one objective and at least one subjective response to therapy. Previously, response was more general and according to the prescriber. **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Indeterminate Colitis:** The definition of indeterminate colitis (colitis that cannot be classified with certainty as either ulcerative colitis or Crohn's disease) was moved to a note; previously this was included in the indication. Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Juvenile Idiopathic Arthritis:** Initial approval duration was changed to 6 months (previously was 3 months). Note was clarified to state that a previous trial of a biologic applies to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. For continuation, approvals were changed to be 1 year in duration. Previously, response was more general and according to the prescriber, and approvals were for 3 years. **Pyoderma Gangrenosum:** For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 4 months. Requirements were added that for a patient who is currently receiving an infliximab product, the patient must have at least one objective and at least one subjective response to therapy. Previously, response was more general and according to the prescriber. **Sarcoidosis:** To align with guidelines, the note that includes examples of immunosuppressive medications was updated to add leflunomide, mycophenolate mofetil, and hydroxychloroquine; cyclosporine, chlorambucil, and thalidomide were removed from the examples. Cardiologist and neurologist were added to the list of specialists who must prescribe or be consulted for this indication. For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 90 days. Requirements were added that for a patient who is currently receiving an infliximab product, the patient must have at least one objective and at least one subjective response to therapy. Previously, response was more general and according to the prescriber. **Scleritis or Sterile Corneal Ulceration:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Spondyloarthritis, Other Subtypes:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab	

	product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Still's Disease:** Initial approval duration was changed to 6 months (previously was 3 months). Note was updated to state that a previous trial of one biologic other than the requested drug counts towards a requirement for previous therapy. A biosimilar of the requested biologic does not count. For a patient currently receiving, it was clarified that this applies to a patient who is receiving an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Uveitis:** Initial approval duration was changed to 6 months (previously was 3 months). Note was clarified to state that a previous trial of a biologic applies to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber.	
Annual Revision	**Ulcerative Colitis:** For a patient currently taking, a note was added to clarify that a mesalamine product does not count as a systemic therapy for ulcerative colitis. **Conditions Not Recommended for Approval:** Inflammatory Myopathies and Large Vessel Vasculitis were removed.	11/15/2023
Selected Revision	**Plaque Psoriasis:** For a patient currently taking an infliximab product, the timeframe for established on therapy was changed from 90 days to 3 months. **Behcet's Disease:** For a patient currently taking an infliximab product, the timeframe for established on therapy was changed from 90 days to 3 months. **Hidradenitis Suppurativa:** For a patient currently taking an infliximab product, the timeframe for established on therapy was changed from 90 days to 3 months. **Sarcoidosis:** For a patient currently taking an infliximab product, the timeframe for established on therapy was changed from 90 days to 3 months.	03/27/2024

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Zymfentra® (infliximab-dyyb SC injection)	Inhibition of TNF	CD, UC
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA, PMR
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17RA	PsO
Bimzelx® (bimekizumab-bkzx SC injection)	Inhibition of IL-17A and IL-17F	PsO
Cosentyx® (secukinumab SC injection, secukinumab IV infusion)	Inhibition of IL-17A	SC formulation: AS, ERA, nr-axSpA, PsO, PsA
		IV formulation: AS, nr-axSpA, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion)	Inhibition of IL-23	SC formulation: CD, PSA, PsO
		IV formulation: CD
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion, vedolizimab SC injection)	Integrin receptor antagonist	SC formulation: UC
		IV formulation: CD, UC
Oral Therapies/Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Cibinqo™ (abrocitinib tablets)	Inhibition of JAK pathways	AD
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	AD, AS, nr-axSpA, RA, PsA, UC
Sotyktu™ (deucravacitinib tablets)	Inhibition of TYK2	PsO
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; PMR – Polymyalgia rheumatic; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

EXPRESS SCRIPTS®

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Inflammatory Conditions – Omvoh Intravenous Utilization Management Medical Policy
- Omvoh® (mirikizumab-mrkz intravenous infusion – Eli Lilly)

REVIEW DATE: 11/08/2023

OVERVIEW

Omvoh intravenous, a monoclonal antibody against the p19 subunit of the interleukin (IL)-23 cytokine, is indicated for **induction treatment of ulcerative colitis** (UC), in adults with moderate to severe active disease.[1]

In UC, a three-dose induction regimen (300 mg at Weeks 0, 4, and 8) is administered by IV infusion.[1] Following induction therapy with the IV product, the recommended maintenance is Omvoh subcutaneous injection, given as a 200 mg subcutaneous injection administered at Week 12 (4 weeks following the last induction dose), then once every 4 weeks thereafter.

Guidelines

Current guidelines do not address the use of Omvoh for UC. The American Gastroenterological Association (2020) and the American College of Gastroenterology (2019) have clinical practice guidelines on the management of moderate to severe UC and make recommendations for the use of biologics for induction and maintenance of remission in adults.[2,3] Generally TNF inhibitors, Entyvio® (vedolizumab intravenous infusion/subcutaneous injection), Stelara® (ustekinumab intravenous infusion/subcutaneous injection), or Xeljanz®/Xeljanz® XR (tofacitinib tablets, tofacitinib extended-release tablets) are recommended for induction treatment of moderate to severe disease (strong recommendations, moderate quality of evidence). The guidelines also recommend that any drug that effectively treats induction should be continued for maintenance.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Omvoh IV. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). Because of the specialized skills required for evaluation and diagnosis of patients treated with Omvoh as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Omvoh IV to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for three months, which is an adequate duration for the patient to receive three doses.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Omvoh intravenous is recommended in those who meet one of the following:

FDA-Approved Indication

1. **Ulcerative Colitis.** Approve three doses for induction if the patient meets the following (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** The medication will be used as induction therapy; AND
   - **C)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has tried one systemic therapy; OR
       Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone or methylprednisolone. A trial of a mesalamine product does not count as a systemic therapy for ulcerative colitis. A trial of one biologic other than the requested medication also counts as a trial of one systemic agent for ulcerative colitis. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for ulcerative colitis.
     - **ii.** Patient meets BOTH of the following (a and b):
       - **a)** Patient has pouchitis; AND
       - **b)** Patient has tried an antibiotic, probiotic, corticosteroid enema, or mesalamine enema; AND
         Note: Examples of antibiotics include metronidazole and ciprofloxacin. Examples of corticosteroid enemas include hydrocortisone enema.
   - **D)** The medication is prescribed by or in consultation with a gastroenterologist.

   Dosing: Approve 300 mg as an intravenous infusion administered at Weeks 0, 4, and 8.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Omvoh intravenous is not recommended in the following situations:

1. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Omvoh intravenous should not be administered in combination with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples). Data are lacking evaluating concomitant use of Omvoh with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples). Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects and lack of controlled data supporting additive efficacy. Note: This does NOT exclude the use of conventional agents (e.g., methotrexate, 6-mercaptopurine, azathioprine, and sulfasalazine) in combination with Omvoh intravenous.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Omvoh injection [prescribing information]. Indianapolis, IN: Eli Lilly; October 2023.
2. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384-413.
3. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology*. 2020 Apr158(5):1450-1461.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	-	11/08/2023
Update	11/14/2023: No criteria changes. Added Note stating trial of a mesalamine product does not count as systemic therapy.	NA

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Zymfentra® (infliximab-dyyb SC injection)	Inhibition of TNF	CD, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx® (secukinumab SC injection)	Inhibition of IL-17A	AS, ERA, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion)	Inhibition of IL-23	SC formulation: CD, PSA, PsO
		IV formulation: CD
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion, vedolizimab SC injection)	Integrin receptor antagonist	SC: UC
		IV: CD, UC
Oral Therapies/Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Cibinqo™ (abrocitinib tablets)	Inhibition of JAK pathways	AD
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	AD, AS, nr-axSpA, RA, PsA, UC
Sotyktu™ (deucravacitinib tablets)	Inhibition of TYK2	PsO
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC
Zeposia® (ozanimod tablets)	Sphingosine 1 phosphate receptor modulator	UC
Velsipity® (etrasimod tablets)	Sphingosine 1 phosphate receptor modulator	UC

* Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Inflammatory Conditions – Orencia Intravenous Utilization Management Medical Policy
- Orencia® (abatacept intravenous infusion – Bristol-Myers Squibb)

REVIEW DATE: 03/13/2024

OVERVIEW

Orencia intravenous, a selective T-cell costimulation modulator, is indicated for the following uses:[1]

- **Graft-versus-host disease (GVHD)**, for prophylaxis of acute GVHD in combination with a calcineurin inhibitor and methotrexate, in patients ≥ 2 years of age undergoing hematopoietic stem cell transplantation from a matched or 1 allele-mismatched unrelated donor.
- **Juvenile idiopathic arthritis**, in patients ≥ 2 years of age with moderately to severely active polyarticular disease.
- **Psoriatic arthritis (PsA)**, in adults with active disease.
- **Rheumatoid arthritis**, in adults with moderately to severely active disease.

Orencia is not recommended for use concomitantly with other potent immunosuppressants such as biologics or Janus kinase inhibitors. Orencia is available as an intravenous infusion that is dosed on body weight. There is also a subcutaneous injection available in prefilled syringes. Some patients initiating therapy with Orencia subcutaneous will receive a single loading dose with Orencia intravenous.

Guidelines

Orencia is addressed in guidelines for treatment of various inflammatory conditions.

- **GVHD:** Guidelines for hematopoietic cell transplantation for pre-transplant recipient evaluation and management of GVHD are available from the National Comprehensive Cancer Network (NCCN) [version 3.2023 – October 9, 2023].[9] Immunosuppresive agents are commonly used for the prevention of GVHD. Orencia is among the therapies listed for treatment of steroid-refractory chronic GVHD.
- **Juvenile Idiopathic Arthritis:** Guidelines from American College of Rheumatology (ACR) [2019] list biologics among the treatment options for subsequent therapy in patients with polyarthritis.[3] Initial therapy with a biologic may be considered for patients with risk factors and involvement of high-risk joints (e.g., cervical spine, wrist, or hip), high disease activity, and/or those judged to be at high risk of disabling joint damage. In patients with active sacroiliitis or enthesitis despite nonsteroidal anti-inflammatory drug use, a tumor necrosis factor inhibitor (TNFi) is recommended.
- **PsA:** Guidelines from ACR (2018) recommend TNFis over other biologics for use in treatment-naïve patients with PsA and in those who were previously treated with an oral therapy.[4] However, Orencia may be considered over other biologics in patients with recurrent or serious infections.
- **Rheumatoid Arthritis:** Guidelines from the ACR (2021) recommend addition of a biologic or a targeted synthetic disease modifying anti-rheumatic drug (DMARD) for a patient taking the maximum tolerated dose of methotrexate who is not at target.[2]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Orencia intravenous. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). Because of the specialized skills required for evaluation and diagnosis of patients treated with Orencia intravenous as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Orencia intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. For prevention of GVHD, the approval duration is for 30 days, which is an adequate duration for the patient to receive four doses.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Orencia intravenous is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. Graft-Versus-Host Disease – Prevention. Approve for 4 doses if the patient meets ALL of the following (A, B, C, D, E, and F):

A) Patient is ≥ 2 years of age; AND

B) Orencia is being used for prevention of acute graft-versus-host disease; AND

C) Patient will also receive a calcineurin inhibitor for prevention of acute graft-versus-host disease; AND

Note: Examples of calcineurin inhibitors include cyclosporine and tacrolimus.

D) Patient will also receive methotrexate for prevention of acute graft-versus-host disease; AND

E) Patient will undergo hematopoietic stem cell transplantation from one of the following donors (i or ii):

i. Matched unrelated donor; OR

ii. 1-allele-mismatched unrelated donor; AND

F) The medication is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center.

Dosing. Approve if dosing meets the following (A and B):

A) The dose meets ONE of the following (i or ii):

i. Patient is ≥ 6 years of age: Approve up to 10 mg/kg to a maximum of 1,000 mg per dose; OR

ii. Patient is ≥ 2 and < 6 years of age: Approve up to 15 mg/kg.

B) A dose is administered the day before transplantation, then on Days 5, 14, and 28 after transplantation.

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2. Juvenile Idiopathic Arthritis (JIA). Approve for the duration noted if the patient meets ONE of the following (A or B):

Note: This includes JIA regardless of type of onset. JIA is also referred to as Juvenile Rheumatoid Arthritis.

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

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i. Patient meets one of the following (a, b, c, or d):
- **a)** Patient has tried one other agent for this condition; OR
  Note: Examples of therapies which could have been tried include methotrexate, sulfasalazine, leflunomide, and a nonsteroidal anti-inflammatory drug (NSAID). A biologic other than the requested drug also counts as a trial of one agent for JIA. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for JIA.
- **b)** Patient will be starting on therapy concurrently with methotrexate, sulfasalazine, or leflunomide; OR
- **c)** Patient has an absolute contraindication to methotrexate, sulfasalazine, or leflunomide; OR
  Note: Examples of absolute contraindications to methotrexate include pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, blood dyscrasias.
- **d)** Patient has aggressive disease, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Orencia (Intravenous or Subcutaneous). Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):
- **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
  Note: Examples of objective measures include Physician Global Assessment (MD global), Parent/Patient Global Assessment of Overall Well-Being (PGA), Parent/Patient Global Assessment of Disease Activity (PDA), Juvenile Arthritis Disease Activity Score (JDAS), Clinical Juvenile Arthritis Disease Activity Score (cJDAS), Juvenile Spondyloarthritis Disease Activity Index (JSpADA), serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.
- **b)** Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue, improved function or activities of daily living.

Dosing. Approve if dosing meets the following (A and B):

A) The weight-based dose meets ONE of the following (i, ii, or iii):
- **i.** 10 mg/kg if the patient weighs < 75 kg; OR
- **ii.** 750 mg if the patient weighs 75 kg to 100 kg; OR
- **iii.** 1,000 mg if the patient weights > 100 kg; AND

B) The dose is administered at Weeks 0, 2, and 4, then every 4 weeks thereafter.

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3. Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving Orencia (Intravenous or Subcutaneous). Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requesting drug); OR
Note: Examples of standardized measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortuium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths).

Dosing. Approve if dosing meets the following (A and B):

A) The dose is based on the patient's weight and meets ONE of the following (i, ii, or iii):
- **i.** 500 mg if the patients weighs < 60 kg; OR
- **ii.** 750 mg if the patient weighs 60 kg to 100 kg; OR
- **iii.** 1,000 mg if the patient weighs > 100 kg; AND

B) The dose is administered at Weeks 0, 2, and 4, then every 4 weeks thereafter.

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4. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i and ii):

i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND
Note: Examples of conventional synthetic DMARDs include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already had a 3-month trial of at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic is not required to "step back" and try a conventional synthetic DMARD.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Orencia (Intravenous or Subcutaneous). Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
Note: Examples of standardized and validated measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II,

Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

Dosing. Approve if dosing meets the following (A and B):

A) The dose is based on the patient's weight and meets ONE of the following (i, ii, or iii):
- **i.** 500 mg if the patients weighs < 60 kg; OR
- **ii.** 750 mg if the patient weighs 60 kg to 100 kg; OR
- **iii.** 1,000 mg if the patient weighs > 100 kg; AND

B) The dose is administered at Weeks 0, 2, and 4, then every 4 weeks thereafter.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Orencia intravenous is not recommended in the following situations:

1. **Ankylosing Spondylitis.** In an open-label Phase II trial, Orencia was administered intravenously on Days 1, 15, 29, and every 28 days thereafter to patients with active ankylosing spondylitis.[5] Patients received a fixed dosage of Orencia of approximately 10 mg/kg based on body weight. The primary endpoint was a 40% improvement in disease activity at Week 24 in the Assessment of SpondyloArthritis international Society criteria (ASAS 40). At Week 24, the ASAS 40 was 13.3% (n = 2/15) in tumor necrosis factor inhibitor (TNFi)-naïve patients compared with no responses in patients who had previously failed TNFis (n = 15). ASAS 20 response was 26.7% (n = 4/15) in TNFi-naïve patients compared with 20% (n = 3/15) in those who had previously failed TNFis. A major response was not shown with treatment to Orencia.

2. **Concurrent Use with a Biologic or with a Targeted Synthetic DMARD.** Orencia intravenous should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see Appendix for examples).[1] Combination therapy is generally not recommended due to a higher rate of adverse events with combinations and lack of data supportive of additional efficacy. Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Orencia intravenous.

3. **Inflammatory Bowel Disease (i.e., Crohn's Disease, Ulcerative Colitis).** In placebo-controlled trials evaluating the efficacy of Orencia intravenous for induction and maintenance in adults with active, moderate to severe Crohn's disease (n = 451) and ulcerative colitis (n = 490), Orencia was no more effective than placebo.[6] Patients were randomized to Orencia 30, 10, or 3 mg/kg (according to body weight) or placebo and dosed at Weeks 0, 2, 4, and 8. A total of 90 patients with Crohn's disease and 131 patients with ulcerative colitis who responded to induction were then randomized to Orencia 10 mg/kg or placebo every 4 weeks through Week 52. When used for induction of Crohn's disease, 17.2%, 10.2%, and 15.5% of patients receiving Orencia 30 mg, 10 mg, and 3 mg/kg achieved a clinical response at Weeks 8 and 12 compared with 14.4% of patients receiving placebo (P = not significant [NS] for all comparisons). In patients with Crohn's disease, response and remission at Week 52 was not significantly different between the Orencia intravenous and placebo treatment groups. When used as induction therapy in ulcerative colitis, 21.4%, 19.0%, and 20.3% of patients receiving Orencia 30 mg, 10 mg, and 3 mg/kg achieved a clinical response at Week 12 compared with 29.5% of patients receiving placebo (P = 0.043 for 10 mg/kg vs. placebo; other comparisons P = NS). At Week 52, 12.5% (n =

8/64) and 14.1% (n = 9/64) of patients with ulcerative colitis were in remission (P = NS) and 17.2% of patients in each treatment group (n = 11/64 for each group) had achieved a response.

4. **Psoriasis**. (Note: Patients with concomitant plaque psoriasis and psoriatic arthritis may be reviewed under the psoriatic arthritis criteria above.) In the pivotal trial evaluating Orencia subcutaneous for psoriatic arthritis, there was not a significant difference at Week 24 in the proportion of patients with a 50% reduction in the Psoriasis Area and Severity Index (PASI 50) response vs. placebo ± conventional synthetic (cs)DMARD (27% vs. 20% with placebo ± csDMARD; P = NS).[8] In a multicenter, Phase I, 26-week, open-label dose-escalation study, 43 patients with stable plaque psoriasis (10% to 49% body surface area involvement) received four doses of Orencia given as a 1-hour intravenous infusion on Days 1, 3, 16, and 29.[7] The starting dose was 0.5 mg/kg. Four to six patients were accrued to each of eight dose levels: 0.5, 1, 2, 4, 8, 16, 25, and 50 mg/kg. A parallel control group was matched for age and overall disease severity. In all, 46% of patients on Orencia achieved a 50% or greater sustained improvement in clinical disease activity (Physician's Global Assessment of disease activity) compared with baseline psoriasis evaluation. Progressively greater effects were observed with the highest doses. Further studies are needed to establish safety and efficacy, as well as appropriate dosing in plaque psoriasis.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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2. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2021;73(7):1108-1123.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	02/22/2023
Annual Revision	No criteria changes.	03/13/2024

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Zymfentra® (infliximab-dyyb SC injection)	Inhibition of TNF	CD, UC
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA, PMR
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17RA	PsO
Bimzelx® (bimekizumab-bkzx SC injection)	Inhibition of IL-17A and IL-17F	PsO
Cosentyx® (secukinumab SC injection, secukinumab IV infusion)	Inhibition of IL-17A	SC formulation: AS, ERA, nr-axSpA, PsO, PsA
		IV formulation: AS, nr-axSpA, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Omvoh® (mirikizumab-mrkz SC injection, mirikizumab-mrkz IV infusion)	Inhibition of IL-23	UC
Skyrizi® (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion)	Inhibition of IL-23	SC formulation: CD, PSA, PsO
		IV formulation: CD
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion, vedolizimab SC injection)	Integrin receptor antagonist	SC formulation: UC
		IV formulation: CD, UC
Oral Therapies/Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Cibinqo™ (abrocitinib tablets)	Inhibition of JAK pathways	AD
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	AD, AS, nr-axSpA, RA, PsA, UC
Sotyktu™ (deucravacitinib tablets)	Inhibition of TYK2	PsO
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC
Velsipity® (etrasimod tablets)	Sphingosine 1 phosphate receptor modulator	UC
Zeposia® (ozanimod tablets)	Sphingosine 1 phosphate receptor modulator	UC

* Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; PMR – Polymyalgia rheumatic; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Inflammatory Conditions – Simponi Aria Utilization Management Medical Policy
- Simponi Aria® (golimumab intravenous infusion – Janssen)

REVIEW DATE: 12/20/2023

OVERVIEW

Simponi Aria, a tumor necrosis factor inhibitor (TNFi), is indicated for the following conditions:[1]
- **Ankylosing spondylitis**, in adults with active disease.
- **Polyarticular juvenile idiopathic arthritis**, in patients ≥ 2 years of age with active disease.
- **Psoriatic arthritis**, in patients ≥ 2 years of age with active disease.
- **Rheumatoid arthritis**, in combination with methotrexate for treatment of adults with moderately to severely active disease.

Simponi Aria is administered by intravenous infusion by a healthcare professional. Efficacy has not been established for patients switching between the Simponi Aria and Simponi subcutaneous.

Guidelines

TNFis feature prominently in guidelines for treatment of inflammatory conditions.
- **Juvenile Idiopathic Arthritis (JIA):** There are guidelines from American College of Rheumatology (ACR) and the Arthritis Foundation for the treatment of JIA (2021) which address oligoarthritis and temporomandibular joint (TMJ) arthritis. For oligoarthritis, a biologic is recommended following a trial of a conventional synthetic DMARD.[9] In patients with TMJ arthritis, scheduled nonsteroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular glucocorticoids are recommended first-line. A biologic is a therapeutic option if there is an inadequate response or intolerance. Additionally, rapid escalation to a biologic ± conventional synthetic DMARD (methotrexate preferred) is often appropriate given the impact and destructive nature of TMJ arthritis. In these guidelines, there is not a preferred biologic that should be initiated for JIA. Simponi (golimumab, route not specified) is among the TNFis recommended in the ACR/Arthritis Foundation guidelines for the treatment of JIA (2019) specific to juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[4] TNFis are the biologics recommended for polyarthritis, sacroiliitis, enthesitis. Biologics are recommended following other therapies (e.g., following a conventional synthetic disease-modifying antirheumatic drug [DMARD] for active polyarthritis or following a nonsteroidal anti-inflammatory drug [NSAID] for active JIA with sacroiliitis or enthesitis). However, there are situations where initial therapy with a biologic may be preferred over other conventional therapies (e.g., if there is involvement of high-risk joints such as the cervical spine, wrist, or hip; high disease activity; and/or those judged to be at high risk of disabling joint damage).
- **Psoriatic Arthritis:** Guidelines from ACR (2019) recommend TNFis over other biologics for use in treatment-naïve patients with psoriatic arthritis, and in those who were previously treated with an oral therapy.[5]
- **Rheumatoid Arthritis:** Guidelines from the ACR (2021) recommend addition of a biologic or a targeted synthetic DMARD for a patient taking the maximum tolerated dose of methotrexate who is not at target.[6]
- **Spondyloarthritis:** Guidelines for ankylosing spondylitis and non-radiographic axial spondyloarthritis are published by the ACR/Spondylitis Association of America/Spondyloarthritis

Research and Treatment Network (2019).[2] Following primary nonresponse to a TNFi, an interleukin (IL)-17 blocker is recommended; however, if the patient is a secondary nonresponder, a second TNFi is recommended over switching out of the class. In patients with a contraindication to a TNFi, use of an IL-17 blocker is recommended over traditional oral agents such as methotrexate or sulfasalazine.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Simponi Aria. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration listed below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Simponi Aria as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Simponi Aria to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Simponi Aria is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Ankylosing Spondylitis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving Simponi Aria or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):
     - **i.** Patient has been established on therapy for at least 6 months; AND
       Note: A patient who has received < 6 months of therapy or who is restarting therapy with Simponi Aria or subcutaneous is reviewed under criterion A (Initial Therapy).
     - **ii.** Patient meets at least one of the following (a or b):
       - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Simponi Aria or subcutaneous); OR
         Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).
       - **b)** Compared with baseline (prior to initiating Simponi Aria or subcutaneous), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

Dosing. Approve up to 2 mg/kg as an intravenous infusion at Weeks 0 and 4, then not more frequently than once every 8 weeks thereafter.

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2. Juvenile Idiopathic Arthritis (JIA). Approve for the duration noted if the patient meets ONE of the following (A or B):
Note: This includes JIA regardless of type of onset, including a patient with juvenile spondyloarthropathy/active sacroiliac arthritis. JIA is also referred to as Juvenile Rheumatoid Arthritis.

A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i and ii):
- **i.** Patient meets ONE of the following conditions (a or b):
  - **a)** Patient has tried one other medication for this condition; OR
    Note: Examples of other medications for JIA include methotrexate, sulfasalazine, leflunomide, or a nonsteroidal anti-inflammatory drug (NSAID) [e.g., ibuprofen, naproxen]. A previous trial of a biologic other than the requested medication also counts as a trial of one medication. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for JIA.
  - **b)** Patient has aggressive disease, as determined by the prescriber; AND
- **ii.** The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Simponi Aria or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on therapy for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with Simponi Aria or subcutaneous is reviewed under criterion A (Initial Therapy).
- **ii.** Patient meets at least one of the following (a or b):
  - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Simponi Aria or subcutaneous); OR
    Note: Examples of objective measures include Physician Global Assessment (MD global), Parent/Patient Global Assessment of Overall Well-Being (PGA), Parent/Patient Global Assessment of Disease Activity (PDA), Juvenile Arthritis Disease Activity Score (JDAS), Clinical Juvenile Arthritis Disease Activity Score (cJDAS), Juvenile Spondyloarthritis Disease Activity Index (JSpADA), serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.
  - **b)** Compared with baseline (prior to initiating Simponi Aria or subcutaneous), patient experienced an improvement in at least one symptom, such as improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue, or improved function or activities of daily living.

Dosing. Approve up to 80 mg/m^2 as an intravenous infusion at Weeks 0 and 4, then not more frequently than once every 8 weeks thereafter.

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3. Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist or dermatologist.

B) Patient is Currently Receiving Simponi Aria or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with Simponi Aria or subcutaneous is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Simponi Aria or subcutaneous); OR
Note: Examples of objective measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating Simponi Aria or subcutaneous), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; or decreased soft tissue swelling in joints or tendon sheaths.

Dosing. Approve ONE of the following regimens (A or B):

A) Patient is ≥ 18 years of age: Approve up to 2 mg/kg as an intravenous infusion at Weeks 0 and 4, then not more frequently than once every 8 weeks thereafter; OR

B) Patient is < 18 years of age: Approve up to 80 mg/m^2 as an intravenous infusion at Weeks 0 and 4, then not more frequently than once every 8 weeks thereafter.

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4. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND
Note: Examples of conventional synthetic DMARDs include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already had a 3-month trial of at least one biologic other than the requested medication. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic for rheumatoid arthritis is not required to "step back" and try a conventional synthetic DMARD.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Simponi Aria or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Simponi Aria or subcutaneous is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
Note: Examples of objective measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate or C-reactive protein, Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; or decreased soft tissue swelling in joints or tendon sheaths.

Dosing. Approve up to 2 mg/kg as an intravenous infusion at Weeks 0 and 4, then not more frequently than once every 8 weeks thereafter.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Simponi Aria is not recommended in the following situations:

1. **Concurrent Use with Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Data are lacking evaluating concomitant use of Simponi Aria in combination with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of adverse events with combinations and lack controlled trial data in support of additive efficacy. Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Simponi Aria.

2. **Ulcerative Colitis.** Simponi subcutaneous injection is indicated for treatment of ulcerative colitis.[7] A single-dose induction study in patients with ulcerative colitis (n = 176) evaluated doses of 1 mg/kg, 2 mg/kg, and 4 mg/kg; however, enrollment was stopped due to lower than expected efficacy in the dose-ranging Phase II portion of the study.[8] Appropriate dosing of Simponi Aria in ulcerative colitis is unclear.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Ankylosing Spondylitis:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving Simponi Aria or subcutaneous, it was clarified that this applies to a patient who has received the product for ≥ 6 months. A requirement was added for a patient who is currently receiving Simponi Aria or subcutaneous to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Juvenile Idiopathic Arthritis:** Initial approval duration was changed to 6 months (previously was 3 months). Note was clarified to state that a previous trial of a biologic applies to at least one biologic other than the requested drug. For a patient currently receiving Simponi Aria or subcutaneous, it was clarified that this applies to a patient who has received the product for ≥ 6 months. A requirement was added for a patient who is currently receiving Simponi Aria or subcutaneous to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Psoriatic Arthritis:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving Simponi Aria or subcutaneous, it was clarified that this applies to a patient who has received the product for ≥ 6 months. A requirement was added for a patient who is currently receiving Simponi Aria or subcutaneous to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Rheumatoid Arthritis:** Initial approval duration was changed to 6 months (previously was 3 months). Note was clarified to state that a previous trial of a biologic applies to at least one biologic other than the requested drug. For a patient currently receiving Simponi Aria or subcutaneous, it was clarified that this applies to a patient who has received the product for ≥ 6 months. A requirement was added for a patient who is currently receiving Simponi Aria or subcutaneous to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber.	11/30/2022
Annual Revision	No criteria changes.	12/20/2023

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Zymfentra® (infliximab-dyyb SC injection)	Inhibition of TNF	CD, UC
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA, PMR
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17RA	PsO
Bimzelx® (bimekizumab-bkzx SC injection)	Inhibition of IL-17A and IL-17F	PsO
Cosentyx® (secukinumab SC injection, secukinumab IV infusion)	Inhibition of IL-17A	SC formulation: AS, ERA, nr-axSpA, PsO, PsA
		IV formulation: AS, nr-axSpA, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion)	Inhibition of IL-23	SC formulation: CD, PSA, PsO
		IV formulation: CD
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion, vedolizimab SC injection)	Integrin receptor antagonist	SC formulation: UC
		IV formulation: CD, UC
Oral Therapies/Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Cibinqo™ (abrocitinib tablets)	Inhibition of JAK pathways	AD
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	AD, AS, nr-axSpA, RA, PsA, UC
Sotyktu™ (deucravacitinib tablets)	Inhibition of TYK2	PsO
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; PMR – Polymyalgia rheumatic; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Inflammatory Conditions – Spevigo Intravenous Utilization Management Medical Policy
- Spevigo® (spesolimab-sbzo intravenous infusion – Boehringer Ingelheim)

REVIEW DATE: 04/10/2024

OVERVIEW
Spevigo, an interleukin-36 receptor antagonist, is indicated for the treatment of generalized pustular psoriasis in adults and pediatric patients ≥ 12 years old and ≥ 40 kilogram (kg).[1]

Spevigo intravenous (IV) use is only for the treatment of generalized pustular psoriasis flares. IV infusion of Spevigo is only to be administered by a healthcare professional in a healthcare setting.[1]

Dosing Information
Spevigo is given as a single 900 mg dose by intravenous (IV) infusion over 90 minutes. If the generalized pustular psoriasis flare symptoms persist, an additional 900 mg dose given IV (over 90 minutes) may be administered one week after the initial dose.[1]

Guidelines
Spevigo is not listed in guidelines for generalized pustular psoriasis. Treatment guidelines from the Medical Board of the National Psoriasis Foundation (2012) address the management of generalized pustular psoriasis in different clinical scenarios.[2] Recommended therapies include acitretin, cyclosporine, methotrexate, and infliximab for adults with generalized pustular psoriasis as first-line therapy. Second-line therapy includes Humira, Enbrel, topical therapy (e.g. corticosteroids, calcipotriene, and tacrolimus), and PUVA (psoralen and ultraviolet A). There are also separate recommendations for pediatric and pregnant patients.

POLICY STATEMENT
Prior Authorization is recommended for medical benefit coverage of Spevigo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for 1 month (30 days). Because of the specialized skills required for evaluation and diagnosis of patients treated with Spevigo approval requires Spevigo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Spevigo is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Generalized Pustular Psoriasis Flare.** Approve for up to two doses if the patient meets ALL of the following (A, B, C, D, E and F:
   - **A)** Patient is ≥ 12 years of age; AND
   - **B)** Patient weighs ≥ 40 kilograms (kg); AND
   - **C)** Patient is experiencing a flare of a moderate-to-severe intensity; AND
   - **D)** Patient meets ONE of the following (i or ii):
     - **i.** Patient is not currently receiving Spevigo subcutaneous injection and meets ALL of the following (a, b, c, and d):
       - **a)** Patient has Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score of ≥ 3 points; AND
         Note: The Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score ranges from 0 (clear skin) to 4 (severe disease).
       - **b)** Patient has a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of ≥ 2 points; AND
       - **c)** Patient has new or worsening pustules; AND
       - **d)** Patient has erythema and pustules which affects ≥ 5% of body surface area; OR
     - **ii**. Patient is currently receiving Spevigo subcutaneous injection and meets BOTH of the following (a and b):
       - **a)** Patient has had an increase in Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score of ≥ 2 points; AND
       - **b)** Patient has Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of ≥ 2 points; AND
   - **E)** If patient has already received Spevigo intravenous, patient meets BOTH of the following (i and ii):
     - **i.** Patient has not already received two doses of Spevigo intravenous for treatment of the current flare; AND
     - **ii.** If patient has previously received two doses of Spevigo intravenous, at least 12 weeks have elapsed since the last dose of Spevigo; AND
   - **F)** The medication is prescribed by or in consultation with a dermatologist.

   Dosing. Approve the following dosing regimens (A, B, and C):
   - **A)** Approve 900 mg per dose administered by intravenous (IV) infusion; AND
   - **B)** If a second dose is administered, 7 days elapse between the doses; AND
   - **C)** If this a new flare, at least 12 weeks have elapsed since the last dose of Spevigo.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Spevigo is not recommended in the following situations:

1. **Concomitant use with Another Biologic Prescribed for Treatment of Generalized Pustular Psoriasis.** Although not approved, there are case reports documenting use of some biologics approved for plaque psoriasis (see Appendix for examples) for treatment of generalized pustular psoriasis. In the pivotal study, patients were required to discontinue therapy for generalized pustular psoriasis prior to receiving Spevigo.
   Note: Patients with concomitant plaque psoriasis and generalized pustular psoriasis may be receiving a biologic for treatment of plaque psoriasis.

2. **Plaque Psoriasis.** Spevigo has not been studied in patients with plaque psoriasis without generalized pustular psoriasis.
   Note: Patients with concomitant plaque psoriasis and generalized pustular psoriasis may be reviewed under the generalized pustular psoriasis criteria above.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Spevigo® intravenous infusion and subcutaneous injection [prescribing information]. Ridgefield, CT: Boehringer Ingelheim; March 2024.
2. Robinson A, Van Voorhees AS, Hsu S, et al. Treatment of pustular psoriasis: from the medical board of the National Psoriasis Foundation. *J Am Acad Dermatol.* 2012;67(2):279-288.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	10/04/2023
Early Annual Revision	The name of the policy was changed to Inflammatory Conditions – Spevigo Intravenous UM Medical Policy. Previously it was Inflammatory Conditions – Spevigo UM Medical Policy. **Generalized Pustular Psoriasis Flare**: The word "flare" was added the condition of approval. The age requirement was changed from ≥ 18 years of age to ≥ 12 years of age. The weight requirement of ≥ 40 kilogram (kg) was added. Clarification was added that the following criteria apply to a patient who is not currently taking Spevigo subcutaneous: patient has Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score of ≥ 3 points; and patient has a GPPGA pustulation subscore of ≥ 2 points; and patient has new or worsening pustules; and patient has erythema and pustules which affects ≥ 5% of body surface area. Criteria was added for patient currently taking Spevigo subcutaneous which are: patient has had an increase in GPPGA total score of ≥ 2 points and patient has GPPGA pustulation subscore of ≥ 2 points. Reference to Spevigo was reworded to Spevigo intravenous in the following criterion "if patient has already received Spevigo intravenous (IV), patient has not already received two doses of Spevigo IV for treatment of the current flare". The following criterion was reworded from "if this is a new flare" to state "if patient has previously received two doses of Spevigo IV" at least 12 weeks have elapsed since the last dose of Spevigo.	04/10/2024

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PsA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx® (secukinumab SC injection)	Inhibition of IL-17A	AS, ERA, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion)	Inhibition of IL-23	SC formulation: CD, PsA, PsO
		IV formulation: CD
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC

* Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Inflammatory Conditions – Tocilizumab Intravenous Products Utilization Management Medical Policy
- Actemra® (tocilizumab intravenous infusion – Genentech/Roche)
- Tyenne® (tocilizumab-aazg intravenous infusion – Fresenius Kabi)

REVIEW DATE: 04/24/2024

OVERVIEW

Tocilizumab intravenous infusion, an interleukin-6 (IL-6) receptor inhibitor, is indicated for the following conditions:[1]

- **Coronavirus Disease 2019 (COVID-19)**, in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).
- **Cytokine release syndrome**, in patients ≥ 2 years of age with severe or life-threatening disease associated with chimeric antigen receptor (CAR) T-cell therapy.
- **Giant cell arteritis** in adults.
- **Polyarticular juvenile idiopathic arthritis**, for the treatment of active disease in patients ≥ 2 years of age.
- **Rheumatoid arthritis**, for treatment of adults with moderate to severe active disease who have had an inadequate response to one or more disease modifying antirheumatic drugs (DMARDs).
- **Systemic juvenile idiopathic arthritis**, for the treatment of active disease in patients ≥ 2 years of age.

Dosing Information

In rheumatoid arthritis, many dose modifications are recommended for the management of dose-related laboratory changes such as increased liver enzymes, neutropenia, and thrombocytopenia.[1] In conditions other than rheumatoid arthritis, reduced dosing of tocilizumab intravenous generally follows the recommendations for rheumatoid arthritis. Dose interruptions of tocilizumab intravenous are recommended for certain laboratory abnormalities and are similar to those recommended in rheumatoid arthritis. Dosing modifications are determined by the prescriber. Specifically for cytokine release syndrome associated with CAR T-cell therapy, the median number of tocilizumab intravenous doses administered in the pivotal trial was one dose (range, 1 to 4 doses).

Guidelines/Clinical Efficacy

IL-6 blockers are mentioned in multiple guidelines for treatment of inflammatory conditions. Clinical data also support use of tocilizumab in other conditions.

- **Cytokine Release Syndrome:** The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for Management of Immunotherapy-Related Toxicities (version 1.2024 – December 7, 2023) give specific recommendations for use of tocilizumab in the management of inflammatory arthritis, cytokine release syndrome, and CAR T-cell-related toxicities.[6]
  - For cytokine release syndrome and CAR T-cell-related toxicities, tocilizumab is recommended for all grades of disease.
  - For immune checkpoint inhibitor-related inflammatory arthritis, infliximab and tocilizumab are among the alternatives that may be considered for severe arthritis not responding to steroids.

- **Giant Cell Arteritis and Polymyalgia Rheumatica:** Recommendations from the European League Against Rheumatism (EULAR) [2023] state the diagnosis of giant cell arteritis may be made without biopsy if there is a high suspicion of giant cell arteritis and a positive imaging test.[25] In the pivotal trial evaluating tocilizumab subcutaneous for giant cell arteritis (n = 251), patients were treated with corticosteroids in an open-label fashion (20 mg to 60 mg/day) during the screening period prior to treatment with tocilizumab subcutaneous.[31,32] Sustained remission at Week 52 was achieved in 56% of patients who received tocilizumab subcutaneous every week + 26-week prednisone taper and 53% of patients who received Actemra every other week + 26-week prednisone taper vs. in 14% of patients in the 26-week prednisone taper and 18% of patients in the 52-week prednisone taper.
- **Polyarticular Juvenile Idiopathic Arthritis:** Guidelines for the treatment of juvenile idiopathic arthritis from the American College of Rheumatology (ACR) [2021] address oligoarthritis and temporomandibular joint (TMJ) arthritis.[31] For oligoarthritis, a biologic is recommended following a trial of a conventional synthetic DMARD. In patients with TMJ arthritis, scheduled nonsteroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular glucocorticoids are recommended first-line. A biologic is a therapeutic option if there is an inadequate response or intolerance. Additionally, rapid escalation to a biologic ± conventional synthetic DMARD (methotrexate preferred) is often appropriate given the impact and destructive nature of TMJ arthritis. In these guidelines, there is not a preferred biologic that should be initiated for JIA. ACR/Arthritis Foundation has guidelines for the treatment of juvenile idiopathic arthritis (2019) specific to juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[7] For patients without risk factors, initial therapy with a DMARD is conditionally recommended over a biologic (including tocilizumab). Biologics (e.g., Actemra) are conditionally recommended as initial treatment when combined with a DMARD over biologic monotherapy.
- **Rheumatoid Arthritis:** Guidelines from ACR (2021) recommend addition of a biologic or a targeted synthetic DMARD for a patient taking the maximum tolerated dose of methotrexate who is not at target.[9]
- **Systemic Juvenile Idiopathic Arthritis:** Guidelines for the treatment of JIA from the ACR (2021) address systemic juvenile idiopathic arthritis (SJIA).[8] A brief trial of NSAIDs and/or an interleukin (IL)-1 or IL-6 inhibitor are recommended as initial monotherapy for patients with SJIA without macrophage activation syndrome. In a patient who presents with macrophage activation syndrome, an IL-1 or IL-6 blocker and/or systemic glucocorticoids are recommended.
- **Castleman's Disease:** The NCCN clinical practice guidelines for Castleman Disease (version 1.2024 – January 18, 2024) mention tocilizumab as a second-line therapy for relapsed or refractory unicentric Castleman disease in patients who are negative for the human immunodeficiency virus and human herpesvirus-8.[10] For multicentric Castleman's disease, the guidelines list tocilizumab as a subsequent therapy for relapsed, refractory, or progressive disease.
- **COVID-19 (Coronavirus Disease 2019):** By inhibiting IL-6, tocilizumab is speculated to be associated with better clinical outcomes in COVID-19, such as decreased systemic inflammation, improved survival rate, better hemodynamics, and improvement of respiratory distress.[24]
- **Still's Disease:** Still's disease presents in adults with features similar to those of SJIA.[11] Tocilizumab IV has been effective in reducing fever, symptoms, and markers of inflammation in patients who were refractory to treatment with prednisone, methotrexate, Kineret, and/or a tumor necrosis factor inhibitor.[11-20]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of tocilizumab intravenous products. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended

approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of a patient treated with tocilizumab intravenous as well as the monitoring required for adverse events and long-term efficacy, initial approval requires tocilizumab intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

*Indications and/or approval conditions noted with **[eviCore]** are managed by eviCore healthcare for those clients who use eviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to eviCore at www.eviCore.com.*

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tocilizumab Intravenous Products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **COVID-19 (Coronavirus Disease 2019) – Hospitalized Patient.** For a patient who is hospitalized, forward all requests to the Medical Director. For a non-hospitalized patient, do not approve (refer to Conditions Not Recommended for Approval – COVID-19 – Non-Hospitalized Patient). Tocilizumab intravenous is indicated for COVID-19 only in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[1] For COVID-19, the dose is 8 mg/kg (to a maximum of 800 mg) given as a single intravenous infusion. A second dose may be administered at least 8 hours after the initial infusion if clinical signs or symptoms worsen or do not improve after the first dose.
   Note: This includes requests for cytokine release syndrome in a patient hospitalized with COVID-19.

2. **Cytokine Release Syndrome Associated with Chimeric Antigen Receptor (CAR) T-Cell Therapy.** ***[eviCore]*** Approve for 1 week (which is adequate duration to receive four doses) if prescribed for a patient who has been or will be treated with a CAR T-cell therapy.
   Note: Examples of CAR T-cell therapy include Abecma (idecabtagene vicleucel injection), Breyanzi (lisocabtagene maraleucel intravenous infusion), Kymriah (tisagenlecleucel intravenous infusion), Tecartus (brexucabtagene intravenous infusion), and Yescarta (axicabtagene ciloleucel intravenous infusion). If the patient has **Cytokine Release Syndrome due to COVID-19** (coronavirus disease 2019) refer to criteria for Other Uses With Supportive Evidence (below).

   Dosing. Approve the following regimens:
   A) Each individual dose must meet the following (i or ii):
      i. Patient is < 30 kg: Approve up to 12 mg/kg to a maximum of 800 mg per dose.
      ii. Patient is ≥ 30 kg: Approve up to 8 mg/kg to a maximum of 800 mg per dose.
   B) Approve up to four doses if there will be an interval of at least 8 hours between doses.

3. Giant Cell Arteritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried one systemic corticosteroid; AND
Note: An example of a systemic corticosteroid is prednisone.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving a Tocilizumab Subcutaneous or Intravenous Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating a tocilizumab product); OR
Note: Examples of objective measures are serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), resolution of fever, and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating a tocilizumab product), patient experienced an improvement in at least one symptom, such as decreased headache, scalp, or jaw pain; decreased fatigue; and/or improved vision.

Dosing. Approve dosing that meets the following (A and B):

A) Approve up to 6 mg/kg to a maximum of 600 mg per dose; AND

B) There must be an interval of at least 4 weeks between doses.

4. Polyarticular Juvenile Idiopathic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following conditions (a, b, c, or d):

a) Patient has tried one other systemic therapy for this condition; OR
Note: Examples of other systemic therapies include methotrexate, sulfasalazine, leflunomide, or a nonsteroidal anti-inflammatory drug (NSAID). A biologic (refer to **Appendix** for examples of biologics used for polyarticular juvenile idiopathic arthritis) also counts as a trial of one systemic therapy.

b) Patient will be starting on a tocilizumab intravenous product concurrently with methotrexate, sulfasalazine, or leflunomide; OR

c) Patient has an absolute contraindication to methotrexate, sulfasalazine, or leflunomide; OR
Note: Examples of absolute contraindication to methotrexate include pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, and blood dyscrasias.

d) Patient has aggressive disease, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving a Tocilizumab Intravenous or Subcutaneous Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating a tocilizumab product); OR
Note: Examples of objective measures include Physician Global Assessment (MD global), Parent/Patient Global Assessment of Overall Well-Being (PGA), Parent/Patient Global Assessment of Disease Activity (PDA), Juvenile Arthritis Disease Activity Score (JDAS), Clinical Juvenile Arthritis Disease Activity Score (cJDAS), Juvenile Spondyloarthritis Disease Activity Index (JSpADA), serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating a tocilizumab product), patient experienced an improvement in at least one symptom, such as improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue, improved function or activities of daily living.

Dosing. Approve dosing that meets BOTH of the following (A and B):

A) Each individual dose must meet ONE of the following (i or ii):
- **i.** Patient is < 30 kg: Approve up to 10 mg/kg up to a maximum of 800 mg per dose; OR
- **ii.** Patient is ≥ 30 kg: Approve up to 8 mg/kg up to a maximum of 800 mg per dose.

B) There must be an interval of at least 4 weeks between doses.

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5. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
- **i.** Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND
  Note: Examples of one conventional DMARD tried include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already had a 3-month trial of at least one biologic (refer to **Appendix** for examples of biologics used for rheumatoid arthritis). A patient who has already tried a biologic for rheumatoid arthritis is not required to "step back" and try a conventional synthetic DMARD.
- **iii.** The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving a Tocilizumab Intravenous or Subcutaneous Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on therapy for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).
- **ii.** Patient meets at least ONE of the following (a or b):
  - **a)** Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
    Note: Examples of standardized and validated measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).
  - **b)** Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

Dosing. Approve dosing that meets BOTH of the following (A and B):
A) Approve up to 8 mg/kg to a maximum of 800 mg per dose; AND
B) There must be an interval of at least 4 weeks between doses.

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6. Systemic Juvenile Idiopathic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i and ii):
i. The patient has tried one other systemic therapy for this condition; AND
Note: Examples of other systemic therapies include a corticosteroid (oral, intravenous), a conventional synthetic disease-modifying antirheumatic drug (DMARD) [e.g., methotrexate, leflunomide, sulfasalazine], a 1-month trial of a nonsteroidal anti-inflammatory drug (NSAID), Kineret (anakinra subcutaneous injection), or Ilaris (canakinumab subcutaneous injection). A biosimilar of Actemra does not count.
ii. The medication is prescribed by or in consultation with a rheumatologist.
B) Patient is Currently Receiving a Tocilizumab Intravenous or Subcutaneous Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):
i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).
ii. Patient meets at least ONE of the following (a or b):
a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.
b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

Dosing. Approve the following dosing regimens:
A) Each individual dose must meet ONE of the following (i or ii):
i. Patient is < 30 kg: Approve up to 12 mg/kg per dose; OR
ii. Patient is ≥ 30 kg: Approve up to 8 mg/kg per dose.
B) There must be an interval of at least 1 week between doses.

Other Uses with Supportive Evidence

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7. Castleman Disease. ***[eviCore]*** Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Approval. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
i. Patient is negative for the human immunodeficiency virus (HIV) and human herpesvirus-8 (HHV-8); AND
ii. The medication is being used for relapsed or refractory disease; AND
iii. The medication is prescribed by or in consultation with an oncologist or hematologist.
B) Patient is Currently Receiving a Tocilizumab Intravenous or Subcutaneous Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate, fibrinogen, albumin, and/or hemoglobin), increased body mass index, and/or reduction in lymphadenopathy.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as improvement or resolution of constitutional symptoms (e.g., fatigue, physical function).

Dosing. Approve the following dosing regimen:

A) Approve up to 8 mg/kg per dose.

B) There must be an interval of at least 1 week between doses.

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8. Inflammatory Arthritis Associated with Checkpoint Inhibitor Therapy. Approve for the duration noted if the patient meets ONE of the following (A or B):
Note: Examples of checkpoint inhibitors are Keytruda (pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), Yervoy (ipilimumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion), Bavencio (avelumab intravenous infusion), Imfinzi (durvalumab intravenous infusion), and Libtayo (cemiplimab-rwlc intravenous infusion).

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient is symptomatic despite a trial of at least ONE systemic corticosteroid; AND
Note: Examples of a corticosteroid include methylprednisolone and prednisone.

ii. Patient has tried at least ONE systemic nonsteroidal anti-inflammatory agent (NSAID); AND
Note: Examples of systemic NSAIDs include ibuprofen and naproxen.

iii. The medication is prescribed by or in consultation with a rheumatologist or an oncologist.

B) Patient is Currently Receiving a Tocilizumab Intravenous or Subcutaneous Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate) and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

Dosing. Approve dosing that meets the following (A and B):

A) Approve up to 8 mg/kg to a maximum of 800 mg per dose.

B) There must be an interval of at least 4 weeks between doses.

9. Polymyalgia Rheumatica. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried one systemic corticosteroid; AND
Note: An example of a systemic corticosteroid is prednisone.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving a Tocilizumab Subcutaneous or Intravenous Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating a tocilizumab product); OR
Note: Examples of objective measures are serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), resolution of fever, and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating a tocilizumab product), patient experienced an improvement in at least one symptom, such as decreased shoulder, neck, upper arm, hip, or thigh pain or stiffness; improved range of motion; and/or decreased fatigue.

Dosing. Approve dosing that meets the following (A and B):

A) Approve up to 6 mg/kg to a maximum of 600 mg per dose; AND

B) There must be an interval of at least 4 weeks between doses.

10. Still's Disease, Adult Onset. Approve for the duration noted if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient meets ONE of the following (a, b, or c):

a) Patient meets BOTH of the following [(1) and (2)]:

(1) Patient has tried one corticosteroid; AND

(2) Patient has tried one conventional synthetic disease-modifying antirheumatic drug (DMARD) such as methotrexate given for at least 2 months or was intolerant to a conventional synthetic DMARD; OR

b) Patient has at least moderate to severe active systemic features of this condition, according to the prescriber; OR
Note: Examples of moderate to severe active systemic features include fever, rash, lymphadenopathy, hepatomegaly, splenomegaly, and serositis.

c) Patient has active systemic features with concerns of progression to macrophage activation syndrome, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving a Tocilizumab Intravenous or Subcutaneous Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on this medication for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

Dosing. Approve dosing that meets the following (A and B):
A) Approve up to 8 mg/kg per dose.
B) There must be an interval of at least 2 weeks between doses.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of a Tocilizumab Intravenous Product is not recommended in the following situations:

1. **COVID-19 (Coronavirus Disease 2019) – Non-Hospitalized Patient.** Tocilizumab intravenous is only indicated in hospitalized adults with COVID who are receiving systemic corticosteroids and requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[1] For COVID-19, the dose is 8 mg/kg (to a maximum of 800 mg) given as a single intravenous infusion. A second dose may be administered at least 8 hours after the initial infusion if clinical signs or symptoms worsen or do not improve after the first dose.

2. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Data are lacking evaluating concomitant use of a tocilizumab intravenous in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see **Appendix** for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of adverse effects and lack of controlled trial data in support of additive efficacy.[21-22]
Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with tocilizumab intravenous.

3. **Crohn's Disease.** In a 12-week pilot study conducted in Japan, 36 adults with active Crohn's disease (Crohn's Disease Activity Index [CDAI] ≥ 150 and increased C-reactive protein) were randomized, in a double-blind fashion to tocilizumab 8 mg/kg intravenous every 2 weeks; or alternating infusions of tocilizumab 8 mg/kg every 4 weeks and placebo (i.e., alternating with placebo every 2 weeks), or to placebo every 2 weeks.[23] At baseline the CDAI means ranged from 287 to 306. Patients had been treated with corticosteroids, mesalamine-type drugs, metronidazole, or elemental diet. Six patients in the placebo group, four patients on tocilizumab intravenous every 4 weeks and one patient on tocilizumab intravenous every 2 weeks dropped out. The mean reduction in the CDAI score in the tocilizumab 8 mg/kg every 2 week group was 88 points (from mean 306 to 218). Further studies are needed.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	05/10/2023
Early Annual Revision	Tyenne (biosimilar to Actemra Intravenous) was added to the policy with the same criteria as Actemra Intravenous. Policy was renamed as Inflammatory Conditions – Tocilizumab Intravenous Products. Throughout the policy, wording was changed from Actemra to tocilizumab. **Systemic Juvenile Idiopathic Arthritis:** The Note was revised to remove tumor necrosis factor inhibitors from the examples of other systemic therapies that could have been tried prior to Actemra subcutaneous. **Still's Disease, Adult Onset:** The condition was changed to as listed (previously was Still's Disease). Exceptions were added for a patient who, according to the prescriber, had moderate to severe active systemic features or active systemic features and concerns of progression to macrophage activation syndrome; a patient with these features is not required to try a corticosteroid or a disease-modifying antirheumatic drug prior to tocilizumab intravenous. **Castleman Disease:** For initial therapy, requirements were added that the patient is negative for the human immunodeficiency virus and human herpesvirus-8 and that the patient has relapsed or refractory disease.	04/24/2024

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Zymfentra® (infliximab-dyyb SC injection)	Inhibition of TNF	CD, UC
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA, PMR
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17RA	PsO
Bimzelx® (bimekizumab-bkzx SC injection)	Inhibition of IL-17A and IL-17F	PsO
Cosentyx® (secukinumab SC injection, secukinumab IV infusion)	Inhibition of IL-17A	SC formulation: AS, ERA, nr-axSpA, PsO, PsA
		IV formulation: AS, nr-axSpA, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion)	Inhibition of IL-23	SC formulation: CD, PSA, PsO
		IV formulation: CD
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion, vedolizimab SC injection)	Integrin receptor antagonist	SC formulation: UC
		IV formulation: CD, UC
Oral Therapies/Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Cibinqo™ (abrocitinib tablets)	Inhibition of JAK pathways	AD
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	AD, AS, nr-axSpA, RA, PsA, UC
Sotyktu™ (deucravacitinib tablets)	Inhibition of TYK2	PsO
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; PMR – Polymyalgia rheumatic; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Iron Replacement – Feraheme Utilization Management Medical Policy
- Feraheme® (ferumoxytol intravenous infusion – AMAG, generic)

REVIEW DATE: 1/10/2024

OVERVIEW

Feraheme, an iron replacement product, is indicated for the treatment of **iron deficiency anemia** in patients ≥ 18 years of age for the following uses:[1]
- **Chronic kidney disease** (CKD).
- **Intolerance to oral iron or have had unsatisfactory response to oral iron**.

Dosing Information

Feraheme is administered by intravenous (IV) infusion and treatment may be repeated if iron deficiency remains persistent or recurring.[1] The recommended dose of Feraheme is an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later per treatment cycle.

Guidelines

The Kidney Disease: Improving Global Outcomes guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[2] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of IV iron (or in non-dialysis patients with CKD, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in hemoglobin (Hb) concentration without starting ESA treatment is desired and transferrin saturation (TSAT) is ≤ 30% and ferritin is ≤ 500 ng/mL. For adults with CKD on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in non-dialysis CKD patients, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For all pediatric patients with CKD with anemia not on iron or ESA therapy, oral iron (or IV iron in patients receiving hemodialysis) is recommended when TSAT is ≤ 20% and ferritin is ≤ 100 ng/mL. For all pediatric patients with CKD who are receiving ESA therapy but not receiving iron supplementation, it is recommended to administer oral iron (or IV iron for patients receiving hemodialysis) to maintain TSAT > 20% and ferritin > 100 ng/dL.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 2.2024 – December 12, 2023) discuss the management of cancer- and chemotherapy-induced anemia.[3] Treatment for iron deficiency is guided by iron status which is defined in the guidelines as: absolute iron deficiency, functional iron deficiency, possible functional iron deficiency, or no iron deficiency. IV iron therapy is considered an option for patients with absolute iron deficiency (ferritin < 30 ng/mL and TSAT < 20%), functional iron deficiency (ferritin = 30 to 500 ng/mL and TSAT < 50%) in patients who are also receiving an ESA, and for select patients with possible functional iron deficiency (ferritin = 501 to 800 ng/mL and TSAT < 50%).

The American College of Cardiology/American Heart Association guideline for the management of heart failure (2022) states that in patients with heart failure with reduced ejection fraction (left ventricular ejection fraction ≤ 40%), absolute iron deficiency (ferritin < 100 ng/mL) or functional iron deficiency (ferritin = 100 to 300 mg/mL if TSAT is < 20%), and with or without anemia, IV iron replacement is reasonable to improve functional status and quality of life (2a recommendation).[4]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Feraheme. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Feraheme as well as the monitoring required for adverse events and long-term efficacy, particular approvals require Feraheme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Feraheme is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis**. Approve for 3 years.

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2. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis**. Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Feraheme is prescribed by or in consultation with a nephrologist or hematologist.

   Dosing. Approve up to a maximum cumulative total dose of 1020 mg given intravenously per 30 days.

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3. **Iron Deficiency Anemia, Other.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets ONE of the following (i, ii, iii, or iv):
     - **i.** Patient meets BOTH of the following (a and b):
       - **a)** Patient has tried oral iron supplementation; AND
       - **b)** According to the prescriber, oral iron supplementation was ineffective or intolerable; OR
     - **ii.** Patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease)C; OR
     - **iii.** Patient is currently receiving an erythroid stimulating agent; OR
       Note: Examples of erythroid stimulating agents include an epoetin alfa product, a darbepoetin alfa product, or a methoxy polyethylene glycol-epoetin beta product.
     - **iv.** The medication is being requested for cancer- or chemotherapy-related anemia.

   Dosing. Approve up to a maximum cumulative total dose of 1020 mg given intravenously per 30 days.

Other Uses with Supportive Evidence

4. **Iron Deficiency Associated with Heart Failure.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Feraheme is being prescribed by or in consultation with a cardiologist or hematologist.

   Dosing. Approve up to a maximum cumulative total dose of 1020 mg given intravenously per 30 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Feraheme is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/14/2022
Annual Revision	No criteria changes	01/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Iron Replacement – Ferrlecit Utilization Management Medical Policy
- Ferrlecit® (sodium ferric gluconate complex in sucrose intravenous infusion – sanofi-aventis, generic)

REVIEW DATE: 01/10/2024

OVERVIEW

Ferrlecit, an iron replacement product, is indicated for the treatment of **iron deficiency anemia** in patients ≥ 6 years of age with **chronic kidney disease** (CKD) **receiving hemodialysis** who are receiving supplemental epoetin therapy.[1]

Dosing Information

The recommended dosage of Ferrlecit for the repletion treatment of iron deficiency in hemodialysis patients is 10 mL of Ferrlecit (125 mg of elemental iron).[1] For repletion treatment most adult patients may require a cumulative dose of 1000 mg of elemental iron administered over 8 dialysis sessions. The recommended pediatric dosage in hemodialysis patients is 0.12 mL/kg Ferrlecit (1.5 mg/kg of elemental iron) administered by intravenous (IV) infusion per dialysis session. The maximum pediatric dosage should not exceed 125 mg per dose.

Guidelines

The Kidney Disease: Improving Global Outcomes guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[2] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of IV iron (or in non-dialysis patients with CKD, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in hemoglobin (Hb) concentration without starting ESA treatment is desired, and transferrin saturation (TSAT) is ≤ 30% and ferritin is ≤ 500 ng/mL. For adults with CKD on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in non-dialysis CKD patients, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration or a decrease in ESA dose is desired, and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For all pediatric patients with CKD with anemia not on iron or ESA therapy, oral iron (or IV iron in patients receiving hemodialysis) is recommended when TSAT is ≤ 20% and ferritin is ≤ 100 ng/mL. For all pediatric patients with CKD who are receiving ESA therapy but not receiving iron supplementation, it is recommended to administer oral iron (or IV iron for patients receiving hemodialysis) to maintain TSAT > 20% and ferritin > 100 ng/dL.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 2.2024 – December 12, 2023) discuss the management of cancer- and chemotherapy-induced anemia.[3] Treatment for iron deficiency is guided by iron status which is defined in the guidelines as: absolute iron deficiency, functional iron deficiency, possible functional iron deficiency, or no iron deficiency. IV iron therapy is considered an option for patients with absolute iron deficiency (ferritin < 30 ng/mL and TSAT < 20%) in patients who are also receiving an ESA, functional iron deficiency (ferritin = 30 to 500 ng/mL and TSAT < 50%), and for select patients with possible functional iron deficiency (ferritin = 501 to 800 ng/mL and TSAT < 50%).

The American College of Cardiology/American Heart Association guideline for the management of heart failure (2022) states that in patients with heart failure with reduced ejection fraction (left ventricular ejection fraction ≤ 40%), absolute iron deficiency (ferritin < 100 ng/mL) or functional iron deficiency (ferritin =

100 to 300 mg/mL if TSAT is < 20%), and with or without anemia, IV iron replacement is reasonable to improve functional status and quality of life (2a recommendation).[4]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Ferrlecit. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ferrlecit as well as the monitoring required for adverse events and long-term efficacy, particular approvals require Ferrlecit to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ferrlecit is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis**. Approve for 3 years.

Other Uses with Supportive Evidence

2. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis**. Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient is ≥ 6 years of age; AND
   - **B)** Ferrlecit is prescribed by or in consultation with a nephrologist or hematologist.

   Dosing. Approve up to a maximum cumulative total dose of 1000 mg given intravenously per 30 days.

3. **Iron Deficiency Anemia, Other.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient is ≥ 6 years of age; AND
   - **B)** Patient meets ONE of the following (i, ii, iii, or iv):
     - **i.** Patient meets BOTH of the following (a and b):
       - **a)** Patient has tried oral iron supplementation; AND
       - **b)** According to the prescriber, oral iron supplementation was ineffective or intolerable; OR
     - **ii.** Patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR
     - **iii.** Patient is currently receiving an erythroid stimulating agent; OR
       Note: Examples of erythroid stimulating agents include an epoetin alfa product, a darbepoetin alfa product, or a methoxy polyethylene glycol-epoetin beta product.
     - **iv.** The medication is being requested for cancer- or chemotherapy-related anemia.

Dosing. Approve up to a maximum cumulative total dose of 1000 mg given intravenously per 30 days.

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4. Iron Deficiency Associated with Heart Failure. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient is ≥ 6 years of age; AND
- **B)** Ferrlecit is being prescribed by or in consultation with a cardiologist or hematologist.

Dosing. Approve up to a maximum cumulative total dose of 1000 mg given intravenously per 30 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ferrlecit is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Ferrlecit® [prescribing information]. Bridgewater, NJ: sanofi-aventis; March 2022.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int*. 2012;2(Suppl):279-335.
3. The NCCN Hematopoietic Growth Factors Guidelines in Oncology (version 2.2024 – December 12, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 4, 2024.
4. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in *J Am Coll Cardiol*. 2023 Apr 18;81(15):1551]. *J Am Coll Cardiol*. 2022;79(17):e263-e421.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/14/2022
Annual Revision	No criteria changes.	01/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Iron Replacement – INFeD Utilization Management Medical Policy
- INFeD® (iron dextran intravenous or intramuscular injection – Allergan)

REVIEW DATE: 01/10/2024

OVERVIEW

INFeD, an iron replacement product, is indicated for the treatment of documented **iron deficiency** in patients ≥ 4 months of age who have intolerance to oral iron or have had an unsatisfactory response to oral iron.[1]

Dosing Information

INFeD is administered by intravenous (IV) or intramuscular injection and treatment may be repeated if iron deficiency remains persistent or recurring.[1] The INFeD prescribing information gives formulas and table guides for individualized dosages.

Guidelines

The Kidney Disease: Improving Global Outcomes guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[2] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of IV iron (or in non-dialysis patients with CKD, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in hemoglobin (Hb) concentration without starting ESA treatment is desired, and transferrin saturation (TSAT) is ≤ 30% and ferritin is ≤ 500 ng/mL. For adults with CKD on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in non-dialysis CKD patients, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration or a decrease in ESA dose is desired, and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For all pediatric patients with CKD with anemia not on iron or ESA therapy, oral iron (or IV iron in patients receiving hemodialysis) is recommended when TSAT is ≤ 20% and ferritin is ≤ 100 ng/mL. For all pediatric patients with CKD who are receiving ESA therapy but not receiving iron supplementation, it is recommended to administer oral iron (or IV iron for patients receiving hemodialysis) to maintain TSAT > 20% and ferritin > 100 ng/dL.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 2.2024 – December 12, 2023) discuss the management of cancer- and chemotherapy-induced anemia.[3] Treatment for iron deficiency is guided by iron status which is defined in the guidelines as: absolute iron deficiency, functional iron deficiency, possible functional iron deficiency, or no iron deficiency. IV iron therapy is considered an option for patients with absolute iron deficiency (ferritin < 30 ng/mL and TSAT < 20%), functional iron deficiency (ferritin = 30 to 500 ng/mL and TSAT < 50%) in patients who are also receiving an ESA, and for select patients with possible functional iron deficiency (ferritin = 501 to 800 ng/mL and TSAT < 50%).

The American College of Cardiology/American Heart Association guideline for the management of heart failure (2022) states that in patients with heart failure with reduced ejection fraction (left ventricular ejection fraction ≤ 40%), absolute iron deficiency (ferritin < 100 ng/mL) or functional iron deficiency (ferritin = 100 to 300 mg/mL if TSAT is < 20%), and with or without anemia, IV iron replacement is reasonable to improve functional status and quality of life (2a recommendation).[4]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of INFeD. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with INFeD as well as the monitoring required for adverse events and long-term efficacy, particular approvals require INFeD to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of INFeD is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **Iron Deficiency Anemia, Other.** Approve for 1 year if the patient meets ONE of the following (A, B, C, or D):
   - **A)** Patient meets BOTH of the following (i and ii):
     - **i.** Patient has tried oral iron supplementation; AND
     - **ii.** According to the prescriber, oral iron supplementation was ineffective or intolerable; OR
   - **B)** Patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR
   - **C)** Patient is currently receiving an erythroid stimulating agent; OR
     Note: Examples of erythroid stimulating agents include an epoetin alfa product, a darbepoetin alfa product, or a methoxy polyethylene glycol-epoetin beta product.
   - **D)** The medication is being requested for cancer- or chemotherapy-related anemia.

   Dosing. Approve up to a maximum cumulative total dose of 1000 mg given intravenously or intramuscularly per 30 days.

Other Uses with Supportive Evidence

2. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis**. Approve for 3 years.

3. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis**. Approve for 1 year if the medication is prescribed by or in consultation with a nephrologist or hematologist.

   Dosing. Approve up to a maximum cumulative total dose of 1000 mg given intravenously or intramuscularly per 30 days.

4. **Iron Deficiency Associated with Heart Failure.** Approve for 1 year if the medication is being prescribed by or in consultation with a cardiologist or hematologist.

   Dosing. Approve up to a maximum cumulative total dose of 1000 mg given intravenously or intramuscularly per 30 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of INFeD is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. INFeD® [prescribing information]. Madison, NJ: Allergan; September 2021.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int*. 2012;2(Suppl):279-335.
3. The NCCN Hematopoietic Growth Factors Guidelines in Oncology (version 2.2024 – December 12, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 4, 2024.
4. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in *J Am Coll Cardiol*. 2023 Apr 18;81(15):1551]. *J Am Coll Cardiol*. 2022;79(17):e263-e421.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/14/2022
Annual Revision	No criteria changes.	01/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Iron Replacement – Injectafer Utilization Management Medical Policy
- Injectafer® (ferric carboxymaltose intravenous infusion or slow injection – American Regent)

REVIEW DATE: 01/10/2024

OVERVIEW

Injectafer, an iron replacement product, is indicated for the treatment of:[1]
- **Iron deficiency anemia** (IDA), in patients ≥ 1 year of age, with either an intolerance or unsatisfactory response to oral iron.
- **IDA,** in patients ≥ 18 years of age, with **non-dialysis dependent chronic kidney disease** (CKD).
- **Iron deficiency**, in patients ≥ 18 years of age, with **heart failure** and New York Heart Association class II/III to improve exercise capacity.

Dosing Information

Injectafer is administered by intravenous (IV) infusion or slow injection and treatment may be repeated if iron deficiency remains persistent or recurring. For treatment of IDA, patients weighing ≥ 50 kg, the recommended dose is up to 750 mg per dose with a total cumulative dose not to exceed 1500 mg per treatment course. For patients weighing < 50 kg, the recommended dose is 15 mg/kg in two doses separated by at least 7 days per course. See Table 1 for recommended dosage of Injectafer for the treatment of iron deficiency with heart failure.

Table 1. Recommended Dosage of Injectafer (ferric carboxymaltose injection) in Patients with Iron Deficiency with Heart Failure.[1]

	Weight < 70 kg			**Weight ≥ 70 kg**		
	Hb < 10 g/dL	**Hb 10-14 g/dL**	**Hb >14 to <15 g/dL***	**Hb < 10 g/dL**	**Hb 10-14 g/dL**	**Hb >14 to < 15 g/dL***
Day 1	1,000 mg	1,000 mg	500 mg	1,000 mg	1,000 mg	500 mg
Week 6	500 mg	No dose	No dose	1,000 mg	500 mg	No dose
Beyond Week 6	Administer a **maintenance dose** of 500 mg at 12, 24 and 36 weeks if serum ferritin < 100 ng/mL or serum ferritin 100 to 300 ng/mL with transferrin saturation < 20%.*					

Hb – hemoglobin; *There are no data available to guide dosing beyond 36 weeks or with Hb ≥15 g/dL.

Guidelines

The Kidney Disease: Improving Global Outcomes guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[2] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of IV iron (or in non-dialysis patients with CKD, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in hemoglobin (Hb) concentration without starting ESA treatment is desired, and transferrin saturation (TSAT) is ≤ 30% and ferritin is ≤ 500 ng/mL. For adults with CKD on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in non-dialysis CKD patients, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration or a decrease in ESA dose is desired, and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For all pediatric patients with CKD with anemia not on iron or ESA therapy, oral iron (or IV iron in patients receiving hemodialysis) is recommended when TSAT is ≤ 20% and ferritin is ≤ 100 ng/mL. For all pediatric patients with CKD who are receiving ESA therapy but not receiving iron supplementation,

it is recommended to administer oral iron (or IV iron for patients receiving hemodialysis) to maintain TSAT > 20% and ferritin > 100 ng/dL.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 2.2024 – December 12, 2023) discuss the management of cancer- and chemotherapy-induced anemia.[3] Treatment for iron deficiency is guided by iron status which is defined in the guidelines as: absolute iron deficiency, functional iron deficiency, possible functional iron deficiency, or no iron deficiency. IV iron therapy is considered an option for patients with absolute iron deficiency (ferritin < 30 ng/mL and TSAT < 20%), functional iron deficiency (ferritin = 30 to 500 ng/mL and TSAT < 50%) in patients who are also receiving an ESA, and for select patients with possible functional iron deficiency (ferritin = 501 to 800 ng/mL and TSAT < 50%).

The American College of Cardiology/American Heart Association guideline for the management of heart failure (2022) states that in patients with heart failure with reduced ejection fraction (left ventricular ejection fraction ≤ 40%), absolute iron deficiency (ferritin < 100 ng/mL) or functional iron deficiency (ferritin = 100 to 300 mg/mL if TSAT is < 20%), and with or without anemia, IV iron replacement is reasonable to improve functional status and quality of life (2a recommendation).[4]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Injectafer. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Injectafer as well as the monitoring required for adverse events and long-term efficacy, particular approvals require Injectafer to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Injectafer is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are NOT on Dialysis**. Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Injectafer is prescribed by or in consultation with a nephrologist or hematologist.

   Dosing. Approve up to a maximum cumulative total dose of 1500 mg given intravenously per 30 days.

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2. **Iron Deficiency Anemia, Other.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient is ≥ 1 year of age; AND
   - **B)** Patient meets ONE of the following (i, ii, iii, or iv):
     - **i.** Patient meets BOTH of the following (a and b):

a) Patient has tried oral iron supplementation; AND
b) According to the prescriber, oral iron supplementation was ineffective or intolerable; OR

ii. Patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR

iii. Patient is currently receiving an erythroid stimulating agent; OR
Note: Examples of erythroid stimulating agents include an epoetin alfa product, a darbepoetin alfa product, or a methoxy polyethylene glycol-epoetin beta product.

iv. The medication is being requested for cancer- or chemotherapy-related anemia.

Dosing. Approve up to a maximum cumulative total dose of 1500 mg given intravenously per 30 days.

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3. Iron Deficiency Associated with Heart Failure. Approve for 1 year if the patient meets the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) Injectafer is being prescribed by or in consultation with a cardiologist or hematologist.

Dosing. Approve up to a maximum cumulative total dose of 1500 mg given intravenously per 30 days.

Other Uses with Supportive Evidence

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4. Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis. Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Injectafer is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Injectafer® intravenous infusion or slow injection [prescribing information]. Shirley, NY: American Regent; May 2023.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int*. 2012;2(Suppl):279-335.
3. The NCCN Hematopoietic Growth Factors Guidelines in Oncology (version 2.2024 – December 12, 2023). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org Accessed on January 4, 2024.
4. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in *J Am Coll Cardiol*. 2023 Apr 18;81(15):1551]. *J Am Coll Cardiol*. 2022;79(17):e263-e421.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/14/2022
Update	**07/25/2023**: No criteria changes. **Iron Deficiency Associated with Heart Failure** indication was moved from "Other Uses with Supportive Evidence" to "FDA-Approved Indications." Overview was updated with recommended dosage in patients with iron deficiency with heart failure.	N/A
Annual Revision	No criteria changes.	01/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Iron Replacement – Monoferric Utilization Management Medical Policy
- Monoferric® (ferric derisomaltose intravenous infusion – Pharmacosmos)

REVIEW DATE: 01/10/2024

OVERVIEW

Monoferric, an iron replacement product, is indicated for the treatment of **iron deficiency anemia** in patients ≥ 18 years of age for the following uses:[1]
- Intolerance to oral iron or have had unsatisfactory response to oral iron.
- Non-hemodialysis **chronic kidney disease** (CKD).

Dosing Information

The recommended dose of Monoferric is 1000 mg in patients weighing ≥ 50 kg administered by intravenous (IV) infusion as a single dose per treatment cycle.[1] For patients weighing < 50 kg, the recommended dose is 20 mg/kg administered as a single dose per treatment cycle.

Guidelines

The Kidney Disease: Improving Global Outcomes guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[2] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of IV iron (or in non-dialysis patients with CKD, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in hemoglobin (Hb) concentration without starting ESA treatment is desired, and transferrin saturation (TSAT) is ≤ 30% and ferritin is ≤ 500 ng/mL. For adults with CKD on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in non-dialysis CKD patients, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration or a decrease in ESA dose is desired, and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For all pediatric patients with CKD with anemia not on iron or ESA therapy, oral iron (or IV iron in patients receiving hemodialysis) is recommended when TSAT is ≤ 20% and ferritin is ≤ 100 ng/mL. For all pediatric patients with CKD who are receiving ESA therapy but not receiving iron supplementation, it is recommended to administer oral iron (or IV iron for patients receiving hemodialysis) to maintain TSAT > 20% and ferritin > 100 ng/dL.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 2.2024 – December 12, 2023) discuss the management of cancer- and chemotherapy-induced anemia.[3] Treatment for iron deficiency is guided by iron status which is defined in the guidelines as: absolute iron deficiency, functional iron deficiency, possible functional iron deficiency, or no iron deficiency. IV iron therapy is considered an option for patients with absolute iron deficiency (ferritin < 30 ng/mL and TSAT < 20%), functional iron deficiency (ferritin = 30 to 500 ng/mL and TSAT < 50%) in patients who are also receiving an ESA, and for select patients with possible functional iron deficiency (ferritin = 501 to 800 ng/mL and TSAT < 50%).

The American College of Cardiology/American Heart Association guideline for the management of heart failure (2022) states that in patients with heart failure with reduced ejection fraction (left ventricular ejection fraction ≤ 40%), absolute iron deficiency (ferritin < 100 ng/mL) or functional iron deficiency (ferritin = 100 to 300 mg/mL if TSAT is < 20%), and with or without anemia, IV iron replacement is reasonable to improve functional status and quality of life (2a recommendation).[4]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Monoferric. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Monoferric as well as the monitoring required for adverse events and long-term efficacy, particular approvals require Monoferric to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Monoferric is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis**. Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Monoferric is prescribed by or in consultation with a nephrologist or hematologist.

   Dosing. Approve up to a maximum dose of 1000 mg given intravenously per 30 days.

2. **Iron Deficiency Anemia, Other.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets ONE of the following (i, ii, iii, or iv):
     - **i.** Patient meets BOTH of the following (a and b):
       - **a)** Patient has tried oral iron supplementation; AND
       - **b)** According to the prescriber, oral iron supplementation was ineffective or intolerable; OR
     - **ii.** Patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR
     - **iii.** Patient is currently receiving an erythroid stimulating agent; OR
       Note: Examples of erythroid stimulating agents include an epoetin alfa product, a darbepoetin alfa product, or a methoxy polyethylene glycol-epoetin beta product.
     - **iv.** The medication is being requested for cancer- or chemotherapy-related anemia.

   Dosing. Approve up to a maximum dose of 1000 mg given intravenously per 30 days.

Other Uses with Supportive Evidence

3. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis**. Approve for 3 years.

4. **Iron Deficiency Associated with Heart Failure.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Monoferric is being prescribed by or in consultation with a cardiologist or hematologist.

   Dosing. Approve up to a maximum dose of 1000 mg given intravenously per 30 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Monoferric is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Monoferric® intravenous infusion [prescribing information]. Holbaek, Denmark: Pharmacosmos; August 2022.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int*. 2012;2(Suppl):279-335.
3. The NCCN Hematopoietic Growth Factors Guidelines in Oncology (version 2.2024 – December 12, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 4, 2024.
4. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in *J Am Coll Cardiol*. 2023 Apr 18;81(15):1551]. *J Am Coll Cardiol*. 2022;79(17):e263-e421.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/14/2022
Annual Revision	No criteria changes.	01/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Iron Replacement – Venofer Utilization Management Medical Policy
- Venofer® (iron sucrose intravenous infusion or slow injection – American Regent)

REVIEW DATE: 01/10/2024

OVERVIEW

Venofer, an iron replacement product, is indicated for the treatment of **iron deficiency anemia** in patients with **chronic kidney disease** (CKD).[1]

Dosing Information

Venofer is administered by intravenous (IV) infusion or slow injection and treatment may be repeated if iron deficiency remains persistent or recurring.[1] Dosage and dosing frequency varies depending on patient age, if there is a need for dialysis, and if needed, what type if dialysis (hemodialysis or peritoneal). The recommended maximum total course dose is 1000 mg per treatment cycle.

Guidelines

The Kidney Disease: Improving Global Outcomes guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[2] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of IV iron (or in non-dialysis patients with CKD, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in hemoglobin (Hb) concentration without starting ESA treatment is desired, and transferrin saturation (TSAT) is ≤ 30% and ferritin is ≤ 500 ng/mL. For adults with CKD on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in non-dialysis CKD patients, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration or a decrease in ESA dose is desired, and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For all pediatric patients with CKD with anemia not on iron or ESA therapy, oral iron (or IV iron in patients receiving hemodialysis) is recommended when TSAT is ≤ 20% and ferritin is ≤ 100 ng/mL. For all pediatric patients with CKD who are receiving ESA therapy but not receiving iron supplementation, it is recommended to administer oral iron (or IV iron for patients receiving hemodialysis) to maintain TSAT > 20% and ferritin > 100 ng/dL.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 2.2024 – December 12, 2023) discuss the management of cancer- and chemotherapy-induced anemia.[3] Treatment for iron deficiency is guided by iron status which is defined in the guidelines as: absolute iron deficiency, functional iron deficiency, possible functional iron deficiency, or no iron deficiency. IV iron therapy is considered an option for patients with absolute iron deficiency (ferritin < 30 ng/mL and TSAT < 20%), functional iron deficiency (ferritin = 30 to 500 ng/mL and TSAT < 50%) in patients who are also receiving an ESA, and for selected patients with possible functional iron deficiency (ferritin = 501 to 800 ng/mL and TSAT < 50%).

The American College of Cardiology/American Heart Association guideline for the management of heart failure (2022) states that in patients with heart failure with reduced ejection fraction (left ventricular ejection fraction ≤ 40%), absolute iron deficiency (ferritin < 100 ng/mL) or functional iron deficiency (ferritin = 100 to 300 mg/mL if TSAT is < 20%), and with or without anemia, IV iron replacement is reasonable to improve functional status and quality of life (2a recommendation).[4]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Venofer. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Venofer as well as the monitoring required for adverse events and long-term efficacy, particular approvals require Venofer to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Venofer is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis**. Approve for 3 years.

2. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis**. Approve for 1 year if the medication is prescribed by or in consultation with a nephrologist or hematologist.

   Dosing. Approve up to a maximum cumulative total dose of 1000 mg given intravenously per 30 days.

Other Uses with Supportive Evidence

3. **Iron Deficiency Anemia, Other.** Approve for 1 year if the patient meets ONE of the following (A, B, C, or D):
   - **A)** Patient meets BOTH of the following (i and ii):
     - **i.** Patient has tried oral iron supplementation; AND
     - **ii.** According to the prescriber, oral iron supplementation was ineffective or intolerable; OR
   - **B)** Patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR
   - **C)** Patient is currently receiving an erythroid stimulating agent; OR
     Note: Examples of erythroid stimulating agents include an epoetin alfa product, a darbepoetin alfa product, or a methoxy polyethylene glycol-epoetin beta product.
   - **D)** The medication is being requested for cancer- or chemotherapy-related anemia.

   Dosing. Approve up to a maximum cumulative total dose of 1000 mg given intravenously per 30 days.

4. **Iron Deficiency Associated with Heart Failure.** Approve for 1 year if the medication is being prescribed by or in consultation with a cardiologist or hematologist.

   Dosing. Approve up to a maximum cumulative total dose of 1000 mg given intravenously per 30 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Venofer is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Venofer® intravenous infusion or slow injection [prescribing information]. Shirley, NY: American Regent; June 2022.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int*. 2012;2(Suppl):279-335.
3. The NCCN Hematopoietic Growth Factors Guidelines in Oncology (version 2.2024 – December 12, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 4, 2024.
4. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in *J Am Coll Cardiol*. 2023 Apr 18;81(15):1551]. *J Am Coll Cardiol*. 2022;79(17):e263-e421.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/14/2022
Annual Revision	No criteria changes.	01/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Lupus – Benlysta Intravenous Utilization Management Medical Policy
- Benlysta® (belimumab intravenous infusion – GlaxoSmithKline)

REVIEW DATE: 03/13/2024

OVERVIEW

Benlysta intravenous, a B-lymphocyte stimulator (BLyS)-specific inhibitor, is indicated for the following uses:[1]

- **Lupus nephritis**, in patients ≥ 5 years of age with active disease who are receiving standard therapy.
- **Systemic lupus erythematosus** (SLE), in patients ≥ 5 years of age with active, autoantibody-positive, systemic disease who are receiving standard therapy.

Benlysta has not been studied and is not recommended in patients with severe active central nervous system lupus.

Guidelines

European League Against Rheumatism (EULAR) guidelines for SLE (2023) recommend hydroxychloroquine for all patients, unless contraindicated.[2] Depending on the type and severity of organ involvement, glucocorticoids can be used but dosing should be minimized or withdrawn. Methotrexate, azathioprine, mycophenolate, and/or biologic agents (Benlysta, Saphnelo® [anifrolumab-fnia intravenous infusion]) should be considered in patients who do not respond to hydroxychloroquine ± glucocorticoids. EULAR also states biologic agents (Benlysta, Saphnelo) should be considered as second-line therapy for the treatment of active skin disease. Patient with active proliferative lupus nephritis should also consider combination therapy with biologic agents (Benlysta, Lupkynis™ [voclosporin capsules]). In general, the pharmacological interventions are directed by patient characteristics and the type/severity of organ involvement.

Guidelines for the management of lupus nephritis from Kidney Disease: Improving Global Outcomes (KDIGO) [2024] recommendations include Benlysta or Lupkynis in combination with other medications plus glucocorticoids as initial treatment options for patients with active Class III or IV biopsy confirmed lupus nephritis (strong recommendation, moderate certainty of evidence).[3] No preference is given between the treatment protocol options; however, the KDIGO guidelines do provide individual patient clinical factors to consider, including but not limited to, kidney function and histology, risk of disease flare, proteinuria, background suppression, and need for parenteral therapy.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Benlysta intravenous. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Benlysta intravenous as well as the monitoring required for adverse events and long-term efficacy, approval requires Benlysta intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Benlysta intravenous is recommended in those who meet one of the following:

FDA-Approved Indications

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1. Lupus Nephritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, and iv):

- **i.** Patient is ≥ 5 years of age; AND
- **ii.** Diagnosis of lupus nephritis has been confirmed on biopsy; AND
  Note: For example, World Health Organization class III, IV, or V lupus nephritis.
- **iii.** The medication is being used concurrently with an immunosuppressive regimen; AND
  Note: Examples of an immunosuppressive regimen include azathioprine, cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil, and/or a systemic corticosteroid.
- **iv.** The medication is prescribed by or in consultation with a nephrologist or rheumatologist.

B) Patient is Currently Receiving Benlysta Intravenous or Subcutaneous. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

- **i.** The medication is being used concurrently with an immunosuppressive regimen; AND
  Note: Examples of an immunosuppressive regimen include azathioprine, cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil, and/or a systemic corticosteroid.
- **ii.** The medication is prescribed by or in consultation with a nephrologist or rheumatologist; AND
- **iii.** Patient has responded to Benlysta subcutaneous or intravenous, as determined by the prescriber.
  Note: Examples of a response include improvement in organ dysfunction, reduction in flares, reduction in corticosteroid dose, decrease of anti-dsDNA titer, and improvement in complement levels (i.e., C3, C4).

Dosing. Approve the following dosing regimen (A and B):

A) The dose is up to 10 mg/kg given as an intravenous infusion; AND

B) Doses are administered at Weeks 0, 2, and 4, with subsequent doses separated by at least 4 weeks.

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2. Systemic Lupus Erythematosus. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets ALL of the following (i, ii, iii, and iv):

- **i.** Patient is ≥ 5 years of age; AND
- **ii.** Patient has autoantibody-positive systemic lupus erythematosus (SLE), defined as positive for antinuclear antibodies (ANA) and/or anti-double-stranded DNA (anti-dsDNA) antibody; AND
  Note: Not all patients with SLE are positive for anti-dsDNA, but most will be positive for ANA.
- **iii.** Patient meets ONE of the following (a or b):
  - **a)** The medication is being used concurrently with at least one other standard therapy; OR
    Note: Examples of standard therapies include an antimalarial (e.g., hydroxychloroquine), systemic corticosteroid (e.g., prednisone), and other immunosuppressants (e.g., azathioprine, mycophenolate mofetil, methotrexate).
  - **b)** Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND

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iv. The medication is prescribed by or in consultation with a rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist.

B) Patient is Currently Receiving Benlysta Intravenous or Subcutaneous. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient meets ONE of the following (a or b):

a) The medication is being used concurrently with at least one other standard therapy; OR
Note: Examples of standard therapies include an antimalarial (e.g., hydroxychloroquine), systemic corticosteroid (e.g., prednisone), and other immunosuppressants (e.g., azathioprine, mycophenolate mofetil, methotrexate).

b) Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist; AND

iii. Patient has responded to Benlysta subcutaneous or intravenous, as determined by the prescriber.
Note: Examples of a response include reduction in flares, reduction in corticosteroid dose, decrease of anti-dsDNA titer, improvement in complement levels (i.e., C3, C4), or improvement in specific organ dysfunction (e.g., musculoskeletal, blood, hematologic, vascular, others).

Dosing. Approve the following dosing regimen (A and B):

A) The dose is up to 10 mg/kg given as an intravenous infusion; AND

B) Doses are administered at Weeks 0, 2, and 4, with subsequent doses separated by at least 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Benlysta intravenous is not recommended in the following situations:

1. **Concurrent Use with Other Biologics.** Benlysta intravenous has not been studied and is not recommended in combination with other biologics.[1] Safety and efficacy have not been established with these combinations. See APPENDIX for examples of other biologics that should not be taken in combination with Benlysta.

2. **Concurrent Use with Lupkynis (voclosporin capsules).** Lupkynis has not been studied in combination with biologics such as Benlysta.[1]

3. **Rheumatoid Arthritis.** A Phase II dose-ranging study evaluating patients with rheumatoid arthritis showed only small American College of Rheumatology (ACR) 20 responses with Benlysta (e.g., ACR 20 response at Week 24 was 28% with Benlysta 10 mg/kg).[4] Numerous other agents are available with higher ACR responses and established efficacy for RA.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Benlysta® injection [prescribing information]. Durham, NC: GlaxoSmithKline; February 2024.
2. Fanouriakis A, Kostopoulou M, Andersen J, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. *Ann Rheum Dis*. 2024;83(1):15-29.
3. Kidney Disease: Improving Global Outcomes (KDIGO) Lupus Nephritis Work Group. KDIGO 2024 Clinical Practice Guideline for the management of LUPUS NEPHRITIS. *Kidney Int.* 2024;105(1S):S1-S69.
4. Stohl W, Merrill JT, McKay JD, et al. Efficacy and safety of belimumab in patients with rheumatoid arthritis: a phase II, randomized, double-blind, placebo-controlled, dose-ranging study. *J Rheumatol.* 2013;40(5):579-589.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	03/08/2023
Selected Revision	**Lupus Nephritis:** For initial therapy, a requirement was added that the patient has biopsy-confirmed lupus nephritis. For initial therapy and a patient currently receiving Benlysta, the requirement that the patient is taking with standard therapy was changed to more generally require that the patient is taking an immunosuppressive regimen. Leflunomide, methotrexate, and/or systemic corticosteroids were added to existing concurrent medication examples. The exception for a patient who is intolerant to standard therapy due to significant toxicity as determined by the prescriber was removed from the policy.	04/26/2023
Selected Revision	**Lupus Nephritis:** For initial therapy, the requirement that the "Patient has autoantibody-positive systemic lupus erythematosus (SLE), defined as positive for antinuclear antibodies (ANA) and/or anti-double-stranded DNA (anti-dsDNA) antibody" was removed from the policy.	07/05/2023
Annual Revision	No criteria changes.	03/13/2024

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Benlysta® (belimumab SC injection, IV infusion)	BLyS inhibitor	SLE, lupus nephritis
Saphnelo™ (anifrolumab-fnia IV infusion)	IFN receptor antagonist	SLE
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PsA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx® (secukinumab SC injection)	Inhibition of IL-17A	AS, ERA, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection)	Inhibition of IL-23	PsA, PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; IV – Intravenous; BLyS – B-lymphocyte stimulator-specific inhibitor; SLE – Systemic lupus erythematosus; IFN – Interferon; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Lupus – Saphnelo Utilization Management Medical Policy
- Saphnelo® (anifrolumab-fnia intravenous infusion – AstraZeneca)

REVIEW DATE: 03/13/2024

OVERVIEW

Saphnelo, a type 1 interferon (IFN) receptor antagonist, is indicated for the treatment of moderate to severe **systemic lupus erythematosus (SLE)** in adults who are receiving standard therapy.[1]

Saphnelo efficacy has not been evaluated and is not recommended in patients with severe active lupus nephritis or severe active central nervous system lupus.

Guidelines

European League Against Rheumatism (EULAR) guidelines for SLE (2023) recommend hydroxychloroquine for all patients, unless contraindicated.[2] Depending on the type and severity of organ involvement, glucocorticoids can be used but dosing should be minimized or withdrawn. Methotrexate, azathioprine, mycophenolate, and/or biologic agents (Benlysta® [belimumab intravenous or subcutaneous infusion], Saphnelo) should be considered in patients who do not respond to hydroxychloroquine ± glucocorticoids. EULAR also states biologic agents (Benlysta, Saphnelo) should be considered as second-line therapy for the treatment of active skin disease. Patient with active proliferative lupus nephritis should also consider combination therapy with biologic agents (Benlysta, Lupkynis™ [voclosporin capsules]). In general, the pharmacological interventions are directed by patient characteristics and the type/severity of organ involvement.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Saphnelo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Saphnelo as well as the monitoring required for adverse events and long-term efficacy, approval requires Saphnelo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Saphnelo is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Systemic Lupus Erythematosus.** Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, and iv):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has autoantibody-positive SLE, defined as positive for at least one of the following: antinuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA) antibodies, anti-Smith (anti-Sm) antibodies; AND
  Note: Not all patients with SLE are positive for anti-dsDNA, but most will be positive for ANA.
- **iii.** Patient meets ONE of the following (a or b):
  - **a)** The medication is being used concurrently with at least one other standard therapy; OR
    Note: Examples of standard therapies include an antimalarial (e.g., hydroxychloroquine), systemic corticosteroid (e.g., prednisone), and other immunosuppressants (e.g., azathioprine, mycophenolate mofetil, methotrexate).
  - **b)** Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND
- **iv.** The medication is prescribed by or in consultation with a rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist.

B) Patient is Currently Receiving Saphnelo. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient meets ONE of the following (a or b):
  - **a)** The medication is being used concurrently with at least one other standard therapy; OR
    Note: Examples of standard therapies include an antimalarial (e.g., hydroxychloroquine), systemic corticosteroid (e.g., prednisone), and other immunosuppressants (e.g., azathioprine, mycophenolate mofetil, methotrexate).
  - **b)** Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND
- **ii.** Patient responded to Saphnelo, as determined by the prescriber; AND
  Note: Examples of a response include reduction in flares, reduction in corticosteroid dose, decrease of anti-dsDNA titer, improvement in complement levels (i.e., C3, C4), or improvement in specific organ dysfunction (e.g., musculoskeletal, blood, hematologic, vascular, others).
- **iii.** The medication is prescribed by or in consultation with a rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist.

Dosing. Approve 300 mg given as an intravenous infusion administered not more frequently than once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Saphnelo is not recommended in the following situations:

1. **Concurrent Use with Other Biologics.** Saphnelo has not been studied and is not recommended in combination with other biologics (e.g., Benlysta [belimumab intravenous infusion or subcutaneous injection], rituximab).[1] Safety and efficacy have not been established with these combinations. See APPENDIX for examples of other biologics that should not be taken in combination with Saphnelo.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Saphnelo®injection, for intravenous use [prescribing information]. Wilmington DE: AstraZeneca; September 2022.
2. Fanouriakis A, Kostopoulou M, Andersen J, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. Ann Rheum Dis. 2024;83(1):15-29.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/23/2023
Early Annual Revision	No criteria changes.	03/13/2024

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Saphnelo™ (anifrolumab-fnia IV infusion)	IFN receptor antagonist	SLE
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PsA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx® (secukinumab SC injection)	Inhibition of IL-17A	AS, ERA, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion)	Inhibition of IL-23	SC formulation: CD, PsA, PsO
		IV formulation: CD
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO, PsA
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC

* Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; IFN – Interferon; SLE – Systemic lupus erythematosus; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Metabolic Disorders – Imcivree Utilization Management Medical Policy
- Imcivree® (setmelanotide subcutaneous injection – Rhythm)

REVIEW DATE: 01/10/2024

OVERVIEW

Imcivree, a melanocortin 4 receptor agonist, is indicated for chronic weight management in patients ≥ 6 years of age with monogenic or syndromic obesity due to:[1]

- **Proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency**, as determined by an FDA-approved test demonstrating variants in *POMC, PCSK1,* or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance.
- **Bardet-Biedl Syndrome**.

As a limitation of use, Imcivree is not indicated for obesity due to suspected POMC, PCSK1, or LEPR deficiency with *POMC*, *PCSK1*, or *LEPR* variants classified as benign or likely benign.[1] Imcivree is also not indicated for obesity not related to POMC, PCSK1, or LEPR deficiency or not related to Bardet-Biedl syndrome, including obesity associated with other genetic syndromes and general (polygenic) obesity.

In the pivotal trial for Imcivree regarding obesity due to POMC deficiency (homozygous or compound heterozygous variants in *POMC* or *PCSK1*) or LEPR deficiency (homozygous or compound heterozygous variants in *LEPR*), obesity was defined according to patient age.[2] For patients 6 to < 18 years of age, obesity was defined as body weight ≥ 95th percentile for age on growth chart assessment. For patients ≥ 18 years of age, obesity was defined as a body mass index (BMI) ≥ 30 kg/m^2.

Per the Imcivree prescribing information, select patients for treatment with Imcivree who have a clinical diagnosis of Bardet-Biedl syndrome.[1] It is noted that in the pivotal trial, adults had a BMI ≥ 30 kg/m^2 and pediatric patients had a weight ≥ 97th percentile using growth chart assessments. Patients were enrolled who had a clinical diagnosis of Bardet-Biedl syndrome. The clinical diagnosis was based on Beales criteria, which require that four primary features, or three primary and two secondary features, of Bardet-Biedl syndrome be met.[3]

For obesity due to POMC, PCSK1, or LEPR deficiency, weight loss should be evaluated after 12 to 16 weeks of Imcivree treatment.[1] If a patient has not lost at least 5% of baseline body weight, or 5% of baseline body mass index for a patient with continued growth potential, Imcivree should be discontinued as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment. For obesity and a clinical diagnosis of Bardet-Biedl syndrome, evaluate weight loss after 1 year of treatment. If a patient has not lost at least 5% of baseline body weight, or 5% of baseline BMI for a patient < 18 years of age, discontinue Imcivree.

Disease Overview

Monogenic obesity is a rare and severe early-onset form of obesity.[4] Unlike general obesity, environmental factors are much less impactful on obesity development in these patients. Fewer than 50 patients worldwide have been identified with POMC deficiency (*POMC* or *PCSK1* mutations); the prevalence of LEPR deficiency is unknown but is expected to account for less than 3% of severe early-onset obesity. The true prevalence of these disorders is unknown and likely underestimated due to lack of provider awareness and

genetic testing.[2] Clinical presentation is mainly characterized by major hyperphagia and ravenous hunger.[3] Patients with these disorders experience very rapid and early increase in weight, occurring within the first few days of life to early childhood. Lifestyle interventions may provide initial weight loss but are very difficult to maintain long-term in this population due to constant, insatiable hunger.[5] Isolated case reports of bariatric surgery have demonstrated some efficacy but are generally regarded as disappointing relative to the general population, likely related to the underlying energy imbalance. Caution is urged before considering bariatric surgery in patients with monogenic obesity disorders.

Bardet-Biedl syndrome is a rare genetic disease of obesity with an estimated prevalence of 1:100,000 individuals in Northern Europe and America, although the prevalence can be higher in certain consanguineous populations.[6] It is generally inherited in an autosomal recessive fashion. There are many gene mutations which are known to lead to the development of Bardet-Biedl syndrome. Additionally, an estimated 20% to 30% of patients with Bardet-Biedl syndrome do not have an identified genetic mutation. Diagnosis is based on the presence of characteristic clinical findings.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Imcivree. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Imcivree as well as the monitoring required for adverse events and long-term efficacy, approval requires Imcivree to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Imcivree is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Obesity Due to Proopiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency.** Approve for the duration noted if the patient meets the following (A or B):
   - **A)** Initial Therapy. Approve for 4 months if the patient meets the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 6 years of age; AND
     - **ii.** Patient meets both of the following (a and b):
       - **a)** Genetic testing demonstrates homozygous or compound heterozygous mutations in one of the following genes: *POMC*, *PCSK1*, or *LEPR*; AND
       - **b)** The genetic variant is interpreted as pathogenic, likely pathogenic, or of uncertain significance; AND
     - **iii.** Patient meets one of the following (a or b):
       - **a)** Patient is ≥ 18 years of age: Patient currently has a body mass index (BMI) ≥ 30 kg/m^2; OR

b) Patient is 6 to 17 years of age: Patient currently has a body weight ≥ 95th percentile for age on growth chart assessment; AND

iv. The medication is prescribed by or in consultation with an endocrinologist, a geneticist, or a physician who specializes in metabolic disorders.

B) Patient is Currently Receiving Imcivree. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):
Note: For a patient who has not completed at least 4 months of Imcivree therapy, refer to Initial Therapy criteria.

i. Patient is ≥ 6 years of age; AND

ii. Patient meets both of the following (a and b):

a) Genetic testing demonstrates homozygous or compound heterozygous mutations in one of the following genes: *POMC*, *PCSK1*, or *LEPR*; AND

b) The genetic variant is interpreted as pathogenic, likely pathogenic, or of uncertain significance; AND

iii. Patient meets one of the following (a or b):

a) Patient has lost ≥ 5% of baseline body weight since initiating Imcivree therapy; OR

b) Patient meets both of the following [(1) and (2)]:

(1) Patient has continued growth potential; AND

(2) Patient has lost ≥ 5% of baseline BMI since initiating Imcivree therapy; AND

iv. The medication is prescribed by or in consultation with an endocrinologist, a geneticist, or a physician who specializes in metabolic disorders.

Dosing. Approve up to a maximum dose of 3 mg injected subcutaneously once daily.

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2. Obesity Due to Bardet-Biedl Syndrome. Approve for 1 year if the patient meets one of the following (A or B):

A) Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, and iv):

i. Patient is ≥ 6 years of age; AND

ii. Patient has a clinical diagnosis of Bardet-Biedl Syndrome by meeting one of the following (a or b):

a) Patient has at least FOUR of the following primary features of Bardet-Biedl Syndrome: rod-cone dystrophy, polydactyly, obesity, learning disability, renal anomalies, or male hypogonadism; OR

b) Patient meets both of the following [(1) and (2)]:

(1) Patient has at least THREE of the following primary features of Bardet-Biedl Syndrome: rod-cone dystrophy, polydactyly, obesity, learning disability, renal anomalies, or male hypogonadism; AND

(2) Patient has at least TWO of the following secondary features of Bardet-Biedl Syndrome: speech disorder/delay, strabismus/cataracts/astigmatism, brachydactyly/syndactyly, developmental delay, polyuria/polydipsia (nephrogenic diabetes insipidus), ataxia/poor coordination/imbalance, mild spasticity, diabetes mellitus, dental crowding/hypodontia/small roots/high arched palate, left ventricular hypertrophy/congenital heart disease, or hepatic fibrosis; AND

iii. Patient meets one of the following (a or b):

a) Patient is ≥ 18 years of age: Patient currently has a body mass index (BMI) ≥ 30 kg/m^2; OR

b) Patient is < 18 years of age: Patient currently has a body weight ≥ 97th percentile for age on growth chart assessment; AND

iv. The medication is prescribed by or in consultation with an endocrinologist, a geneticist, or a physician who specializes in metabolic disorders.

B) Patient is Currently Receiving Imcivree. Approve if the patient meets the following (i, ii, and iii):
Note: For a patient who has not completed at least 1 year of Imcivree therapy, refer to Initial Therapy criteria.
- **i.** Patient is ≥ 6 years of age; AND
- **ii.** Patient meets one of the following (a or b):
  - **a)** Patient has lost ≥ 5% of baseline body weight since initiating Imcivree therapy; OR
  - **b)** Patient meets both of the following [(1) and (2)]:
    - **(1)** Patient is < 18 years of age; AND
    - **(2)** Patient has lost ≥ 5% of baseline BMI since initiating Imcivree therapy; AND
- **iii.** The medication is prescribed by or in consultation with an endocrinologist, a geneticist, or a physician who specializes in metabolic disorders.

Dosing. Approve up to a maximum dose of 3 mg injected subcutaneously once daily.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Imcivree is not recommended in the following situations:

1. **Other Genetic Obesity Syndromes.** Imcivree is not indicated for genetic obesity syndromes other than POMC-, PCSK1-, or LEPR-deficient obesity or Bardet-Biedl syndrome. A Phase III trial included six patients with Alström syndrome, none of the six patients met the primary endpoint (≥ 10% weight loss after 52 weeks of Imcivree).[7]
   Note: Examples of genetic obesity syndromes include Prader-Willi syndrome and Alström syndrome.

2. **General Obesity.** Imcivree is not indicated in this setting and there are no clinical data to support its use.[1]

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Imcivree® subcutaneous injection [prescribing information]. Boston, MA: Rhythm; November 2023.
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3. Haws RM, Gordon G, Han JC, et al. The efficacy and safety of setmelanotide in individuals with Bardet-Biedl syndrome or Alström syndrome: Phase 3 trial design. *Contemp Clin Trials Commun*. 2021 May 3;22:100780.
4. Huvenne H, Dubern B, Clément K, Poitou C. Rare genetic forms of obesity: clinical approach and current treatments in 2016. *Obes Facts*. 2016;9(3):158-73.
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7. Haqq AM, Chung WK, Dolfus H, et al. Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alström syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period. *Lancet Diabetes Endocrinol.* 2022;10(12):859-868.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	No criteria changes.	01/04/2023
Annual Revision	No criteria changes.	01/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Metabolic Disorders – Nulibry Utilization Management Medical Policy
- Nulibry™ (fosdenopterin intravenous infusion – Origin Biosciences)

REVIEW DATE: 04/19/2024

OVERVIEW

Nulibry, a cyclic pyranopterin monophosphate (cPMP), is indicated to reduce the risk of mortality in **molybdenum cofactor deficiency** (MoCD) **Type A**.[1] Treatment is initiated based on a confirmed diagnosis or presumptive diagnosis of MoCD. In patients with a presumptive diagnosis, Nulibry should be discontinued after genetic testing does not confirm MoCD Type A.

MoCD is a rare, life-threatening, autosomal-recessive disorder characterized by the deficiency of three molybdenum-dependent enzymes: sulfite oxidase (SOX), xanthine dehydrogenase, and aldehyde oxidase.[2] Patients with MoCD Type A have mutations in the *MOCS1* gene leading to deficiency of the intermediate substrate, cPMP.[1] Substrate replacement therapy with Nulibry provides an exogenous source of cPMP, which is converted to molybdopterin. Molybdopterin is then converted to molybdenum cofactor, which is needed for the activation of molybdenum-dependent enzymes, including SOX, an enzyme that reduces levels of neurotoxic sulfites. Onset of the disease is often seen at birth with median survival estimated at 4 years of age without intervention.[3] The most common symptoms of MoCD are seizures, feeding difficulties, and hypotonia. Patients usually experience irreversible neurological damage leading to severe developmental delays (trouble speaking or sitting) and brain abnormalities (atrophy of brain tissue). Biochemical features suggestive of MoCD include elevated urine S-sulfocysteine (SSC), thiosulfate, hypoxanthine, xanthine, or decreased serum uric acid. Genetic testing gives confirmation for differential diagnosis of MoCD Type A, B, or C.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Nulibry. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nulibry as well as the monitoring required for adverse events and long-term efficacy, approval require Nulibry to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nulibry is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Molybdenum Cofactor Deficiency (MoCD) Type A.** Approve for the duration noted if the patient meets ALL of the following (A, B, and C):

A) According to the prescriber, the diagnosis was confirmed by ONE of the following (i or ii):
- **i.** Approve for 1 year if the patient has genetic testing confirmation of a mutation in the *MOCS1* gene; OR
- **ii.** Approve for 1 month if the patient has laboratory findings suggestive of molybdenum cofactor deficiency (MoCD) and genetic testing is in progress; AND
  Note: Laboratory findings include elevated urinary S-sulfocysteine, thiosulfate, xanthine, hypoxanthine, or decreased serum uric acid.

B) According to the prescriber, based on the current condition, the patient is expected to derive benefit with Nulibry and the disease state is NOT considered to be too advanced; AND

C) The medication is prescribed by or in consultation with a pediatrician, geneticist, or a physician who specializes in molybdenum cofactor deficiency (MoCD) Type A.

Dosing. Approve up to 0.9 mg/kg given by intravenous infusion once daily.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nulibry is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Nulibry intravenous infusion [prescribing information]. Boston, MA: Origin Biosciences; October 2022.
2. Mechler K, Mountford WK, Hoffmann GF, et al. Ultra-orphan diseases: a quantitative analysis of the natural history of molybdenum cofactor deficiency. *Genet Med*. 2015 Dec;17(12):965-70.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	03/29/2023
Annual Revision	**Molybdenum Cofactor Deficiency (MoCD) Type A:** Added option of approval for one month based on laboratory findings suggestive of MoCD while genetic testing is in progress.	04/19/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Metabolic Disorders – Primary Hyperoxaluria – Oxlumo Utilization Management Medical Policy

- Oxlumo™ (lumasiran subcutaneous injection – Alnylam)

REVIEW DATE: 11/01/2023

OVERVIEW

Oxlumo is a hydroxyacid oxidase 1 (*HAO1*)-directed small interfering RNA indicated for the treatment of **primary hyperoxaluria type 1** to lower urinary and plasma oxalate levels in pediatric and adult patients.[1]

Disease Overview

Primary hyperoxaluria type 1 is a rare autosomal recessive inborn error of glyoxylate metabolism that results in the overproduction of oxalate, which forms insoluble calcium oxalate crystals that accumulate in the kidney and other organs, leading to issues such as nephrocalcinosis, formation of renal stones, and renal impairment.[2] Mutations in the alanine:glyoxylate aminotransferase gene (AGXT) cause primary hyperoxaluria type 1.[3] Liver transplantation is the only curative intervention for primary hyperoxaluria type 1 as it corrects the underlying enzymatic defect due to mutations of the AGXT gene.[2-4]

Clinical Efficacy

The efficacy of Oxlumo for the treatment of primary hyperoxaluria type 1 has been evaluated in three pivotal studies.[1,5,6,7] One study included patients ≥ 6 years of age with confirmed AGXT mutations and urinary oxalate excretion ≥ 0.7 mmol/24 hr/1.73 m^2.[5] A second, single-arm study included patients < 6 years of age with a genetically-confirmed primary hyperoxaluria type 1 diagnosis and an elevated spot urinary oxalate:creatinine ratio for age/weight.[6] Efficacy in regard to the urinary oxalate:creatinine ratio was evaluated at Month 6. A third clinical trial evaluated patients of any age with genetically-confirmed primary hyperoxaluria type 1 and a plasma oxalate level ≥ 20 µmol/L.[7] The primary efficacy endpoint of the mean reduction in plasma oxalate was assessed following 6 months of Oxlumo therapy.

Dosing

Dosing of Oxlumo is weight-based and consists of loading doses followed by maintenance dosing that begins 1 month after the last loading dose.[1] If the patient is receiving hemodialysis, administer Oxlumo after hemodialysis if administered on dialysis days.

Table 1. Oxlumo Weight-Based Dosing Regimen.[1]

Body Weight	Loading Dose	Maintenance Dose*
Less than 10 kg	6 mg/kg once monthly for 3 doses	3 mg/kg once monthly
10 kg to less than 20 kg	6 mg/kg once monthly for 3 doses	6 mg/kg once every 3 months (quarterly)
20 kg and above	3 mg/kg once monthly for 3 doses	3 mg/kg once every 3 months (quarterly)

* Begin 1 month after the last loading dose.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Oxlumo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Oxlumo as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Oxlumo to be prescribed by or in consultation with a physician who specializes in the condition being treated. All reviews will be forwarded to the Medical Director for evaluation.

Documentation: Documentation is required for use of Oxlumo as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Oxlumo Utilization Management Medical Policy* through the Coverage Review Department, and who is requesting reauthorization, the criteria utilized do NOT require re-submission of documentation for reauthorization, except for the criterion requiring documentation of a continued benefit from Oxlumo therapy.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Oxlumo is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. **Primary Hyperoxaluria Type 1.** Approve Oxlumo for the duration noted if the patient meets one of the following criteria (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, and iv):
     - **i.** Patient has had a genetic test confirming the diagnosis of Primary Hyperoxaluria Type 1 via identification of an alanine:glyoxylate aminotransferase gene (AGXT) mutation **[documentation required]**; AND
     - **ii.** Patient has meets ONE of the following (a, b, or c):
       - **a)** Patient has a urinary oxalate excretion ≥ 0.7 mmol/24 hours/1.73 meters^2 **[documentation required]**; OR
       - **b)** Patient has a urinary oxalate:creatinine ratio above the age-specific upper limit of normal **[documentation required]**; OR
       - **c)** Patient has a plasma oxalate level ≥ 20 µmol/L **[documentation required]**; AND
     - **iii.** Patient has not previously received a liver transplant for Primary Hyperoxaluria Type 1; AND
     - **iv.** The medication is prescribed by or in consultation with a nephrologist or urologist.
   - **B)** Patient is Currently Receiving Oxlumo. Approve for 1 year if, according to the prescriber, the patient is continuing to derive benefit from Oxlumo as determined by the most recent (i.e., within the past 6 months) objective measurement **[documentation required]**.
     Note: Examples of objective measurements of a response to Oxlumo therapy are reduced urinary oxalate excretion, decreased urinary oxalate:creatinine ratio, or reduced plasma oxalate levels from baseline (i.e., prior to Oxlumo therapy) or improved or stabilized clinical signs/symptoms of

Primary Hyperoxaluria Type 1 (e.g., nephrocalcinosis, formation of renal stones, renal impairment).

Dosing. Approve the following dosing regimens.

A) Initially, approve up to 6 mg/kg administered subcutaneously not more frequently than once every month for three doses; AND/OR

B) For maintenance dosing, approve one of the following (i or ii):

i. 3 mg/kg administered subcutaneously not more frequently than once every month; OR

ii. 6 mg/kg administered subcutaneously not more frequently than once every 3 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Oxlumo is not recommended in the following situations:

1. **Primary Hyperoxaluria Type 2 (PH2).** Oxlumo is not expected to be effective for the treatment of PH2 because its mechanism of action does not affect the metabolic pathways causing hyperoxaluria in PH2.[1] Oxlumo has not been studied for the treatment of patients with PH2.

2. **Primary Hyperoxaluria Type 3 (PH3).** Oxlumo is not expected to be effective for the treatment of PH3 because its mechanism of action does not affect the metabolic pathways causing hyperoxaluria in PH3.[1] Oxlumo has not been studied for the treatment of patients with PH3.

3. **Concurrent use of Oxlumo with Rivfloza (nedosiran subcutaneous injection).** Rivfloza is another small interfering RNA agent and should not be used with Oxlumo.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Oxlumo™ subcutaneous injection [prescribing information]. Cambridge, MA: Alnylam; October 2022.
2. Milliner DS, Harris PC, Cogal AG, et al. Primary Hyperoxaluria Type 1. Gene Reviews® Available at: https://www.ncbi.nlm.nih.gov/books/NBK1283/. Updated February 10, 2022. Accessed on September 14, 2023.
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7. Michael M, Groothoff JW, Shasha-Lavsky H, et al. Lumasiran for advanced primary hyperoxaluria type 1: phase 3 ILLUMINATE-C. *Am J Kidney Dis*. 2022 July 14. [Epub ahead of print].

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Primary Hyperoxaluria Type 1:** For initial therapy, an option was added for the patient to have a plasma oxalate level ≥ 20 µmol/L (documentation is required) as an alternative to an elevated urinary oxalate excretion. Previously, only elevated urinary oxalate excretion was listed in the requirement.	10/12/2022
Annual Revision	It was added under Conditions not recommended for approval that concurrent use of Oxlumo and Rivfloza should not be used. Policy name changed from Metabolic Disorders – Oxlumo Utilization Management Medical Policy to Metabolic Disorders – Primary Hyperoxaluria – Oxlumo Utilization Management Medical Policy.	11/01/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Metabolic Disorders – Primary Hyperoxaluria Medications – Rivfloza Utilization Management Medical Policy
- Rivfloza™ (nedosiran subcutaneous injection – Novo Nordisk)

REVIEW DATE: 11/22/2023

OVERVIEW

Rivfloza, a lactate dehydrogenase A-directing (LDHA) small interfering RNA, is indicated for the treatment of **primary hyperoxaluria type 1** (PH1) to lower urinary and plasma oxalate levels in adults and children ≥ 9 years of age with relatively preserved kidney function.[1]

Disease Overview

Primary hyperoxaluria type 1 is a rare autosomal recessive inborn error of glyoxylate metabolism that results in the overproduction of oxalate, which forms insoluble calcium oxalate crystals that accumulate in the kidney and other organs, leading to issues such as nephrocalcinosis, formation of renal stones, and renal impairment.[2] Mutations in the alanine:glyoxylate aminotransferase gene (AGXT) cause primary hyperoxaluria type 1.[3] Liver transplantation is the only curative intervention for primary hyperoxaluria type 1 as it corrects the underlying enzymatic defect due to mutations of the AGXT gene.[2-4]

Clinical Efficacy

The efficacy of Rivfloza for the treatment of primary hyperoxaluria type 1 has been evaluated in one pivotal study.[1,5] The study included patients ≥ 9 years of age with genetically confirmed PH1 and urinary oxalate excretion ≥ 0.7 mmol/24 hr/1.73 m^2. An ongoing open-label extension trial is following patients for up to 4 years.[6] The primary efficacy endpoint of the area under the curve (AUC) percent change from baseline in 24-hour urinary oxalate excretion was assessed following 6 months of Rivfloza therapy.

Dosing

Dosing of Rivfloza is a weight-based monthly subcutaneous injection.[1]

Table 1. Rivfloza Dosing Regimen.[1]

Age	Body Weight	Dosing Regimen
Adults and adolescents ≥ 12 years of age	≥ 50 kg	160 mg once monthly
	< 50 kg	128 mg once monthly
Children 9 to 11 years of age	≥ 50 kg	160 mg once monthly
	< 50 kg	3.3 mg/kg once monthly, not to exceed 128 mg

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Rivfloza. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rivfloza as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Rivfloza to be prescribed by or in consultation with a physician

who specializes in the condition being treated. All reviews will be forwarded to the Medical Director for evaluation.

Documentation: Documentation is required for use of Rivfloza as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Rivfloza Utilization Management Medical Policy* through the Coverage Review Department, and who is requesting reauthorization, are NOT required to re-submit documentation for reauthorization, except for the criterion requiring documentation of a continued benefit from Rivfloza therapy.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rivfloza is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Primary Hyperoxaluria Type 1.** Approve Rivfloza for the duration noted if the patient meets one of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, iv, v, and vi):
     - **i.** Patient is ≥ 9 years of age; AND
     - **ii.** Patient has had a genetic test confirming the diagnosis of Primary Hyperoxaluria Type 1 via identification of an alanine:glyoxylate aminotransferase gene (AGXT) mutation **[documentation required]**; AND
     - **iii.** Patient has an estimated glomerular filtration rate (eGFR) ≥ 30 ml/min per 1.73 m^2 **[documentation required]**; AND
     - **iv.** Patient meets ONE of the following (a, b, or c):
       - **a)** Patient has a urinary oxalate excretion ≥ 0.7 mmol/24 hours/1.73 $meters^2$ **[documentation required]**; OR
       - **b)** Patient has a urinary oxalate:creatinine ratio above the age-specific upper limit of normal **[documentation required]**; OR
       - **c)** Patient has a plasma oxalate level ≥ 20 µmol/L **[documentation required]**; AND
     - **v.** Patient has not previously received a liver transplant for Primary Hyperoxaluria Type 1; AND
     - **vi.** The medication is prescribed by or in consultation with a nephrologist or urologist.
   - **B)** Patient is Currently Receiving Rivfloza. Approve for 1 year if, according to the prescriber, the patient is continuing to derive benefit from Rivfloza as determined by the most recent (i.e., within the past 6 months) objective measurement **[documentation required]**.
     Note: Examples of objective measurements of a response to Rivfloza therapy are reduced urinary oxalate excretion, decreased urinary oxalate:creatinine ratio, or reduced plasma oxalate levels from baseline (i.e., prior to Rivfloza therapy) or improved or stabilized clinical signs/symptoms of Primary Hyperoxaluria Type 1 (e.g., nephrocalcinosis, formation of renal stones, renal impairment).

   Dosing. Approve the following dosing regimens.
   - **i.** If weight is ≥ 50 kg, approve for 160mg once monthly.
   - **ii.** If weight is < 50 kg, approve 3.3 mg/kg once monthly, not to exceed 128mg.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rivfloza is not recommended in the following situations:

1. **Primary Hyperoxaluria Type 2 (PH2).** Rivfloza may have benefit in PH2; however, the efficacy and safety of Rivfloza in patients with PH2 have not been established. Clinical trials are ongoing.

2. **Primary Hyperoxaluria Type 3 (PH3).** Rivfloza may have benefit in PH3; however, the efficacy and safety of Rivfloza in patients with PH3 have not been established. Clinical trials are ongoing.

3. **Primary Hyperoxaluria with end stage renal disease (ESRD).** Rivfloza may have benefit in patients with PH1 or PH2 and ESRD; however, the efficacy and safety of Rivfloza in this patient population have not been established. Clinical trials are ongoing.

4. **Concurrent use of Rivfloza with Oxlumo (lumasiran subcutaneous injection).** Oxlumo is another small interfering RNA agent and should not be used with Rivfloza.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Rivfloza™ subcutaneous injection [prescribing information]. Plainsboro, NJ: Novo Nordisk; September 2023.
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4. Cochat P, Rumsby G. Primary hyperoxaluria. *N Engl J Med*. 2013;369(7):649-658.
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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy		11/22/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Migraine – Calcitonin Gene-Related Peptide Inhibitors – Vyepti Utilization Management Medical Policy

- Vyepti® (eptinezumab-jjmr intravenous infusion – Lundbeck)

REVIEW DATE: 04/10/2024

OVERVIEW

Vyepti, a calcitonin gene-related peptide (CGRP) inhibitor, is indicated for the **preventive treatment of migraine** in adults.[1]

The recommended dosage is 100 mg administered by intravenous (IV) infusion over approximately 30 minutes once every 3 months; however, some patients may benefit from a dosage of 300 mg IV once every 3 months.[1] Vyepti must be administered by a healthcare provider.

Disease Overview

Migraines have been defined as chronic or episodic. Chronic migraine is described by the International Headache Society as headache occurring on ≥ 15 days/month for > 3 months and has the features of migraine headache on ≥ 8 days/month.[2] Episodic migraine is characterized by headaches that occur < 15 days/month.[3,4] Episodic migraine is more common than chronic migraine; however, chronic migraine is associated with a markedly greater personal and societal burden.

Guidelines

An updated assessment of the **preventive and acute treatment of migraine** by the **American Headache Society** (AHS) [2018; update 2021] reaffirms previous migraine guidelines.[5,6] Patients with migraine should be considered for preventive treatment in the following situations: when attacks significantly interfere with patients' daily routines despite acute treatment; frequent attacks (≥ 4 monthly headache days); at least moderate disability (Migraine Disability Assessment [MIDAS] score ≥ 11 or six-item Headache Impact Test [HIT-6] score > 50); contraindication to, failure, overuse, or adverse events with acute treatments; or patient preference. Before developing a preventive treatment plan, the appropriate use (e.g., drug type, route and timing of administration, frequency) of acute treatments should be initiated and coupled with education and lifestyle modifications. All patients with migraine should be offered a trial of acute treatment. Based on the level of evidence for efficacy and the American Academy of Neurology scheme for classification of evidence, the following oral treatments have established efficacy and should be offered for migraine prevention: antiepileptic drugs (**divalproex sodium, valproate sodium, topiramate** [not for women of childbearing potential without a reliable method of birth control]); beta-blockers (**metoprolol, propranolol, timolol**); and **frovatriptan** (for short-term preventive treatment of menstrual migraine). The following treatments are probably effective and should be considered for migraine prevention: antidepressants (**amitriptyline, venlafaxine**); beta-blockers (**atenolol, nadolol**); and angiotensin receptor blockers (**candesartan**).

The **AHS** issued an update to their position statement (2024) specifically regarding therapies targeting CGRP for the prevention of migraine.[7] The evidence for the efficacy, tolerability, and safety of CGRP-targeting migraine preventive therapies (specifically, the monoclonal antibodies: Aimovig® [erenumab-aooe subcutaneous {SC} injection], Ajovy® [fremanezumab-vfrm SC injection], Emgality® [galcanezumab-gnlm SC injection], and Vyepti), and the gepants: Nurtec® ODT (rimegepant orally disintegrating tablets) and Qulipta® (atogepant tablets) is substantial and consistent across different

individual CGRP-targeting treatments. Extensive "real-world" clinical experience corroborates clinical trials. This data indicates that the efficacy and tolerability of CGRP-targeting therapies are equal to or greater than those of previous first-line therapies. The CGRP-targeting therapies should be considered as a first-line approach for migraine prevention along with previous first-line treatments without a requirement for prior failure of other classes of migraine preventive treatment. Additionally, Botox® (onabotulinumtoxinA SC injection) is considered a first-line therapy for prevention of chronic migraine.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Vyepti. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vyepti is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Migraine Headache Prevention.** Approve Vyepti for 1 year if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has ≥ 4 migraine headache days per month (prior to initiating a migraine-preventative medication); AND
   - **C)** If the patient is currently taking Vyepti, the patient has had a significant clinical benefit from the medication as determined by the prescriber.
     Note: Examples of significant clinical benefit include a reduction in the overall number of migraine days per month or a reduction in number of severe migraine days per month from the time that Vyepti was initiated.

   Dosing. Approve up to 300 mg administered by intravenous infusion once every 3 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vyepti is not recommended in the following situations:

1. **Acute Treatment of Migraine.** Clinical data are currently lacking for the use of Vyepti in the acute treatment of migraine.

2. **Cluster Headache, Treatment or Prevention.** Clinical data are currently lacking for the use of Vyepti in patients with cluster headache. The pivotal trials of Vyepti excluded patients with this condition.[8,9]

3. **Concurrent use with another calcitonin gene-related peptide (CGRP) inhibitor being prescribed for migraine headache prevention.**

Note: CGRP inhibitors that are indicated for migraine headache prevention include Aimovig (erenumab-aooe subcutaneous injection), Ajovy (fremanezumab-vfrm subcutaneous injection), Emgality (galcanezumab-gnlm subcutaneous injection), and Qulipta (atogepant tablets). Aimovig, Ajovy, Emgality, and Vyepti are injectable CGRP inhibitors and have not been studied for use in combination with another agent in the same class.[1,10-12] Qulipta is an oral CGRP inhibitor for the preventive treatment of migraine in adults.[13]

4. **Concurrent use with Nurtec ODT (rimegepant sulfate orally disintegrating tablet) when used as a preventive treatment of migraine.** Nurtec ODT is an oral CGRP inhibitor for the acute treatment of migraine and for the preventive treatment of episodic migraine in adults.[14]

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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12. Emgality® injection for subcutaneous use [prescribing information]. Indianapolis, IN: Lilly; May 2022.
13. Qulipta® tablets [prescribing information]. Madison, NJ: AbbVie; April 2023.
14. Nurtec® ODT [prescribing information]. New Haven, CT: Biohaven; April 2022.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Policy Name:** The initial descriptor "Migraine" was added to the policy name. **Migraine Headache Prevention:** The note with examples of standard prophylactic (preventive) pharmacologic therapies was expanded to include the statement: Of note, "standard prophylactic (preventive) pharmacologic therapies" do **not** include oral or injectable CGRP inhibitors.	05/24/2023
Selected Revision	**Migraine Headache Prevention:** • The note with standard prophylactic (preventive) pharmacologic therapies was changed to remove "Examples of" and to remove the statement: Of note, "standard prophylactic (preventive) pharmacologic therapies" do **not** include oral or injectable CGRP inhibitors. • A new statement was added to the note: A patient who has already tried an oral or injectable calcitonin gene-related peptide (CGRP) inhibitor indicated for the prevention of migraine or Botox (onabotulinumtoxinA injection) for the prevention of migraine is not required to try two standard prophylactic pharmacologic therapies.	08/02/2023
Early Annual Revision	**Migraine Headache Prevention:** The criteria requiring a patient to have tried at least two standard prophylactic (preventive) pharmacologic therapies, each from a different pharmacologic class, and requiring that a patient have had inadequate efficacy or adverse event(s) severe enough to warrant discontinuation of those therapies have been removed.	04/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Multiple Sclerosis – Briumvi Utilization Management Medical Policy
- Briumvi® (ublituximab-xiiy intravenous infusion – TG Therapeutics)

REVIEW DATE: 11/15/2023

OVERVIEW

Briumvi, a CD20-directed cytolytic antibody, is indicated for the treatment of relapsing forms of **multiple sclerosis** (MS), to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease, in adults.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses with minimal magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders.[2-4] Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria.

Guidelines

Briumvi is not addressed in guidelines. In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Briumvi. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Briumvi as well as the monitoring required for adverse events and long-term efficacy, approval requires Briumvi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Briumvi is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Multiple Sclerosis, Relapsing Forms.** Approve for 1 year if the patient meets one of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has a relapsing form of multiple sclerosis; AND
       Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
     - **iii.** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR
   - **B)** Patient is Currently Receiving Briumvi for ≥ 1 Year. Approve if the patient meets all of the following (i, ii, iii, and iv):
     Note: A patient who has received < 1 year of therapy or who is restarting therapy with Briumvi should be considered under criterion 1A (Multiple Sclerosis [Relapsing Forms], Initial Therapy).
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has a relapsing form of multiple sclerosis; AND
       Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
     - **iii.** Patient meets one of the following [(1) or (2)]:
       - **(1)** Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
         Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability Status Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item Multiple Sclerosis Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.
       - **(2)** Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND
     - **iv.** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

   Dosing. Approve the following dosing regimens (A or B):
   - **A)** 150 mg by intravenous infusion, followed 2 weeks later by a second 450 mg intravenous infusion; OR
   - **B)** 450 mg by intravenous infusion once every 24 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Briumvi is not recommended in the following situations:

1. **Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis (MS).** These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/04/2023
Selected Revision	**Multiple Sclerosis, Relapsing Forms:** For initial criteria, the criterion was removed that according to the prescriber, the patient has experienced inadequate efficacy or significant intolerance to one disease-modifying agent used for multiple sclerosis. The criteria regarding use of Briumvi for < 1 year was deleted as now it is the same as initial criteria. For the criteria regarding the patient is currently receiving Briumvi for 1 year or more, a Note was added stating that a patient who has received < 1 year of therapy or who is restarting therapy with Briumvi should be considered under criteria for Multiple Sclerosis (Relapsing Forms) [Initial Therapy].	03/01/2023
Early Annual Revision	No criteria changes.	11/15/2023

APPENDIX

Medication	Mode of Administration
Aubagio® (teriflunomide tablets, generic)	Oral
Avonex® (interferon beta-1a intramuscular injection)	Injection (self-administered)
Bafiertam® (monomethyl fumarate delayed-release capsules)	Oral
Betaseron® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Briumvi® (ublituximab-xiiy intravenous infusion)	Intravenous infusion
Copaxone® (glatiramer acetate subcutaneous injection, generic)	Injection (self-administered)
Extavia® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Gilenya® (fingolimod capsules, generic)	Oral
Glatopa® (glatiramer acetate subcutaneous injection)	Injection (self-administered)
Kesimpta® (ofatumumab subcutaneous injection)	Injection (self-administered)
Lemtrada® (alemtuzumab intravenous infusion)	Intravenous infusion
Mavenclad® (cladribine tablets)	Oral
Mayzent® (siponimod tablets)	Oral
Ocrevus® (ocrelizumab intravenous infusion)	Intravenous infusion
Plegridy® (peginterferon beta-1a subcutaneous or intramuscular injection)	Injection (self-administered)
Ponvory® (ponesimod tablets)	Oral
Rebif® (interferon beta-1a subcutaneous injection)	Injection (self-administered)
Tascenso ODT® (fingolimod orally disintegrating tablets)	Oral
Tecfidera® (dimethyl fumarate delayed-release capsules, generic)	Oral
Tyruko® (natalizumab-sztn intravenous infusion)	Intravenous infusion
Tysabri® (natalizumab intravenous infusion)	Intravenous infusion
Vumerity® (diroximel fumarate delayed-release capsules)	Oral
Zeposia® (ozanimod capsules)	Oral

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Multiple Sclerosis – Lemtrada Utilization Management Medical Policy
- Lemtrada® (alemtuzumab intravenous infusion – Genzyme)

REVIEW DATE: 11/15/2023

OVERVIEW

Lemtrada, a CD52-directed cytolytic monoclonal antibody, is indicated for the treatment of patients with relapsing forms of **multiple sclerosis** (MS) to include relapsing remitting disease and active secondary progressive MS in adults.[1] Lemtrada is not recommended for use in patients with clinically isolated syndrome because of its safety profile.

Due to its safety profile, use of Lemtrada should generally be reserved for patients who have had an inadequate response to two or more medications indicated for the treatment of MS.[1] Lemtrada contains the same active ingredient found in Campath® (alemtuzumab intravenous infusion). The safety and efficacy of Lemtrada have not been established in patients less than 17 years of age. Lemtrada is administered by intravenous infusion over 4 hours for two or more treatment courses: The dose for the first course is 12 mg/day on five consecutive days. The second course is 12 mg/day on three consecutive days 12 months after the first treatment course. Subsequent treatment courses of 12 mg per day on three consecutive days (36 mg total) may be given, as needed, at least 12 months after the last dose of any prior treatment course.

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

A practice guideline recommendation regarding disease-modifying agents for adults with MS from the American Academy of Neurology (2018) states to consider Lemtrada for patients with MS who have highly active disease.[7]

Safety

Lemtrada is available only through a restricted Risk Evaluation Mitigation Strategy (REMS) program called the LEMTRADA REMS Program due to the risks of autoimmunity, infusion reactions, stroke, and malignancies.[1] Use of Lemtrada is contraindicated in patients who have infection with human immunodeficiency virus (HIV) and those with active infection. Progressive multifocal leukoencephalopathy has occurred in a patient with MS who received Lemtrada.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Lemtrada. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for 30 days which is an adequate duration for the patient to receive the recommended number of doses. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lemtrada, as well as the monitoring required for adverse events and long-term efficacy, approval requires Lemtrada to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Lemtrada at initiation as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, MRI reports, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lemtrada is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Multiple Sclerosis.** Approve for the duration noted if the patient meets one of the following (A or B):
   - **A)** Initial Therapy (this includes patients who have started but not completed the first course of Lemtrada therapy). Approve for five doses in patients who meet all of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 17 years of age; AND
     - **ii.** Patient has a relapsing form of multiple sclerosis; AND
       Note: Examples of relapsing forms of multiple sclerosis include relapsing remitting disease and active secondary progressive disease.
     - **iii.** Patient meets one of the following (a, b, or c):

a) According to the prescriber, the patient has experienced inadequate efficacy or significant intolerance to two disease-modifying agents used for multiple sclerosis; OR
Note: See Appendix for examples.

b) Patient has previously received one of Kesimpta (ofatumumab subcutaneous injection), Tysabri (natalizumab intravenous infusion), Tyruko (natalizumab-sztn intravenous infusion), Briumvi (ublituximab-xiij intravenous infusion), Mavenclad (cladribine tablets), Ocrevus (ocrelizumab intravenous infusion), or Lemtrada; OR

c) According to the prescriber, the patient has highly-active or aggressive multiple sclerosis by meeting one of the following [(1), (2), (3), or (4)]:

(1) Patient has demonstrated rapidly advancing deterioration(s) in physical functioning **[documentation required]**; OR
Note: Examples include loss of mobility or lower levels of ambulation and severe changes in strength or coordination.

(2) Disabling relapse(s) with suboptimal response to systemic corticosteroids **[documentation required]**; OR

(3) Magnetic resonance imaging (MRI) findings suggest highly active or aggressive multiple sclerosis **[documentation required]**; OR
Note: Examples include new, enlarging, or a high burden of T2 lesions or gadolinium-enhancing lesions.

(4) Manifestations of multiple sclerosis-related cognitive impairment **[documentation required]**; AND

iv. Medication is prescribed by or in consultation with a neurologist or a physician that specializes in the treatment of multiple sclerosis; OR

B) Patient Who Has Completed a Previous Course of Lemtrada Therapy. Approve for three doses if the patient meets all of the following (i, ii, iii, iv, and v):

i. Patient is ≥ 17 years of age; AND

ii. Patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis include relapsing remitting disease and active secondary progressive disease.

iii. Patient meets one of the following (a or b):

a) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability Status Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item MS Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.

b) Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND

iv. At least 12 months has elapsed from the last dose of any prior Lemtrada treatment course; AND

v. Medication is prescribed by or in consultation with a neurologist or a physician that specializes in the treatment of multiple sclerosis.

Dosing. Approve the following dosing regimens (A or B):

A) First treatment course is 12 mg/day by intravenous infusion on 5 consecutive days (60 mg total dose); OR
B) For additional treatment courses, the dose is 12 mg/day by intravenous infusion on 3 consecutive days (36 mg total dose) administered 12 months after the last Lemtrada treatment course.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lemtrada is not recommended in the following situations:

1. **Clinically Isolated Syndrome.** Lemtrada is not recommended for use in patients with clinically isolated syndrome due to its safety profile.[1]

2. **Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.** These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

3. **HIV Infection.** Use of Lemtrada is contraindicated in patients who are infected with HIV because Lemtrada causes prolonged reductions of CD4+ lymphocyte counts.[1]

4. **Non-Relapsing Forms of Multiple Sclerosis.** The efficacy of Lemtrada has not been established in patients with MS with non-relapsing forms of the disease.[1]
   Note: An example of a non-relapsing form of MS is primary progressive MS.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/30/2022
Annual Revision	**Multiple Sclerosis:** The following agents were added to the list allowing an exception with previous use: Tyruko (natalizumab-sztn intravenous infusion), Briumvi (ublituximab-xiij intravenous infusion), Mavenclad (cladribine tablets), and Lemtrada.	11/15/2023

APPENDIX

Medication	Mode of Administration
Aubagio® (teriflunomide tablets, generic)	Oral
Avonex® (interferon beta-1a intramuscular injection)	Injection (self-administered)
Bafiertam® (monomethyl fumarate delayed-release capsules)	Oral
Betaseron® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Briumvi® (ublituximab-xiij intravenous infusion)	Intravenous infusion
Copaxone® (glatiramer acetate subcutaneous injection, generic)	Injection (self-administered)
Extavia® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Gilenya® (fingolimod capsules, generic)	Oral
Glatopa® (glatiramer acetate subcutaneous injection)	Injection (self-administered)
Kesimpta® (ofatumumab subcutaneous injection)	Injection (self-administered)
Lemtrada® (alemtuzumab intravenous infusion)	Intravenous infusion
Mavenclad® (cladribine tablets)	Oral
Mayzent® (siponimod tablets)	Oral
Ocrevus® (ocrelizumab intravenous infusion)	Intravenous infusion
Plegridy® (peginterferon beta-1a subcutaneous or intramuscular injection)	Injection (self-administered)
Ponvory® (ponesimod tablets)	Oral
Rebif® (interferon beta-1a subcutaneous injection)	Injection (self-administered)
Tascenso ODT® (fingolimod orally disintegrating tablets)	Oral
Tecfidera® (dimethyl fumarate delayed-release capsules, generic)	Oral
Tyruko® (natalizumab-sztn intravenous infusion)	Intravenous infusion
Tysabri® (natalizumab intravenous infusion)	Intravenous infusion
Vumerity® (diroximel fumarate delayed-release capsules)	Oral
Zeposia® (ozanimod capsules)	Oral

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Multiple Sclerosis – Ocrevus Utilization Management Medical Policy
- Ocrevus® (ocrelizumab intravenous infusion – Biogen)

REVIEW DATE: 11/15/2023

OVERVIEW

Ocrevus is a CD20-directed cytolytic antibody indicated for the treatment of adults with:[1]

- **Relapsing forms of multiple sclerosis** (MS) to include clinically isolated syndrome, relapsing remitting MS, and active secondary progressive MS.
- **Primary progressive MS**.

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders.[2-4] Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Ocrevus. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ocrevus as well as the monitoring required for adverse events and long-term efficacy, approval requires Ocrevus to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ocrevus is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Multiple Sclerosis, Relapsing Forms.** Approve for 1 year if the patient meets one of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has a relapsing form of multiple sclerosis; AND
       Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
     - **iii.** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR
   - **B)** Patient is Currently Receiving Ocrevus for ≥ 1 Year. Approve if the patient meets all of the following (i, ii, iii, and iv):
     Note: A patient who has received < 1 year of therapy or who is restarting therapy with Ocrevus should be considered under criterion 1A (Multiple Sclerosis [Relapsing Forms], Initial Therapy).
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has a relapsing form of multiple sclerosis; AND
       Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive multiple sclerosis.
     - **iii.** Patient meets one of the following [(1) or (2)]:
       - **(1)** Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
         Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability Status Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item Multiple Sclerosis Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.
       - **(2)** Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND
     - **iv.** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

   Dosing. Approve the following dosing regimens (A or B):
   - **A)** 300 mg by intravenous infusion, followed 2 weeks later by a second 300 mg intravenous infusion; OR
   - **B)** 600 mg by intravenous infusion once every 6 months.

2. **Multiple Sclerosis, Primary Progressive.** Approve for 1 year if the patients meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Ocrevus is prescribed by or in consultation with a physician who specializes in the treatment of multiple sclerosis and/or a neurologist.

   Dosing. Approve the following dosing regimens (A or B):
   A) 300 mg by intravenous infusion, followed 2 weeks later by a second 300 mg intravenous infusion; OR
   B) 600 mg by intravenous infusion once every 6 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ocrevus is not recommended in the following situations:

1. **Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.** These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Ocrevus® intravenous infusion [prescribing information]. San Francisco, CA: Genentech/Roche; August 2023.
2. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. Updated September 2019. Available at: https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/DMT_Consensus_MS_Coalition.pdf. Accessed on November 10, 2023.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/30/2022
Selected Revision	**Multiple Sclerosis. Relapsing Forms:** For initial criteria, the criterion was removed that according to the prescriber, the patient has experienced inadequate efficacy or significant intolerance to one disease-modifying agent used for multiple sclerosis. The criteria regarding use of Ocrevus for < 1 year was deleted as now it is the same as initial criteria. For the criteria regarding the patient is currently receiving Ocrevus for 1 year or more, a Note was added stating that a patient who has received < 1 year of therapy or who is restarting therapy with Ocrevus should be considered under criteria for Multiple Sclerosis (Relapsing Forms) [Initial Therapy]. **Conditions Not Recommended for Approval:** Regarding Concurrent Use with Other Disease-Modifying Agents for Multiple Sclerosis, Briumvi was added to the list of examples provided in the Appendix table.	03/01/2023
Early Annual Revision	No criteria changes.	11/15/2023

APPENDIX

Medication	Mode of Administration
Aubagio® (teriflunomide tablets, generic)	Oral
Avonex® (interferon beta-1a intramuscular injection)	Injection (self-administered)
Bafiertam® (monomethyl fumarate delayed-release capsules)	Oral
Betaseron® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Briumvi® (ublituximab-xiiy intravenous infusion)	Intravenous infusion
Copaxone® (glatiramer acetate subcutaneous injection, generic)	Injection (self-administered)
Extavia® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Gilenya® (fingolimod capsules, generic)	Oral
Glatopa® (glatiramer acetate subcutaneous injection)	Injection (self-administered)
Kesimpta® (ofatumumab subcutaneous injection)	Injection (self-administered)
Lemtrada® (alemtuzumab intravenous infusion)	Intravenous infusion
Mavenclad® (cladribine tablets)	Oral
Mayzent® (siponimod tablets)	Oral
Ocrevus® (ocrelizumab intravenous infusion)	Intravenous infusion
Plegridy® (peginterferon beta-1a subcutaneous or intramuscular injection)	Injection (self-administered)
Ponvory® (ponesimod tablets)	Oral
Rebif® (interferon beta-1a subcutaneous injection)	Injection (self-administered)
Tascenso ODT® (fingolimod orally disintegrating tablets)	Oral
Tecfidera® (dimethyl fumarate delayed-release capsules, generic)	Oral
Tyruko® (natalizumab-sztn intravenous infusion)	Intravenous infusion
Tysabri® (natalizumab intravenous infusion)	Intravenous infusion
Vumerity® (diroximel fumarate delayed-release capsules)	Oral
Zeposia® (ozanimod capsules)	Oral

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Multiple Sclerosis and Crohn's Disease – Tysabri Utilization Management Medical Policy
- Tysabri® (natalizumab intravenous infusion – Biogen)

REVIEW DATE: 11/15/2023

OVERVIEW

Tysabri, an integrin receptor antagonist, is indicated for the treatment of:[1]

- Relapsing forms of **multiple sclerosis (MS)** include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults as monotherapy.
- **Crohn's disease**, inducing and maintaining clinical response and remission in adults with moderately to severely active disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies and inhibitors of tumor necrosis factor (TNF)-α.

Tysabri increases the risk of progressive multifocal leukoencephalopathy (PML).[1] When initiating and continuing treatment with Tysabri in patients with MS, physicians should consider whether the expected benefit of Tysabri is sufficient to offset the risks. Tysabri should not be used in combination with immunosuppressants (e.g., azathioprine, 6-mercaptopurine, cyclosporine, methotrexate) or inhibitors of TNFα. The safety and effectiveness in patients with MS or Crohn's disease < 18 years of age have not been established.

Disease Overview

Multiple Sclerosis

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders.[2-4] Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria.

Crohn's Disease

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract.[8] The prevalence has been increasing worldwide.[9] Common symptoms of Crohn's disease include abdominal pain, diarrhea, fatigue, weight loss, fever, anemia, and recurrent fistulas. Adults with Crohn's disease may be at risk of bone fractures, as well as thromboembolism. Other extraintestinal manifestations may occur (e.g., primary

sclerosing cholangitis). Younger patients may experience growth failure.[8,9] The chronic intestinal inflammation over time leads to intestinal complications such as strictures, fistulas, and abscesses. Only 20% to 30% of patients with Crohn's disease will have a nonprogressive or indolent course. Therefore, it is appropriate to identify therapies that will achieve adequate control for the patient. Many different therapies are available including corticosteroids, immunomodulators (e.g., azathiopurine, 6-mercaptopurine), and anti-TNF agents (e.g., infliximab products, adalimumab products, Cimzia® [certolizumab pegol subcutaneous injection]).

Guidelines

A practice guideline recommendation regarding disease-modifying agents for adults with MS from the American Academy of Neurology (2018) states to consider Tysabri for patients with MS who have highly active disease.[7]

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various drug classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

The American College of Gastroenterology has guidelines on management of Crohn's disease in adults (2018).[9] Anti-TNF agents (e.g., infliximab products, adalimumab products, Cimzia) should be used to treat Crohn's disease that is resistant to treatment with corticosteroids, thiopurines, or methotrexate. For patients with moderately to severely active Crohn's disease and objective evidence of active disease, anti-integrin therapy (with Entyvio® [vedolizumab intravenous infusion]) with or without an immunomodulator is more effective than placebo and should be considered for use for induction of symptomatic remission in patients with Crohn's disease. Tysabri is more effective than placebo and should be considered to be used for induction of symptomatic response and remission in patients with active Crohn's disease (strong recommendation; high level of evidence). Tysabri should be used for maintenance of Tysabri-induced remission of Crohn's disease only if serum antibody to John Cunningham virus is negative. Stelara® (ustekinumab subcutaneous injection or intravenous infusion) should be given for moderate to severe Crohn's disease patients who failed treatment with corticosteroids, thiopurines, methotrexate, or anti-TNF agents or who have had no prior exposure to anti-TNF agents.

Safety

Tysabri has a Boxed Warning regarding the risk of PML.[1] Tysabri is available only through a special restricted distribution Risk Evaluation and Mitigation Strategy (REMS) program called the TOUCH® Prescribing Program.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Tysabri. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tysabri as well as the monitoring required for adverse events and long-term efficacy, approval requires Tysabri to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Tysabri at initiation for multiple sclerosis as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, magnetic resonance imaging (MRI) reports, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tysabri is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. **Multiple Sclerosis.** Approve for 1 year if the patient meets one of the following (A or B)
   - **A)** Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has a relapsing form of multiple sclerosis; AND
       Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive multiple sclerosis.
     - **iii.** Patient meets one of the following (a or b):
       - **a)** According to the prescriber, the patient has experienced inadequate efficacy or significant intolerance to one disease-modifying agent used for multiple sclerosis; OR
         Note: See Appendix for examples.
       - **b)** According to the prescriber the patient has highly active or aggressive multiple sclerosis by meeting one of the following [(1), (2), (3), or (4)]:
         - **(1)** Patient has demonstrated rapidly advancing deterioration(s) in physical functioning **[documentation required]**; OR
           Note: Examples include loss of mobility or lower levels of ambulation and severe changes in strength or coordination.
         - **(2)** Disabling relapse(s) with suboptimal response to systemic corticosteroids **[documentation required]**; OR
         - **(3)** Magnetic resonance imaging (MRI) findings suggest highly active or aggressive multiple sclerosis **[documentation required]**; OR
           Note: Examples include new, enlarging, or a high burden of T2 lesions or gadolinium-enhancing lesions.
         - **(4)** Manifestations of multiple sclerosis-related cognitive impairment **[documentation required]**; AND
     - **iv.** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR
   - **B)** Patient is Currently Receiving Tysabri. Approve if the patient meets one of the following (i or ii):
     - **i.** Patient has been receiving Tysabri for < 1 year. Approve if the patient meets all of the following (a, b, and c):
       - **a)** Patient is ≥ 18 years of age; AND
       - **b)** Patient has a relapsing form of multiple sclerosis; AND
         Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
       - **c)** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR
     - **ii.** Patient has been receiving Tysabri for 1 year or more. Approve if the patient meets the following (a, b, c, and d):

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a) Patient is ≥ 18 years of age; AND
b) Patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive multiple sclerosis.
c) Patient meets one of the following [(1) or (2)]:
(1) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability Status Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item Multiple Sclerosis Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.
(2) Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND
d) Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

Dosing. Approve up to 300 mg given by intravenous infusion administered no more frequently than once every 4 weeks.

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2. Crohn's Disease. Approve for the duration noted below if the patient meets one of the following (A or B):
A) Initial Therapy. Approve for 6 months if the patient meets all of the following (i, ii, iii, and iv):
i. Patient is ≥ 18 years of age; AND
ii. Patient has moderately to severely active Crohn's disease; AND
iii. Patient has tried at least two biologics for Crohn's disease; AND
Note: Examples include an adalimumab product (Humira, biosimilars), Cimzia (certolizumab pegol subcutaneous injection), an infliximab intravenous product (Remicade, biosimilars), Zymfentra (infliximab-dyyb subcutaneous injection), Entyvio (vedolizumab intravenous infusion), Skyrizi (risankizumab-rzaa intravenous infusion and subcutaneous injection [on-body injector]), or Stelara (ustekinzumab subcutaneous injection or intravenous infusion).
Note: Each biosimilar tried from the same chemical would only count as a trial of one product.
iv. Tysabri is prescribed by or in consultation with a gastroenterologist; OR
B) Patient is Currently Receiving Tysabri. Approve for 1 year if the patient meets all of the following (i, ii, iii, and iv):
i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criteria A (Initial Therapy).
ii. Patient is ≥ 18 years of age; AND
iii. Patient meets at least one of the following (a or b):
a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Tysabri); OR

Note: Examples of objective measures include fecal markers (e.g., renal lactoferrin, fecal calprotectin), serum markers (e.g., C-reactive protein), imaging studies (magnetic resonance enterography [MRE], computed tomograph enterography [CTE]), endoscopic assessment, and/or reduced dose of corticosteroids.

b) Compared with baseline (prior to initiating Tysabri), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or blood in stool; AND

iv. Medication is prescribed by or in consultation with a gastroenterologist.

Dosing in Crohn's Disease. Approve up to 300 mg given by intravenous infusion administered no more frequently than once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tysabri is not recommended in the following situations:

1. **Concurrent Use with an Immunosuppressant Agent in Patients with Crohn's Disease.** Ordinarily, patients who are receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised immune function should not take Tysabri.[1]
   Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, methotrexate, an infliximab IV product, Zymfentra (infliximab-dyyb subcutaneous injection), an adalimumab product, Cimzia, Entyvio IV, Skyrizi (risankizumab-rzaa intravenous infusion and subcutaneous injection [on-body injector]), Stelara, and Rinvoq (upadacitinib extended-release tablets).

2. **Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.** These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

3. **Non-Relapsing Forms of Multiple Sclerosis.** The safety and efficacy of Tysabri have not been established in patients with primary progressive multiple sclerosis.
   Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

4. **Ulcerative Colitis.** Efficacy data with use of Tysabri are limited.[10]

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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2. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. Updated September 2019. Available at: https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/DMT_Consensus_MS_Coalition.pdf. Accessed on November 10, 2023.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/23/2022
Annual Revision	**Crohn's Disease:** Regarding the requirement that the patient has tried at least two biologics for Crohn's disease, the listing of agents was updated as follows: Zymfentra was added and it was specified that the infliximab formulation was by intravenous infusion. **Conditions Not Recommended for Approval:** Regarding the Exclusion for Concurrent Use with an Immunosuppressant Agent in Patient with Crohn's Disease, the listing of agents was updated as follows: Zymfentra and Rinvoq were added, it was specified that the infliximab formulation was by intravenous infusion, and it was clarified that Entyvio was the intravenous infusion formulation.	11/15/2023

APPENDIX

Medication	Mode of Administration
Aubagio® (teriflunomide tablets, generic)	Oral
Avonex® (interferon beta-1a intramuscular injection)	Injection (self-administered)
Bafiertam® (monomethyl fumarate delayed-release capsules)	Oral
Betaseron® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Briumvi® (ublituximab-xiij intravenous infusion)	Intravenous infusion
Copaxone® (glatiramer acetate subcutaneous injection, generic)	Injection (self-administered)
Extavia® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Gilenya® (fingolimod capsules, generic)	Oral
Glatopa® (glatiramer acetate subcutaneous injection)	Injection (self-administered)
Kesimpta® (ofatumumab subcutaneous injection)	Injection (self-administered)
Lemtrada® (alemtuzumab intravenous infusion)	Intravenous infusion
Mavenclad® (cladribine tablets)	Oral
Mayzent® (siponimod tablets)	Oral
Ocrevus® (ocrelizumab intravenous infusion)	Intravenous infusion
Plegridy® (peginterferon beta-1a subcutaneous or intramuscular injection)	Injection (self-administered)
Ponvory® (ponesimod tablets)	Oral
Rebif® (interferon beta-1a subcutaneous injection)	Injection (self-administered)
Tascenso ODT® (fingolimod orally disintegrating tablets)	Oral
Tecfidera® (dimethyl fumarate delayed-release capsules, generic)	Oral
Tyruko® (natalizumab intravenous infusion)	Intravenous infusion
Tysabri® (natalizumab intravenous infusion)	Intravenous infusion
Vumerity® (diroximel fumarate delayed-release capsules)	Oral
Zeposia® (ozanimod capsules)	Oral

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Muscular Dystrophy – Amondys 45 Utilization Management Medical Policy
- Amondys 45™ (casimersen intravenous infusion – Sarepta)

REVIEW DATE: 02/14/2024

OVERVIEW

Amondys 45, an antisense oligonucleotide, is indicated for the treatment of **Duchenne muscular dystrophy** (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping.[1] This indication was granted accelerated approval based on an increase in dystrophin in skeletal muscle observed in patients treated with Amondys 45. The prescribing information notes that continued FDA-approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

Guidelines

Amondys 45 is not addressed in the guidelines for the diagnosis and management of DMD available from the DMD Care Considerations Working Group (2018).[2] Glucocorticoids slow decline in muscle strength and function in DMD and should be considered for all patients with DMD. Exondys 51 (eteplirsen intravenous infusion) is mentioned as an emerging product, approved by an accelerated pathway for those with a mutation in the dystrophin gene amenable to exon 51 skipping.

POLICY STATEMENT

The prescribing information for Amondys 45 states that approval is based on dystrophin production in a limited number of patients (n = 27 treated with Amondys 45) with DMD, but continued approval may be contingent upon a confirmatory trial. Due to inadequate clinical efficacy data, **approval is not recommended** for Amondys 45.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Amondys 45 is not recommended in the following situations:

1. **Duchenne Muscular Dystrophy.** Approval is not recommended due to the unclear clinical benefit of Amondys 45 and lack of clinical efficacy data. Shortcomings of the clinical data with Amondys 45 are numerous. In the pivotal trial, a minimal increase in dystrophin level was noted, but has not been correlated with a clinical benefit. Available data from the pivotal study did not provide any information to determine if Amondys 45 provides a benefit in regard to cardiac and respiratory complications which contribute greatly to morbidity and mortality in patients with DMD. Further, there are concerns of renal toxicity with utilization of Amondys 45, and available data do not support optimal timing for initiation or discontinuation of Amondys 45. Amondys 45 has not been proven to alter or delay disease progression in patients with DMD amenable to exon 45 skipping. A systematic review and meta-

analysis of other exon skipping therapies (i.e., Exondys 51, drisapersen) did not show benefit of these therapies for DMD.[3] The FDA has required a post-marketing trial to verify the clinical efficacy of Amondys 45; patients are still being recruited for the pivotal Phase III ESSENCE study, to further evaluate safety and efficacy in ambulatory boys with DMD.[4]

Amondys 45 is under evaluation in one ongoing, Phase III pivotal study (ESSENCE) in patients with DMD amenable to exon 45 skipping.[1] The primary endpoint is the effect of Amondys 45 on the change from baseline in the total distance walked during the 6-Minute Walk Test (6MWT) at Week 96.[4] Functional outcomes are among the secondary endpoints. In an interim analysis from 43 evaluable patients (n = 27 treated with Amondys 45; n = 16 treated with placebo), the proportion of normal dystrophin protein level was higher at Week 48 with Amondys 45 (1.74% of normal at Week 48 vs. 0.93% of normal at baseline) vs. placebo (0.76% of normal at Week 48 vs. 0.54% of normal at baseline) [P = 0.004 for Amondys 45 vs. placebo].[1] Results from the primary endpoint (6MWT) and functional outcomes have not been reported. The estimated study completion date is October 2025.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	02/15/2023
Annual Revision	No criteria changes	02/14/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Muscular Dystrophy – Exondys 51 Utilization Management Medical Policy
- Exondys 51™ (eteplirsen intravenous infusion – Sarepta)

REVIEW DATE: 05/15/2024

OVERVIEW

Exondys 51, an antisense oligonucleotide, is indicated for the treatment of **Duchenne muscular dystrophy** (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.[1] Exondys 51 was approved for this indication under accelerated approval based on an increase in dystrophin observed in the skeletal muscle of some patients who received the drug. However, a clinical benefit of Exondys 51 has not been established. The prescribing information notes that continued FDA-approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

Disease Overview

DMD is an X-linked recessive disease affecting 1 in 3,600 to 6,000 newborn male infants.[2] The disease is attributed to large frame-shift deletions in the DMD gene (chromosome Xp21) which lead to loss of a structural protein of muscle cells (dystrophin).[3] Exondys 51 is an antisense oligonucleotide designed to bind to exon 51 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping.[1] These patients represent approximately 13% of all patients with DMD.[5]

Guidelines

There are guidelines for the diagnosis and management of DMD available from the DMD Care Considerations Working Group (2018).[4] Genetic testing for a DMD mutation in a blood sample is always required. By fully characterizing the mutation, the predicted effect on the reading frame can be identified, which is the major determinant of phenotype and will determine eligibility for mutation-specific clinical trials. In patients with no mutation identified but with signs/symptoms of DMD, a muscle biopsy is clinically indicated. Glucocorticoids slow decline in muscle strength and function in DMD. Use of corticosteroids reduces the risk of scoliosis and stabilizes pulmonary function. Continued treatment after the patient loses ambulation provides a reduction in the risk of progressive scoliosis and stabilization of pulmonary function tests. Therefore, glucocorticoids should be considered for all patients with DMD. Exondys 51 is mentioned as an emerging product, approved by an accelerated pathway for those with a mutation in the dystrophin gene amenable to exon 51 skipping.

POLICY STATEMENT

Due to the lack of clinical efficacy data, **approval is not recommended** for Exondys 51.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Exondys 51 has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions:

1. **Duchenne Muscular Dystrophy (DMD).** Approval is not recommended due to the unclear clinical benefit of Exondys 51 and lack of clinical efficacy data. Shortcomings of the clinical data with Exondys 51 are numerous. In the pivotal trials, an increase in dystrophin was observed in a very limited number of patients treated with Exondys 51 and the significance of the increase could not be correlated with clinical benefit. Further, the increase in dystrophin was limited by methodological shortcomings which cast doubt on the reliability of biopsies taken during the first 48 weeks of the pivotal trials. Additional limitations of the data include that the pivotal trials only evaluated Exondys 51 in ambulatory patients; therefore, it is unknown if patients with more advanced disease and greater muscle deterioration would derive any benefit from treatment. There is inadequate information available to determine if Exondys 51 provides a benefit regarding cardiac and respiratory complications which greatly contribute to the morbidity and mortality of patients with DMD. Exondys 51 has not been proven to alter or delay disease progression in patients with DMD amenable to exon 51 skipping. The prescribing information for Exondys 51 states that a clinical benefit has not been established.[1] Furthermore, a systematic review and meta-analysis does not show benefit of exon-skipping therapies for DMD.[10] FDA has required a randomized, controlled trial evaluation post-marketing to establish efficacy of Exondys 51. The anticipated study completion is November 2024.[13]

   The efficacy of Exondys 51 was evaluated in open-label studies in patients with DMD that is amenable to exon 51 skipping.[1,6-9,11] One study (n = 12) assessed the effect of Exondys 51 on dystrophin and the potential clinical benefit; however, there was insufficient information on dystrophin levels prior to treatment so it is not possible to estimate a treatment effect on dystrophin levels. The adjusted mean change in the 6-minute walk test (6MWT) from baseline to Week 24 was -25.8 (± 30.6) meters for placebo; -128.2 (± 31.6) meters for Exondys 51, 30 mg/kg; and -0.3 (± 31.2) meters for Exondys 51, 50 mg/kg. An extension of this study evaluated the same patients and compared disease progression with matched historical controls; at Month 36 the difference in 6MWT distance for Exondys 51 vs. historical control was 121 meters in favor of the Exondys 51 cohort (P = 0.028). Over 36 months, ambulation was lost in 16.7% of patients (n = 2/12) treated with Exondys 51 vs. 46.2% of patients (n = 6/13) in the historical control cohort. The average dystrophin protein level after 180 weeks of treatment with Exondys 51 was 0.93% of the dystrophin level in healthy subjects. But because there was insufficient information on baseline dystrophin levels prior to treatment, it is not possible to estimate a treatment effect. Following 240 weeks of treatment, the percent predicted forced vital capacity (FVC%p) was a decrease of 2.3% per year with Exondys 51 compared with a decrease of 4.1% in a natural history cohort.[11] In patients treated with Exondys 51, the percent predicted maximum inspiratory pressure (MIP%p) decreased by 1% per year, and the percent predicted maximum expiratory pressure (MEP%p) decreased by 2.6% per year. However, MIP and MEP were not assessed in the natural history cohort. Another study included 12 new patients with DMD and reports only on the effect of Exondys 51 on dystrophin levels; further clinical efficacy data are not yet available for these 12 patients.[7-9] After 48 weeks of treatment with Exondys 51 the dystrophin level was 0.44% ± 0.43% of the dystrophin level in healthy subjects (P < 0.05). The median increase after 48 weeks was 0.1%.

   The PROMOVI trial was a Phase III, multicenter, open-label, non-randomized trial evaluating the efficacy and safety of Exondys 51 in patients 7 to 16 years of age with DMD and genetic deletions amenable to exon 51 skipping (n = 79).[12] At Week 96, mean 6MWT distance and mean FVC%p decreased from baseline. The results were consistent with Phase II trials of Exondys 51. Several study limitations including the open-label design with lack of a placebo-control group, lack of a prospective,

mutation-matched untreated control arm, lack of data on treatment effects in patients earlier in the disease course were not addressed.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/26/2023
Annual Revision	No criteria changes.	05/15/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Muscular Dystrophy – Gene Therapy – Elevidys Utilization Management Medical Policy
- Elevidys® (delandistrogene moxeparvovec-rokl intravenous infusion – Sarepta)

REVIEW DATE: 07/19/2023

OVERVIEW

Elevidys, an adeno-associated virus (AAV) vector-based gene therapy, is indicated for the treatment of ambulatory pediatric patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the *DMD* gene.[1] This indication is approved under accelerated approval based on expression of Elevidys micro-dystrophin observed in patients treated with Elevidys. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Disease Overview

DMD is a rare, progressive X-linked disease resulting from mutation(s) of the *DMD* gene, also known as the *Dystrophin* gene.[2-4] The incidence of DMD in the US is approximately 1 in 5,000 live male births. The *DMD* gene is the largest known human gene, totaling 2.3 megabases in size. The gene encodes for a functional dystrophin protein, which is part of a transmembrane protein complex that spans the sarcolemma of skeletal and cardiac muscle cells. This complex links the cytoskeleton to the extracellular matrix providing structural integrity to the sarcolemma and helps to transmit and absorb the shock associated with muscle contraction. Mutations in the *DMD* gene prevent the production of functional dystrophin protein or dystrophin is minimally produced. Without dystrophin, normal activity in patients with DMD causes excessive damage to muscle fiber cells. Over time, the muscle cells are replaced with fat and fibrotic tissue. Progressive muscle weakness is the primary manifestation of DMD. This leads to loss of ambulation, associated motor delays, respiratory impairment, and progressive decline in cardiac function. The first clinical symptoms of DMD are delay in motor development milestones, such as walking, which is observed around 2 years of age. Often there is a delay in diagnosis until the age of 3 to 5 years. Age is an important prognostic factor in the progression of DMD. There is no cure for DMD currently. The goal of treatment is to manage symptoms, slow disease progression, and to delay disability. Boys with DMD typically lose the ability to walk by age 12 or 13 years. In the past, mortality occurs by late adolescence or early twenties, however with advances in respiratory and cardiac management, some patients are living into the fourth decade. The most common cause of death for patients with DMD are respiratory failure, respiratory infection, cardiomyopathy, and cardiac arrhythmias. Corticosteroids are a mainstay of therapy in DMD; however, its mechanism of action in DMD is unknown. Corticosteroids ameliorate the symptoms of the disease and delay time to loss of ambulation and other sequelae. Four anti-sense oligonucleotide therapies (exon-skipping) have been approved by the FDA: Exondys 51® (eteplirsen intravenous infusion), Vyondys 53™ (golodirsen intravenous infusion), Viltepso™ (viltolarsen intravenous infusion), and Amondys 45™ (casimersen intravenous infusion). The clinical benefit of these exon-skipping therapies remains unknown since none of the confirmatory clinical studies have been completed.

Clinical Efficacy

The efficacy of Elevidys was evaluated in two studies:[1-4] a Phase II study and a Phase Ib study.[1] Both studies are unpublished and long-term follow-up is ongoing. The Phase II study (n = 41) included two parts: Part I was a 48-week randomized, double-blind, placebo-controlled study in which patients received a single-dose of Elevidys (n = 20) or placebo (n = 21); in Part II, patients treated with placebo in Part I received Elevidys. Patients in this study were stratified by age (age 4 to 5 years vs. age 6 to 7 years) at

randomization. Retrospective analysis identified that 60% of patients in Part I received a dose lower than Elevidys 1.33 x 10^{14} vector genomes (vg)/kg, due to variability in quantification methods.[1-3] In Part I, only 8 patients received the approved dose of Elevidys 1.33 x 10^{14} vg/kg; 12 patients received one-half to two-thirds of the approved dose. In Part II, all patients from the placebo group received the recommended dose of Elevidys 1.33 x 10^{14} vg/kg.

Guidelines

Elevidys is not addressed in current guidelines for DMD. The guidelines from the DMD Care Considerations Working Group (2018) notes that genetic testing for confirming DMD diagnosis is always required.[5-7] In patients with no mutations identified, but with signs/symptoms of DMD, a muscle biopsy is clinically indicated. Glucocorticoids and physical therapy are the mainstays of treatment and should be continued even after the patient is non-ambulatory. Corticosteroids reduce the risk of scoliosis and stabilizes pulmonary function. In patients who are non-ambulatory, continuing corticosteroid treatment provides a reduction in the risk of progressive scoliosis and stabilization of pulmonary function tests. Due to this benefit, glucocorticoids should be considered in all patients with DMD.

Dosing

The recommended dose is 1.33 x 10^{14} vg/kg of body weight (or 10 mL/kg body weight).[1] Immune responses to the AAVrh74 vector can occur after Elevidys administration. To reduce this risk, corticosteroids should be administered starting one day prior to Elevidys infusion and continued for a minimum of 60 days after the infusion, unless earlier tapering is clinically indicated.

Safety

Elevidys is contraindicated in patients with any deletion in exon 8 and/or exon 9 in the *DMD* gene.[1] Warnings/Precautions are for acute serious liver injury, immune-mediated myositis, myocarditis, and pre-existing immunity against AAVrh74. For administration of Elevidys, the anti-AAVrh74 total antibody binding titer should be < 1:400.

POLICY STATEMENT

Due to the lack of clinical efficacy data, **approval is not recommended** for Elevidys.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Elevidys clinical data are limited and available data are not supportive of general approval for the following conditions:

1. **Duchenne Muscular Dystrophy (DMD).** Approval is not recommended due to the unclear clinical benefit of Elevidys. Elevidys clinical trials had numerous study limitations.[1-4] In the Phase II study, Part I, the only double-blind, placebo-controlled part of the clinical trials, only 40% of the patients randomized to Elevidys (n = 8/20) received the intended gene therapy dose. The other clinical trial was a Phase Ib study that was limited by a single-arm, open-label design. In both these trials, the primary efficacy measure was the change in micro-dystrophin expression level from baseline to Week 12. It is unknown whether increases in micro-dystrophin expression will correlate with clinically meaningful functional improvements. Micro-dystrophin is a novel synthetic protein that is much smaller in size compared with that of the dystrophin protein. So although there was about a 40% increase (compared to control) in micro-dystrophin expression from baseline to post-Elevidys infusion, especially in the Phase II study, this did not translate to an increase in the functional scores, as assessed by the North Star Ambulatory Assessment (NSAA). There is no established baseline minimal percentage expression of micro-dystrophin required to show functional changes in DMD. In the double-blind study, only the subgroup of patients 4 through 5 years of age demonstrated an improvement in the NSAA total score at Week 48 compared with placebo. The subgroup of patients 6 through 7 years of age had a decrease in the NSAA total score compared with placebo, which is contrary to the expected result. Based on this uncompelling NSAA data, the FDA narrowed the age indication for Elevidys to 4 through 5 years, instead of the overall study population (age 4 through 7). Due to this age limitation, the micro-dystrophin primary endpoint in this FDA-approved group, could only be assessed in 3 patients. In the Phase Ib study there was an increase of 4 points in the NSAA total score from baseline to Week 52 in the cohort of patients (n = 20) that received Elevidys. However, the interpretation of data are limited in this study due to its open-label, single-arm design. EMBARK is a randomized, placebo-controlled, double-blind Phase III study with Elevidys that is ongoing. The preliminary results from this study are expected at the end of 2023.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/19/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Muscular Dystrophy – Viltepso Utilization Management Medical Policy
- Viltepso™ (viltolarsen intravenous infusion – Nippon Shinyaku)

REVIEW DATE: 08/30/2023

OVERVIEW

Viltepso, an antisense oligonucleotide, is indicated for the treatment of **Duchenne muscular dystrophy** (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.[1] This indication was granted accelerated approval based on an increase in dystrophin in skeletal muscle observed in patients treated with Viltepso. The prescribing information notes that continued FDA approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

Viltepso is an antisense oligonucleotide designed to bind to exon 53 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 53 skipping.[1] These patients represent up to 10% of all patients with DMD.[2] This genetic manipulation intends to restore the reading frame of the resulting mRNA. The result would be production of a shortened, but partially functional dystrophin protein as seen in less severe forms of muscular dystrophy (e.g., Becker muscular dystrophy). Of note, the reading frame of certain deletions (e.g., exon 52 deletions) can be restored by skipping either exon 51 or exon 53.[3] Approximately 8% of mutations are amenable to skipping exon 53 with Viltepso but are not amenable to skipping of exon 51.

Guidelines

Viltepso and other exon 53 skipping therapies are not addressed in guidelines for DMD. There are guidelines for the diagnosis and management of DMD available from the DMD Care Considerations Working Group (2018).[4] Genetic testing for a DMD mutation in a blood sample is always required. By fully characterizing the mutation, the predicted effect on the reading frame can be identified, which is the major determinant of phenotype and will determine eligibility for mutation-specific clinical trials. In patients with no mutation identified but with signs/symptoms of DMD, a muscle biopsy is clinically indicated. Glucocorticoids slow decline in muscle strength and function in DMD. Use of corticosteroids reduces the risk of scoliosis and stabilizes pulmonary function. Continued treatment after the patient loses ambulation provides a reduction in the risk of progressive scoliosis and stabilization of pulmonary function tests. Therefore, glucocorticoids should be considered for all patients with DMD. Exondys® 51 (eteplirsen intravenous infusion) is mentioned as an emerging product, approved by an accelerated pathway for those with a mutation in the dystrophin gene amenable to exon 51 skipping.

POLICY STATEMENT

The prescribing information for Viltepso states that approval is based on dystrophin production in a limited number of patients (n = 8 treated with the approved dose) with DMD, but approval may be contingent upon a confirmatory trial. Due to inadequate clinical efficacy data, **approval is not recommended** for Viltepso.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Viltepso is not recommended in the following situations:

1. **Duchenne Muscular Dystrophy (DMD).** Approval is not recommended due to the unclear benefit of Viltepso and lack of clinical efficacy data. Shortcomings of the clinical data with Viltepso are numerous. Although the pivotal study demonstrated a measurable increase in dystrophin levels, the significance of this small change has not yet been correlated with a clinical benefit. Data from the pivotal study did not provide any information to determine if Viltepso provides a benefit in regard to cardiac and respiratory complications which contribute greatly to morbidity and mortality in DMD. The pivotal data are also lacking robust functional outcomes related to motor function. Viltepso has not been proven to alter or delay the disease progress in patients with DMD amenable to exon 53 skipping. A systematic review and meta-analysis of other exon skipping therapies (i.e., Exondys 51, drisapersen) does not show benefit of these therapies for DMD.[5] The prescribing information notes that continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.[1] FDA has required a post-marketing trial to verify clinical efficacy of Viltepso. Thus, patients are being recruited for the Phase III RACER53 study, to further evaluate safety and efficacy of Viltepso in 74 ambulatory patients with DMD.

   Viltepso is under evaluation in one ongoing Phase II pivotal study in patients with DMD amenable to exon 53 skipping.[6] The primary endpoint is the effect of Viltepso on dystrophin as a surrogate outcome marker. Functional outcomes were among the secondary endpoints and were compared with a natural history cohort controlled for age, functional status, geographic location, and glucocorticoid treatment status. In this pivotal study (n = 16), the proportion of normal dystrophin protein level was higher at Week 25 (0.6% of normal at baseline vs. 5.9% of normal at Week 24 biopsy). Some functional outcomes were significantly improved from baseline with Viltepso vs. the natural history cohort (time to run walk 10 meters [0.23 meters/second vs. -0.04 meters/second], time to stand from supine [-0.19 seconds vs. 0.66 seconds], and distance on the 6-minute walk test [28.9 meters vs. -65.3 meters]). However, velocity in the time to stand from supine test, time to climb 4 stairs test, North Star Ambulatory Assessment test, and measures of muscle strength by isometric testing were <u>not</u> significantly different from the control group. Data from the long-term extension (out to 109 weeks) of the pivotal trial have been published.[7] All 16 patients who completed the Phase II trial continued into the long-term extension. Functional outcomes (time to stand and time to walk/run 10 meters) were maintained in the Viltepso group over 109 weeks while they were worsened in the natural history cohort. The time to climb 4 stairs was not significantly different from the natural history cohort over the 109 weeks. Final results from the 192-week long-term extension study (4 years post-treatment) showed stabilization of motor function over the first 2 years for the primary endpoint of time to stand and significant slowing of motor function loss (compared to historical control groups) over the following 2 years.[8] Similar results were observed with time to run/walk. Time to climb results were not significantly different between Viltepso and control groups.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/24/2022
Annual Revision	No criteria changes	08/30/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Muscular Dystrophy – Vyondys 53 Utilization Management Medical Policy
- Vyondys 53™ (golodirsen intravenous infusion – Sarepta)

REVIEW DATE: 12/13/2023

OVERVIEW

Vyondys 53, an antisense oligonucleotide, is indicated for the treatment of **Duchenne muscular dystrophy** (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.[1] Vyondys 53 was approved for this indication under accelerated approval based on an increase in dystrophin observed in the skeletal muscle of patients who received the drug. The Prescribing Information notes that continued FDA-approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

Disease Overview

DMD is an X-linked recessive disease affecting 1 in 3,600 to 6,000 newborn male infants.[2] The disease is attributed to large frame-shift deletions in the DMD gene (chromosome Xp21) which lead to loss of a structural protein of muscle cells (dystrophin).[3] Over 4,700 mutations on the DMD gene have been identified which lead to a deficiency in production of dystrophin.[2] Therefore, the type of mutation and its effect on the production of dystrophin accounts for the variable phenotypic expression.[4] Female carriers are usually asymptomatic but some may show mild symptoms.[2] There are wide variances in how quickly DMD progresses, but without intervention death is at approximately 19 years of age.[2-4] With respiratory, cardiac, orthopedic and rehabilitative interventions, and use of corticosteroids, children born today can have a life expectancy of up to 40 years.

Vyondys 53 is designed to bind to exon 53 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 53 skipping.[1] These patients represent up to 10% of all patients with DMD.[5] This genetic manipulation intends to restore the reading frame of the resulting mRNA. The result would be production of a shortened, but partially functional dystrophin protein as seen in less severe forms of muscular dystrophy (e.g., Becker muscular dystrophy). Of note, the reading frame of certain deletions (e.g., exon 52 deletions) can be restored by skipping either exon 51 or exon 53.[6] Approximately 8% of mutations are amenable to skipping exon 53 with Vyondys 53 but are not amenable to skipping of exon 51.

Guidelines

There are guidelines for the diagnosis and management of DMD available from the DMD Care Considerations Working Group (2018).[4] Genetic testing for a DMD mutation in a blood sample is always required. By fully characterizing the mutation, the predicted effect on the reading frame can be identified, which is the major determinant of phenotype and will determine eligibility for mutation-specific clinical trials. In patients with no mutation identified but with signs/symptoms of DMD, a muscle biopsy is clinically indicated. Glucocorticoids slow decline in muscle strength and function in DMD. Use of corticosteroids reduces the risk of scoliosis and stabilizes pulmonary function. Continued treatment after the patient loses ambulation provides a reduction in the risk of progressive scoliosis and stabilization of pulmonary function tests. Therefore, glucocorticoids should be considered for all patients with DMD. Exondys 51 (eteplirsen intravenous infusion) is mentioned as an emerging product, approved by an accelerated pathway for those with a mutation in the dystrophin gene amenable to exon 51 skipping. However, these guidelines do not specifically address exon 53 skipping or mention Vyondys 53.

POLICY STATEMENT

The prescribing information for Vyondys 53 states that approval is based on dystrophin production in a limited number of patients (n = 25) with DMD, but approval may be contingent upon a confirmatory trial. Due to inadequate clinical efficacy data, **approval is not recommended** for Vyondys 53.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vyondys 53 is not recommended in the following situations:

1. **Duchenne Muscular Dystrophy (DMD).** Approval is not recommended due to the unclear clinical benefit of Vyondys 53 and lack of clinical efficacy data. Shortcomings of the clinical data with Vyondys 53 are numerous. In the pivotal trial, a minimal increase in dystrophin level was noted, but has not been correlated with a clinical benefit. Available data from the pivotal study did not provide any information to determine if Vyondys 53 provides a benefit regarding cardiac and respiratory complications which contribute greatly to morbidity and mortality in patients with DMD. Further, there are concerns of renal toxicity with utilization of Vyondys 53, and available data do not support optimal timing for initiation or discontinuation of Vyondys 53. Vyondys 53 has not been proven to alter or delay disease progression in patients with DMD amenable to exon 53 skipping. A systematic review and meta-analysis of other exon skipping therapies (i.e., Exondys 51, drisapersen) does not show benefit of these therapies for DMD.[7] The prescribing information notes that continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.[1] FDA has required a post-marketing confirmatory trial to verify the clinical efficacy of Vyondys 53.[10] This double-blind, placebo-controlled, Phase III study is estimated to be completed by October 2025.

   The efficacy of Vyondys 53 was evaluated in one published, open-label study in patients with DMD that is amenable to exon 53 skipping.[1,8] Dystrophin protein at Week 48 and 6-minute walk test (6MWT) results at Week 144 were the primary clinical endpoints. Among the patients who received Vyondys 53 in Part 2 of the study (n = 25) the normal dystrophin protein increased from baseline (0.10%) through Week 48 (1.02%; $P < 0.001$). In individual patient biopsies at Week 48, the dystrophin level ranged from 0.09% to 4.3%, with a mean per-patient 16.0-fold increase in dystrophin. At Week 48, the mean level of exon 53 skipping increased to 18.6% (SD, 13.2%; range, 2.6% to 48.0%) vs. 2.6% (SD, 4.1%; range, 0.0 to 14.7%) at baseline. The percent dystrophin-positive fibers scoring increased from 1.4% (SD, 2.4%; range, 0.06% to 9.8%) at baseline to 10.5% (SD, 10.1%; range, 0.9% to 32.6%) [$P < 0.001$] at Week 48. There was a mean per-patient 13.5-fold increase in percent dystrophin-positive fibers from baseline through Week 48. 6MWT declined by 26.1 m, 64.6 m, and 99.0 m at Weeks 48, 96, and 144, respectively.[9] When compared with a natural history external control, there was numerically less decline from baseline with Vyondys 53 (-99 m with Vyondys vs. -181 m in the natural history cohort); however, this difference did not reach statistical significance. Two patients in the Vyondys 53 group lost ambulation. The percent predicted forced vital capacity declined by 8.4% (92.7% at baseline to 83.8% at Week 144).

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/07/2022
Annual Revision	No criteria changes	12/13/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Neurology – Brineura Utilization Management Medical Policy
- Brineura® (cerliponase alfa intraventricular infusion – BioMarin)

REVIEW DATE: 04/10/2024

OVERVIEW

Brineura is indicated to slow the loss of ambulation in symptomatic pediatric patients ≥ 3 years of age with **late infantile neuronal ceroid lipofuscinosis type 2** (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency.[1]

Brineura is recombinant human TPP1 produced using recombinant DNA technology.[1] The recommended dose of Brineura is 300 mg administered once every other week (QOW) via intracerebroventricular (ICV) infusion. Following Brineura administration, the patient must also receive an infusion of intraventricular electrolytes. The drug is administered into the cerebral spinal fluid via a surgically implanted reservoir and catheter. It should only be administered by or under the direction of a physician who is knowledgeable in ICV administration.

Disease Overview

CLN2 disease is an extremely rare neurodegenerative disorder that is part of a group of neuronal ceroid lipofuscinoses (NCLs) sometimes referred to as Batten disease.[2] NCL diseases are a heterogeneous group of incurable neurodegenerative lysosomal storage diseases. They manifest as early impairment of vision, loss of cognitive and motor functions, seizures, and premature death. To date, 13 genetic mutations have been discovered to cause the multiple variations of the disease (e.g., CLN1, CLN2, CLN3 etc.). Classic late infantile NCL disease is caused by a mutation in the CLN2 gene, which encodes for lysosomal TPP1. Without TPP1, lysosomal storage materials accumulate, contributing to the progressive and persistent neurodegeneration.[2] In CLN2 disease, symptom onset is typically between 2 and 4 years of age, and lifespan is around 6 to 14 years. Other NCLs result in deficiencies in enzymes other than TPP1. As Brineura is human recombinant TPP1, its efficacy is specific to CLN2 disease.

Guidelines

Recently published expert recommendations state that patients with a suspected NCL disorder require NCL-specific diagnostic testing.[3-5] Patients require assessment by a metabolic specialist/geneticist, an NCL specialist, or a pediatric neurologist with experience in diagnosing NCL disorders. Expert recommendation from 2016 state that the gold standard for laboratory diagnosis is the demonstration of deficient TPP1 enzyme activity (in leukocytes, fibroblasts, or dried blood spots) and the identification of pathogenic variants in both alleles of the TPP1/CLN2 gene for confirmation of CLN2 disease.[4] When it is not possible to perform both analyses, either demonstration of deficient TPP1 enzyme activity in leukocytes or fibroblasts, or detection of two pathogenic variants in the CLN is diagnostic for CLN2 disease.[4] The 2021 guidelines established that the diagnosis of CLN2 can be confirmed by low levels of TPP1 enzyme activity and should be double confirmed by detecting two disease-causing mutations in the CLN2 gene.[5]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Brineura. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing

documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the of the specialized skills required for evaluation and diagnosis of patients treated with Brineura as well as the monitoring required for adverse events and long-term efficacy, approval requires Brineura to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Brineura is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Late Infantile Neuronal Ceroid Lipofuscinosis Type 2 (CLN2).** Approve for 1 year if the patient meets ALL of the following (A, B, C and D):
   - **A)** Patient is ≥ 3 years of age; AND
   - **B)** Patient has two pathogenic mutations in the CLN2 gene as confirmed by genetic testing; AND
   - **C)** Patient has had a test which confirms reduced activity of tripeptidyl peptidase 1 (TPP1); AND
   - **D)** Brineura is prescribed by or in consultation with a metabolic specialist, geneticist, pediatric neurologist, or a physician specializing in the treatment of neuronal ceroid lipofuscinoses (NCLs).

   Dosing. Approve the following dosing (A and B):
   - **A)** 300 mg via intracerebroventricular (ICV) infusion administered once every other week; AND
   - **B)** Each dose is followed by an infusion of intraventricular electrolytes (supplied in the Brineura package).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Brineura is not recommended in the following situations:

1. **Neuronal Ceroid Lipofuscinoses (NCLs) other than late infantile ceroid lipofuscinosis type 2 (CLN2) [e.g., CLN1, CLN3, CLN10, CLN13, and others].** Brineura has not been studied for NCLs involving mutations in genes other than CLN2.[1]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Late Infantile Neuronal Ceroid Lipofuscinosis Type 2 (CLN2):** The requirement that the patient has had a genetic test which confirms the diagnosis of CLN2 disease OR patient has had a test which confirms reduced activity of tripeptidyl peptidase 1 (TPP1) was changed to "Patient has two pathogenic mutations in the CLN2 gene as confirmed by genetic testing AND patient has had a test which confirms reduced activity of tripeptidyl peptidase 1 (TPP1)."	04/12/2023
Annual Revision	No criteria changes	04/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Neurology – Gene Therapy – Lenmeldy Utilization Management Medical Policy
- Lenmeldy™ (atidarsagene autotemcel intravenous infusion – Orchard)

REVIEW DATE: 05/15/2024

OVERVIEW

Lenmeldy, an autologous hematopoietic stem cell (HSC)-based gene therapy, is indicated for the treatment of pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ), or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD) in children.[1]

Lenmeldy is given as a one-time (per lifetime) single dose by intravenous infusion.[1] The minimum recommended dose of Lenmeldy is based on the MLD disease subtype and is 4.2 x 10^6 cluster of differentiation 34+ (CD34+) cells/kg, 9 x 10^6 CD34+ cells/kg, and 6.6 x 10^6 CD34+ cells/kg for patients with PSLI, PSEJ, and ESEJ MLD, respectively; the maximum recommended dose for all disease subtypes is 30 x 10^6 CD34+ cells/kg. The entire treatment process involves several steps. Lenmeldy is prepared from the child's own HSCs, which are collected via mobilization and apheresis procedures. This process takes one or more days to collect an adequate amount of stem cells to manufacture Lenmeldy. The collected stem cells are sent to a manufacturing site and are used to make Lenmeldy; this takes 5 to 6 weeks. Prior to receipt of Lenmeldy, chemotherapy (with busulfan) is given for a few days in a qualified treatment center to prepare the bone marrow to accept the new cells. Following completion of myeloablative conditioning, a minimum of 24 hours of washout must occur before infusion of Lenmeldy. After the Lenmeldy infusion, the child remains in the qualified treatment center for 4 to 12 weeks to monitor recovery. The gene therapy is transduced with a lentiviral vector encoding the human arylsulfatase A (*ARSA*) gene. The agent adds functional copies of the *ARSA* gene into the child's own HSCs.

The safety and effectiveness of Lenmeldy have been established in children with PSLI, PSEJ, and ESEJ MLD.[1] The clinical trial involving Lenmeldy treated 20 children with PSLI, 7 children with PSEJ, and 10 children with ESEJ MLD; children were between the ages of 8 months and 19 months (median age of 12 months), 11 months to 5.56 years (median age of 2.57 years), and 2.54 years to 11.64 years (median age of 5.84 years), respectively. The safety and efficacy of Lenmeldy have not yet been established in children with the late juvenile form of the disease.

Disease Overview

MLD is a rare, inherited, autosomal recessive, neurodegenerative lysosomal storage disease caused by deficiency of *ARSA*, due to mutations in the *ARSA* gene.[2-4] MLD is estimated to impact one in every 40,000 individuals in the US. Reduced *ARSA* activity in patients with MLD (usually 0% to less than or equal to 13%) results in accumulation of sulfatides in the central nervous system and peripheral nervous system, leading to progressive demyelination, neuroinflammation, and neurodegeneration. These events lead to progressive motor and cognitive deterioration. Sulfatides also accumulate in visceral organs, such as the gallbladder and kidneys, and cause a host of systemic manifestations as well. The clinical spectrum of MLD is broad and heterogeneous. Defined clinical forms are commonly described on the basis of age at first symptom onset: late-infantile (≤ 30 months of age), juvenile (subdivided into early juvenile [30 months to < 7 years of age] and late juvenile [7 to 16 years of age]), and adult (≥ 17 years of age), with earlier age at onset or the presence of motor symptoms as initial disease manifestations associated with a more severe and rapid disease course. Regardless of the clinical variant, the underlying disease pathophysiology is

similar for all phenotypic forms of MLD. Patients with MLD gradually lose the ability to move, talk, swallow, eat, and see. Early mortality is noted.

Clinical Efficacy

The efficacy of Lenmeldy was evaluated in 39 children that involved two single-arm, open-label clinical trials, as well as a European Union (EU) expanded access program.[1,5] The data involved 20 children with PSLI, 7 children with PSEJ, and 10 children with ESEJ MLD.[1] All children had biochemical and molecular diagnosis of MLD based on *ARSA* activity below the normal range, as well as the presence of two disease-causing *ARSA* alleles. A 24-hour urine collection was required to show elevated sulfatide levels in selected patients. The main efficacy outcomes with Lenmeldy involved motor and neurocognitive function, as evaluated by gross motor function classification for metachromatic leukodystrophy (GMFC-MLD) levels and standard scores on age-appropriate neurocognitive tests, respectively. Comparisons with Lenmeldy were made with an external untreated natural history cohort of children with late juvenile (n = 28) and early juvenile (n = 21) MLD; data were collected retrospectively and prospectively. The primary endpoint was severe motor impairment-free survival, defined as the interval from birth to the first occurrence of loss of locomotion and loss of sitting without support (GMFC-MLD Level ≥ 5) or death. Treatment with Lenmeldy significantly extended severe motor impairment-free survival in children with PSLI MLD vs. the untreated late infantile natural history children. Patients given Lenmeldy had significantly extended severe motor impairment-free survival in this population compared with untreated late infantile natural history children. Seventeen children with PSLI MLD treated with Lenmeldy have been followed until at least the age of 5 years; all children given Lenmeldy remained event-free compared with none of the untreated children in the late infantile natural history group. In total, 14 children treated with Lenmeldy and 24 children from the natural history group had adequate follow-up to determine survival at 6 years from birth. At this timepoint, all children who had PSLI and were treated with Lenmeldy were alive vs. only 58% of children in the late infantile natural history group. In children with PSEJ and ESEJ MLD, those given Lenmeldy displayed slowing of motor and/or cognitive function. It is notable that retention of cognitive function usually does not occur in patients with early juvenile MLD; motor and cognitive functioning typically decline in tandem in children who are not treated.

Guidelines

A consensus guideline for the monitoring and management of MLD in the US was released in April 2024.[2] In early-onset MLD, including late infantile and early juvenile subtypes, gene therapy (Lenmeldy) should be considered for presymptomatic patients where available. In late-onset MLD, including late juvenile and adult subtypes, HSC transplant (allogeneic) should be considered for patients with no or minimal disease involvement.

Policy Statement

Prior Authorization is recommended for prescription benefit coverage of Lenmeldy. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lenmeldy as well as the specialized training required for administration of Lenmeldy, approval requires Lenmeldy to be prescribed by a physician who specializes in the condition being treated. All approvals are provided for one-time (per lifetime) as a single dose. The approval duration is 1 year to allow for an adequate timeframe to prepare and administer one dose of therapy. If claims history is available, verification is required for certain criteria as noted by **[verification in claims history required]**. For the dosing criteria, verification of the appropriate weight-based dosing is required by a Medical Director as noted by **[verification required]**.

All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with EviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

Documentation: Documentation is required for use of Lenmeldy as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory results, medical test results, claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lenmeldy is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. **Metachromatic Leukodystrophy.** Approve a one-time (per lifetime) single dose if the patient meets ALL of the following (A, B, C, D, E, F, G, H, I, and J):
   - **A)** Patient meets ONE of the following (i, ii, or iii):
     - **i.** Patient has presymptomatic late infantile (PSLI) metachromatic leukodystrophy (MLD) and meets ALL of the following (a, b, and c):
       - **a)** Patient has an arylsulfatase A (*ARSA*) genotype consistent with presymptomatic late infantile MLD **[documentation required]**; AND
       - **b)** The disease onset was at ≤ 30 months of age; AND
       - **c)** According to the prescribing physician, the patient is presymptomatic; OR
         Note: Presymptomatic status is defined as the absence of neurological signs and symptoms of MLD. However, presymptomatic children are allowed to have abnormal reflexes or abnormalities on brain magnetic resonance imaging and/or nerve conduction tests not associated with functional impairment (e.g., no tremor, no peripheral ataxia).
     - **ii.** Patient has presymptomatic early juvenile (PSEJ) metachromatic leukodystrophy (MLD) and meets ALL of the following (a, b, and c):
       - **a)** Patient has an arylsulfatase A (*ARSA*) genotype consistent with presymptomatic early juvenile MLD **[documentation required]**; AND
       - **b)** The disease onset was between > 30 months and < 7 years of age; AND
       - **c)** According to the prescribing physician, the patient is presymptomatic; OR
         Note: Presymptomatic status is defined as the absence of neurological signs and symptoms of MLD or physical examination findings limited to abnormal reflexes and/or clonus. However, presymptomatic children were allowed to have abnormal reflexes or abnormalities on brain magnetic resonance imaging and/or nerve conduction tests not associated with functional impairment (e.g., no tremor, no peripheral ataxia).
     - **iii.** Patient has early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD) and meets ALL of the following (a, b, and c):
       - **a)** Patient has an arylsulfatase A (*ARSA*) genotype consistent with early symptomatic early juvenile MLD **[documentation required]**; AND
       - **b)** The disease onset was between > 30 months and < 7 years of age; AND
       - **c)** The patient has early symptomatic status by meeting BOTH of the following [(1) and (2)]:

(1) Patient is walking independently as defined as being at gross motor function classification for metachromatic leukodystrophy [GMFC-MLD] Level 0 (with or without ataxia) or GMFC-MLD Level 1; AND
(2) Patient has an intelligence quotient ≥ 85; AND

B) Patient has not received Lenmeldy in the past **[verification in claims history required]**; AND
Note: If no claim for Lenmeldy is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Lenmeldy.

C) Patient has low arylsulfatase A (*ARSA*) activity indicative of metachromatic leukodystrophy (MLD) **[documentation required]**; AND
Note: Normal laboratory reference range for *ARSA* activity in the peripheral blood mononuclear cells is 31 to 198 nmol/mg/hour. In patients with MLD, *ARSA* activity is 0% to less than or equal to 13%.

D) Patient has elevated sulfatide levels above the normal laboratory reference range as evaluated by 24-hour urine collection **[documentation required]**; AND

E) According to the prescribing physician, a hematopoietic stem cell transplantation is appropriate for the patient; AND

F) According to the prescribing physician, patient meets ALL of the following (i, ii, and iii):
i. Patient will undergo mobilization, apheresis, and myeloablative conditioning; AND
ii. A granulocyte-colony stimulating factor product with or without a hematopoietic stem cell mobilizer will be utilized for mobilization; AND
Note: Filgrastim products are examples of a granulocyte-colony stimulating factor therapy and Mozobil (plerixafor subcutaneous injection) is an example of a hematopoietic stem cell mobilizer.
iii. Busulfan will be used for myeloablative conditioning; AND

G) Prior to collection of cells for manufacturing, cellular screening is negative for ALL of the following (i, ii, iii, iv, v, and vi):
i. Human immunodeficiency virus (HIV)-1 and HIV-2 **[documentation required]**; AND
ii. Hepatitis B virus **[documentation required]**; AND
iii. Hepatitis C virus **[documentation required]**; AND
iv. Human T-lymphotrophic virus (HTLV)-1 and HTLV-2 **[documentation required]**; AND
v. Cytomegalovirus **[documentation required]**; AND
vi. Mycoplasma **[documentation required]**; AND

H) The medication is prescribed by a hematologist, a neurologist, a medical geneticist physician, or a stem cell transplant specialist physician; AND

I) Current patient body weight has been obtained within 30 days **[documentation required]**; AND

J) If criteria A through I are met, approve one dose of Lenmeldy by intravenous infusion to provide a one-time (per lifetime) single dose within the following dosing ranges according to ONE of the following metachromatic leukodystrophy (MLD) disease types (i, ii, or iii):
i. For presymptomatic late infantile MLD, the minimum recommended dose is 4.2 x 10^6 CD34+ cells/kg up to a maximum recommended dose of 30 x 10^6 CD34+ cells/kg **[verification required]**; OR
ii. Presymptomatic early juvenile MLD, the minimum recommended dose is 9 x 10^6 CD34+ cells/kg up to a maximum recommended dose of 30 x 10^6 CD34+ cells/kg **[verification required]**; OR
iii. Early symptomatic early juvenile MLD, the minimum recommended dose is 6.6 x 10^6 CD34+ cells/kg up to a maximum recommended dose of 30 x 10^6 CD34+ cells/kg **[verification required]**.

Dosing. Lenmeldy is one dose given by intravenous infusion to provide a one-time (per lifetime) single dose within the following dosing ranges according to ONE of the following metachromatic leukodystrophy (MLD) disease types (A, B, or C):

A) For presymptomatic late infantile MLD, the minimum recommended dose is 4.2 x 10^6 CD34+ cells/kg up to a maximum recommended dose of 30 x 10^6 CD34+ cells/kg **[verification required]**; OR

B) Presymptomatic early juvenile MLD, the minimum recommended dose is 9 x 10^6 CD34+ cells/kg up to a maximum recommended dose of 30 x 10^6 CD34+ cells/kg **[verification required]**; OR

C) Early symptomatic early juvenile MLD, the minimum recommended dose is 6.6 x 10^6 CD34+ cells/kg up to a maximum recommended dose of 30 x 10^6 CD34+ cells/kg **[verification required]**.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lenmeldy is not recommended in the following situations:

1. **Late Juvenile Form of Metachromatic Leukodystrophy.** The safety and efficacy have not yet been established in children with the late juvenile form of the disease.[1]

2. **Adult Form of Metachromatic Leukodystrophy.** The safety and efficacy have not yet been established in patients with the adult form of the disease.

3. **Gross Motor Function Classification for Metachromatic Leukodystrophy (GMFC-MLD) > Level 1.** These patients were not included in the clinical studies.

4. **Prior Allogeneic Hematopoietic Stem Cell Transplantation in the Past 6 Months or Evidence of Residual Donor Cells.**
   Note: Prescribing physician must confirm that the patient has not received a prior allogeneic hematopoietic stem cell transplantation in the past 6 months.
   Prior allogeneic hematopoietic stem cell transplant within the past 6 months prevented participation, as well as evidence of residual donor cells in those who had underdone allogeneic hematopoietic stem cell transplantation.

5. **Prior Receipt of Gene Therapy.** Lenmeldy has not been studied in a patient who has received prior gene therapy.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	05/15/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Neurology – Gene Therapy – Skysona Utilization Management Medical Policy
- Skysona® (elivaldogene autotemcel intravenous infusion – Bluebird Bio)

REVIEW DATE: 11/15/2023

OVERVIEW

Skysona, an autologous hematopoietic stem cell-based gene therapy, is indicated to slow the progression of neurologic dysfunction in boys 4 to 17 years of age with early, active **cerebral adrenoleukodystrophy**.[1] Early, active cerebral adrenoleukodystrophy refers to asymptomatic or mildly symptomatic (neurologic function score [NFS] ≤ 1) boys who have gadolinium enhancement on brain magnetic resonance imaging (MRI) and Loes scores of 0.5 to 9 points.[1] This indication was approved under accelerated approval based on 24-month Major Functional Disability (MFD)-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Skysona is given as a single dose by intravenous infusion; the minimum recommended dose is 5.0×10^6 $CD34^+$ cells/kg.

Disease Overview

Cerebral adrenoleukodystrophy is a rare, neurodegenerative X-linked genetic disease in young boys that mainly affects the nervous system and adrenal glands.[2-4] The estimated incidence of adrenoleukodystrophy is 1:20,000 to 1:30,000 males. It is caused by a defect in the adenosine triphosphate-binding cassette, subfamily D, member 1 (*ABCD1*) gene. Very long chain fatty acids accumulate, which causes inflammation in and damage to the brain; other tissue types are also impacted. Around 40% of patients with adrenoleukodystrophy will develop cerebral adrenoleukodystrophy which is associated with rapid, progressive cerebral demyelination which usually occurs when patients are 3 to 12 years of age. Early stages of cerebral adrenoleukodystrophy are clinically asymptomatic and are only detected by performing an MRI of the brain. Irreversible, devastating neurologic decline can result which include MFDs such as loss of communication, cortical blindness, dependence on tube feeding, total incontinence, use of a wheelchair for ambulation, or complete loss of voluntary movement. As the disease progresses, patients often develop profound disability. If an allogeneic hematopoietic stem cell transplantation (HSCT) is not performed, almost one-half of impacted patients will likely die within 5 years of symptom onset.

Clinical Efficacy

The efficacy of Skysona was assessed in two 24-month, open-label, single arm, single-dose, multicenter, multinational pivotal trials involving male patients ≤ 17 years of age with early, active cerebral adrenoleukodystrophy as defined by its FDA-approved indication.[1,5,6] STARBEAM (ALD-102) [published data in 17 patients] {n = 32} was a Phase II/III investigation which is completed and involved patients who did not have a matched sibling donor for allogeneic HSCT. Study 2 (ALD-104) [unpublished] {n = 35} is an ongoing study and patients with a matched sibling donor for allogeneic HSCT could participate. Skysona was compared with a natural history population, as well as patients who underwent allogeneic HSCT. Patients in both studies could enroll in a long-term follow-up study (LTF-304). It should be noted that patients involved in these two studies had elevated very long chain fatty acid levels and confirmed mutations in the *ABCD1* gene. In the published STARBEAM study, at time of the interim analysis (April 2017), a total of 17 boys had received Skysona with a median follow-up of 29.4 months (range 21.6 to 42.0 months). In total, 88% of patients (n = 15/17) who received Skysona were alive and free of an MFD; all maintained an NFS score of 0 to 1.[5] In the symptomatic Skysona subpopulation (n = 11), slower progression to MFD or death (MFD-free survival) from time of symptom onset (first NFS ≥ 1) was observed compared with a similar natural history population (n = 7).[1] Data involving the entire efficacy population (n = 61) analyzed

overall survival compared to early, active allogeneic HSCT subpopulations by various donor type (human leukocyte antigen [HLA]-matched allogeneic HSCT subpopulation [n = 34] and HLA-mismatched allogeneic HSCT subpopulation [n = 17]). A reduced overall survival was noted in the first 9 months after treatment among the subpopulation who received allogeneic HSCT from an HLA-mismatched donor compared with Skysona, as well as the group who received an allogeneic HSCT from an HLA-matched donor (results presented graphically). The earlier mortality in the HLA-mismatched allogeneic HSCT subpopulation was mainly due to allogeneic HSCT-related toxicities.

Guidelines

Skysona has not been addressed in guidelines post FDA-approval. In September 2022, international recommendations for the diagnosis and management of patients with adrenoleukodystrophy (a consensus-based approach) were published.[7] It was noted that allogeneic HSCT is the standard treatment for cerebral adrenoleukodystrophy and can halt progression. Genetically transduced autologous stem cell transplantation (gene therapy [Skysona]) should be considered (if available) in boys if allogeneic donor options are poor. Outcome is poor in patients with advance disease (Loes score > 9 and/or NFS > 1). Regarding gene therapy (Skysona), it states that this therapy is not available for routine care; long-term safety data are not yet available. Treatment for boys or men with advanced disease or progressive lesions without gadolinium enhancement should only be considered after careful assessment in experienced centers.

POLICY STATEMENT

Prior Authorization is recommended for benefit coverage of Skysona. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Skysona as well as the specialized training required for administration of Skysona, approval requires Skysona to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for one dose per lifetime. The approval duration is 6 months to allow for an adequate time frame to prepare and administered one dose of therapy. For certain criteria, verification is required as noted by **[verification in claims history required]**. In the criteria for Skysona, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with eviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

Documentation: Documentation is required for use of Skysona as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Skysona is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Cerebral Adrenoleukodystrophy.** Approve a one-time (lifetime) dose if the patient meets the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R, S, T, and U).
   - **A)** Patient is a male*; AND
   - **B)** Patient is ≥ 4 and < 18 years of age; AND
   - **C)** Patient has early, active cerebral adrenoleukodystrophy as demonstrated by meeting the following (i, ii, and iii):
     - **i.** Patient has a neurologic function score ≤ 1 **[documentation required]**; AND
     - **ii.** Patient has gadolinium enhancement on brain magnetic resonance imaging (MRI) **[documentation required]**; AND
     - **iii.** Patient has a Loes score between 0.5 and 9 **[documentation required]**; AND
   - **D)** Patient has a confirmed mutation in the adenosine triphosphate binding cassette, sub family D member 1 (*ABCD1*) gene **[documentation required]**; AND
   - **E)** Patient has elevated very long chain fatty acid levels according to the standard reference values of the laboratory **[documentation required]**; AND
   - **F)** Patient does not have a Human Leukocyte Antigen (HLA)-matched family donor **[documentation required]**; AND
   - **G)** According to the prescribing physician, the patient is able to undergo monitoring by magnetic resonance imaging; AND
   - **H)** Patient does not currently have an active bacterial, viral, fungal, or parasitic infection; AND
   - **I)** Patient does not have any of the following (i and ii):
     - **i.** Prior or current hematologic malignancy or myeloproliferative disorder; AND
     - **ii.** Familial cancer syndrome or a history of such in his immediate family; AND
   - **J)** According to the prescribing physician, hematopoietic stem cell transplantation is appropriate for the patient; AND
   - **K)** Patient has adequate hepatic function defined by meeting the following (i, ii, and iii):
     - **i.** Aspartate aminotransferase values are normal or ≤ 2.5 times the upper limit of normal **[documentation required]**; AND
     - **ii.** Alanine aminotransferase values are normal or ≤ 2.5 times the upper limit of normal **[documentation required]**; AND
     - **iii.** Total bilirubin values are normal or ≤ 3.0 mg/dL **[documentation required]**; AND
   - **L)** Patient has adequate renal function as defined by meeting the following (i or ii):
     - **i.** Estimated creatinine clearance is ≥ 50 mL/min **[documentation required]**; OR
     - **ii.** Estimated glomerular filtration rate is ≥ 70 mL/minute/1.73 m^2 **[documentation required]**; AND
   - **M)** According to the prescribing physician, patient does not have evidence of cardiac compromise; AND
   - **N)** Prior to collection of cells for manufacturing, patient screening is negative for the following (i, ii, iii, and iv):
     - **i.** Hepatitis B virus **[documentation required]**; AND
     - **ii.** Hepatitis C virus **[documentation required]**; AND
     - **iii.** Human T-lymphotropic virus 1 and 2 **[documentation required]**; AND
     - **iv.** Human immunodeficiency virus 1 and 2 **[documentation required]**; AND
   - **O)** Prior to therapy, patient does not have evidence of hematological compromise as defined by meeting the following (i, ii, iii, and iv):
     - **i.** Peripheral blood absolute neutrophil count ≥ 1,500 cells/mm^3 **[documentation required]**; AND
     - **ii.** Platelet count ≥ 100,000 cells/mm^3 **[documentation required]**; AND

iii. Hemoglobin ≥ 10 g/dL **[documentation required]**; AND
iv. Patient does not have an uncorrected bleeding disorder; AND

P) Patient meets the following (i, ii, iii, and iv):
i. Patient will undergo mobilization, apheresis, myeloablative conditioning, and lymphodepletion; AND
ii. A granulocyte-colony stimulating factor product will be used for mobilization; AND
iii. Busulfan will be used for myeloablative conditioning; AND
iv. Cyclophosphamide or fludarabine will be used for lymphodepletion; AND

Q) Patient has received or is planning to receive prophylaxis for hepatic veno-occlusive disease/hepatic sinusoidal obstruction syndrome before conditioning; AND
Note: Examples of medications used include ursodeoxycholic acid or Defitelio (defibrotide intravenous infusion).

R) The prescribing physician confirms that the patient or his partner of childbearing potential will be using an effective method of contraception from the start of mobilization through at least 6 months after administration of Skysona; AND

S) Patient has not received Skysona in the past **[verification in claims history required]**; AND
Note: Verify through claims history that the patient has not previously received Skysona AND, if no claim for Skysona is present, the prescribing physician confirms that the patient has not previously received Skysona.

T) Medication is prescribed by a hematologist, a neurologist, and/or a stem cell transplant specialist physician; AND

U) The single dose is given intravenously which contains a minimum of 5.0 x 10^6 CD34+ cells/kg of body weight in which body weight is based on patient weight prior to first apheresis.

* Refer to the Policy Statement.

Dosing. The single dose is given intravenously which contains a minimum of 5.0 x 10^6 CD34+ cells/kg of body weight in which body weight is based on patient weight prior to first apheresis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Skysona is not recommended in the following situations:

1. **Patient has a Full *ABCD1* Gene Deletion.** In one patient involved in the Skysona clinical trials who had a full *ABCD1* gene deletion, disease progression occurred. The patient experienced radiologic disease progression, along with declining peripheral blood vector copy number, suggesting a loss of product efficacy which may have been immune mediated. The patient eventually underwent allogeneic HSCT for treatment. A noted limitation of use is that an immune response to Skysona may limit the persistence of descendent cells of Skysona, causing rapid loss of efficacy of Skysona in patients with full deletions of the *ABCD1* transgene.

2. **Prior Hematopoietic Stem Cell Transplantation.**
Note: Prescribing physician must confirm that the patient has not received a prior hematopoietic stem cell transplantation.
Prior allogeneic hematopoietic stem cell transplant was an exclusion criterion in the pivotal studies.

3. **Prior Receipt of Gene Therapy**. This was an exclusion criterion in the pivotal studies.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	11/02/2022
Annual Revision	In the Policy Statement "attestation required by physician" was removed from selected criteria. It was added that for certain criteria, verification is required as noted by "verification in claims history required". In addition, the following changes were made: **Cerebral Adrenoleukodystrophy:** The phrase "as determined by the prescribing physician" was removed from the requirement regarding that the patient is without an active infection (bacterial, viral, fungal, or parasitic). The phrase "plans to" was changed to "will" to be more directive in the requirement that the patient undergoes mobilization, apheresis, myeloablative conditioning, and lymphodepletion. "Documentation required" was added regarding the laboratory parameters that the estimated creatinine clearance is ≥ 50 mL/minute or estimated glomerular filtration rate is ≥ 70 mL/minute/1.73 m^2. It was added that the patient has not received Skysona in the past, with "verification in claims history required". Regarding the specialist requirement, the word "physician" was added after "stem cell transplant specialist". Dosing was added in an additional section with the other standard requirements for alignment with similar policies; dosing requirements were always present with Skysona for this policy. **Conditions Not Recommended for Approval:** For the Exclusion regarding patients with a Prior Hematopoietic Stem Cell Transplantation, the "attestation required by physician" was removed. A Note was added that the prescribing physician must confirm that the patient has not received a prior hematopoietic stem cell transplantation.	11/15/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Neurology – Leqembi Utilization Management Medical Policy
- Leqembi® (lecanemab-irmb intravenous infusion – Eisai/Biogen)

REVIEW DATE: 01/24/2024

OVERVIEW
Leqembi, an amyloid beta-directed antibody, is indicated for the **treatment of Alzheimer's disease**.[1] Treatment with Leqembi should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials.

Disease Overview
An estimated 6.7 million Americans ≥ 65 years of age are living with Alzheimer's dementia in 2023, with 73% of these people ≥ 75 years of age.[2] The number and proportion of older adults who have mild cognitive impairment due to Alzheimer's disease is difficult to estimate; however, a rough approximation suggests that 5 to 7 million older Americans may have mild cognitive impairment due to Alzheimer's disease. People with mild cognitive impairment due to Alzheimer's disease have biomarker evidence of brain changes due to the disease in addition to subtle problems with memory and thinking. Biomarker evidence includes abnormal levels of amyloid beta as evidenced on positron emission tomography (PET) scans and in analysis of cerebrospinal fluid, and decreased metabolism of glucose as shown on PET scans. These cognitive problems may be noticeable to the individual family members and friends, but not to others, and they do not interfere with the person's ability to carry out everyday activities. The mild changes in cognitive abilities occur when the brain can no longer compensate for the damage and death of nerve cells due to Alzheimer's disease. Among those with mild cognitive impairment, about 15% develop dementia after 2 years. Approximately one-third of people with mild cognitive impairment develop Alzheimer's dementia within 5 years.

Clinical Efficacy
The current Leqembi efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits. In the absence of additional clinical trials, there is not enough information to support approval.

POLICY STATEMENT
Due to safety concerns and the lack of clinically significant efficacy data, **approval is not recommended** for Leqembi. The current Leqembi efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits; whereas, safety concerns have been demonstrated in clinical trials. In the absence of additional clinical trials, there is not enough information to support approval.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Leqembi is not recommended in the following situations:

1. **Alzheimer's Disease.** Due to the lack of clinically significant efficacy data, approval is not recommended for Leqembi.

   The efficacy of Leqembi for accelerated approval was evaluated in one Phase IIb randomized, double-blind, placebo-controlled, multicenter, pivotal study in patients with mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's disease dementia (n = 854).[3] In the Phase IIb study, the primary endpoint, change from baseline at 12 months on Alzheimer's Disease Composite Score (ADCOMS), reached a 64% probability of being better than placebo with 25% less decline at 12 months, missing the pre-specified 80% probability threshold. However, the secondary endpoint of least squares mean change from baseline in amyloid PET Standard Uptake Value ratio (SUVr) at 18 months was significantly reduced for all dosage regimens, including Leqembi 10 mg/kg once every 2 weeks ($P < 0.001$ for all doses).

   Additionally, one Phase III, randomized, double-blind, placebo-controlled, multicenter study (CLARITY AD) was conducted in patients with mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's disease dementia (n = 1,795).[4] CLARITY AD provided the basis for traditional FDA approval on July 6, 2023. In CLARITY AD, the adjusted mean change from baseline at Week 78 in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score demonstrated slowing of clinical progression for Leqembi vs. placebo (treatment difference -0.45; $P < 0.001$ [scores range from 0 to 18, with higher scores indicating greater disease severity]). However, this slowing of progression did not achieve clinical significance.[5]

   Leqembi can cause amyloid related imaging abnormalities-edema (ARIA-E) and amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis, which can be observed on magnetic resonance imaging (MRI).[1] A recent (within 1 year) MRI of the brain should be obtained prior to initiating treatment with Leqembi. The safety of Leqembi has not been evaluated in patients with prior cerebral hemorrhage > 1 cm in greatest diameter, more than four microhemorrhages, superficial siderosis, evidence of vasogenic edema, evidence of cerebral contusion, aneurysm, vascular malformation, infective lesions, multiple lacunar infarcts or stroke involving a major vascular territory, and severe small vessel or white matter disease. Enhanced clinical vigilance for asymptomatic amyloid related imaging abnormalities (ARIA) is recommended during the first seven doses of treatment with Leqembi, particularly during titration, because the majority of ARIA was observed during this time. MRIs of the brain should be obtained prior to the fifth infusion, seventh, and 14th infusion of Leqembi to evaluate for the presence of asymptomatic ARIA. There is no experience in patients who continued dosing through symptomatic ARIA-E or through asymptomatic, but radiographically severe, ARIA-E. There is limited experience in patients who continued dosing through asymptomatic but radiographically mild to moderate ARIA-E. There are limited data in dosing patients who experienced recurrent ARIA-E.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/25/2023
Update	7/19/2023: Leqembi received traditional approval by the FDA on July 6, 2023 based on results from the CLARITY AD trial. No criteria changes.	--
Annual Revision	No criteria changes.	01/24/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Neurology – Radicava Intravenous Utilization Management Medical Policy
- Radicava® (edaravone intravenous infusion – Mitsubishi Tanabe)

REVIEW DATE: 05/15/2024

OVERVIEW

Radicava intravenous (IV) is indicated for the treatment of **amyotrophic lateral sclerosis** (ALS).[1]

Radicava IV is an anti-oxidative, free radical scavenger which eliminates lipid peroxide and hydroxyl radicals; however, it is unknown exactly how Radicava IV exerts its therapeutic effect in ALS.[1-2]

Of note, Radicava ORS® (edaravone oral suspension) is indicated for the treatment of ALS.[14] Radicava ORS received FDA-approval under the 505(b)(2) approval pathway which relied upon evaluations of safety and efficacy for Radicava IV. Patients treated with Radicava IV may be switched to Radicava ORS using the same dosing frequency.

Clinical Efficacy

The efficacy of Radicava IV was evaluated in one Phase III, randomized, double-blind, placebo-controlled, Japanese trial (published) [n = 137].[2] This study enrolled patients who had a "definite" or "probable" diagnosis of ALS (based on El Escorial and revised Airlie House criteria; criteria provided in the Appendix) and were living independently at the time of screening. Patients also were required to have functionally retained most activities of daily living (defined as a score of two points or better on each individual item of the ALS Functional Rating Scale – Revised [ALSFRS-R]), have normal respiratory function (i.e., a percent-predicted forced vital capacity [FVC] value ≥ 80%), and have a disease duration of ≤ 2 years. Overall, 91% of patients were also receiving riluzole. The decline in the ALSFRS-R scores from baseline to Week 24 was statistically significantly less with Radicava IV compared with placebo.[1,2] In a separate study involving patients with longer disease duration, reduced respiratory function, and less certain ALS diagnosis, Radicava IV did not demonstrate benefit vs. placebo.[3]

Guidelines

The American Academy of Neurology practice parameter on the care of patients with ALS (last updated 2009; reaffirmed 2023) does not yet address Radicava IV.[4-5] The practice parameter states that riluzole is safe and effective for slowing disease progression to a modest degree and should be offered to patients with ALS. However, riluzole may result in fatigue in some patients and if the risk of fatigue outweighs the modest survival benefits, discontinuation of riluzole may be considered. Referral to a specialized multidisciplinary clinic should be considered for patients with ALS to optimize health care delivery, prolong survival, and enhance quality of life. Additionally, noninvasive mechanical ventilation may lengthen survival and can be considered to improve quality of life and slow FVC decline. The European Federation of Neurological Societies guidelines on the clinical management of ALS (2012) also recommend patients be offered treatment with riluzole as early as possible after diagnosis.[6] However, patients with progressive muscular atrophy, primary lateral sclerosis, or hereditary spastic paraplegia should not be treated with riluzole. The European Academy of Neurology guideline on the management of ALS in collaboration with the European Reference Network of Neuromuscular Diseases (2024) do not recommend the use of IV or oral Radicava outside the context of a clinical trial.[15] The interim recommendation states that the evidence will be reviewed and the recommendation will be updated, once the results from the ongoing phase III trial of oral Radicava in Europe are available.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Radicava IV. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Radicava IV as well as the monitoring required for adverse events and long-term efficacy, approval requires Radicava IV to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Radicava IV is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. Amyotrophic Lateral Sclerosis (ALS). Approve for 6 months if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, iv, v, and vi):
- **i.** According to the prescriber, the patient has a "definite" or "probable" diagnosis of amyotrophic lateral sclerosis (ALS) based on the application of the El Escorial or the revised Airlie House diagnostic criteria; AND
- **ii.** Patient has a score of two points or more on each item of the ALS Functional Rating Scale – Revised (ALSFRS-R) [i.e., has retained most or all activities of daily living]; AND
- **iii.** Patient has a percent-predicted forced vital capacity (FVC) ≥ 80% (i.e., has normal respiratory function); AND
- **iv.** Patient has been diagnosed with ALS for ≤ 2 years; AND
- **v.** Patient has received or is currently receiving riluzole tablets, Tiglutik (riluzole oral suspension), or Exservan (riluzole oral film); AND
- **vi.** The medication is prescribed by or in consultation with a neurologist, a neuromuscular disease specialist, or a physician specializing in the treatment of ALS.

B) Patient is Currently Receiving Radicava IV or Radicava ORS. Approve if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient does not require invasive ventilation; AND
- **ii.** According to the prescriber, the patient continues to benefit from therapy; AND
- **iii.** The medication is prescribed by or in consultation with a neurologist, a neuromuscular disease specialist, or a physician specializing in the treatment of ALS.

Dosing. Approve the following dosing regimens (A and B):

A) 60 mg intravenous infusion once daily; AND

B) Treatment Cycles:
- **i.** Initial Cycle: Administer for 14 days followed by a 14-day drug-free period.
- **ii.** Subsequent cycles: Administer for 10 days out of a 14-day period, followed by a 14-day drug-free period.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Radicava IV is not recommended in the following situations:

1. **Aneurysmal Subarachnoid Hemorrhage.** Radicava IV is not indicated for the treatment of aneurysmal subarachnoid hemorrhage (SAH).[1] One randomized controlled study (published) [n = 91] evaluated the efficacy of Radicava (formulation/dose not specified) in patients with aneurysmal SAH.[7] At 3 months post-SAH, the incidence of delayed ischemic neurologic deficits (DINDs) in patients treated with Radicava was 10% vs. 21% in patients in a control group; the between-group treatment difference was not significant. In patients who had DINDs, 66% of patients in the control group had a cerebral infarction caused by vasospasm compared with 0% of Radicava-treated patients (P = 0.028). Additional, well-designed clinical studies are needed to establish if Radicava has a role in therapy post-SAH.

2. **Myocardial Infarction.** Radicava IV is not indicated for the treatment of myocardial infraction; there are no US or North American studies of Radicava IV for this indication.[1] One randomized, placebo-controlled, open-label, Japanese study (published) [n = 101] evaluated the effect of Radicava IV on the long-term prognosis in patients experiencing an acute myocardial infarction.[8] Patients were randomized to receive either Radicava IV (foreign formulation) 30 mg or placebo immediately prior to reperfusion. In all patients, successful reperfusion was obtained within 6 hours post-symptom onset. Radicava IV significantly attenuated the infarct size and incidence of reperfusion arrhythmia compared with placebo (P = 0.035 and P = 0.031, respectively).

3. **Radiation-Induced Brain Injury.** Radicava IV is not indicated for the treatment of radiation-induced brain injury; there are no US or North American studies of Radicava IV for this indication.[1] One randomized, open-label, 3-month, Chinese study (published) [n = 137] evaluated the protective effect of Radicava IV on radiation-induced brain necrosis in patients with nasopharyngeal carcinoma.[9] Patients were randomized to receive Radicava IV (foreign formulation) 30 mg twice daily for 2 weeks (not FDA-approved dosing) + IV corticosteroid therapy or placebo + IV corticosteroid therapy. Following 3 months of therapy, radiologic improvement (reduction in edema of ≥ 25%) was observed in 55.6% of patients who received Radicava IV (n = 40/72) compared with 35.4% of patients treated with placebo (n = 23/65) [P = 0.025]. The area of T1-weighted contrast enhancement was reduced from baseline with both Radicava IV and placebo (-1.67 cm and -1.20 cm, respectively); however, the difference between the treatment arms was not statistically significant. Improvement in neurologic signs and symptoms evaluated by the Late Effects of Normal Tissues – Subjective, Objective, Management, Analytic (LENT/SOMA) scale was also observed in 61.1% of Radicava IV-treated patients vs. 38.5% of placebo-treated patients (P = 0.006). Further research is warranted to determine if Radicava IV has a place in therapy in the treatment of radiation-induced brain injury.

4. **Retinal Vein Occlusion.** Radicava IV is not indicated for the prevention of macular edema and improvement of visual acuity after arteriovenous sheathotomy in patients with branch retinal vein occlusion; there are no US or North American studies of Radicava IV for this indication.[1] A single, small, prospective, Japanese study [published] (n = 47) evaluated the efficacy of Radicava IV (foreign formulation) in patients with branch retinal vein occlusion undergoing vitrectomy.[10] Patients either received Radicava IV 30 mg at the time of the procedure or no additional therapy. Visual acuity was measured before and 12 months after the procedure. At 12 months following the operation, the logarithm of the minimum angle of resolution (logMAR) units improved from 0.22 to 0.56 logMAR units in patients who had received Radicava IV and from 0.20 to 0.27 logMAR units in patients who

did not receive active treatment (P = 0.016). Additional data are needed to support the use of Radicava IV for this indication.

5. **Sensorineural Hearing Loss.** Radicava IV is not indicated for the treatment of sensorineural hearing loss; there are no US-based studies of Radicava IV for this indication.[1] One small, Japanese study evaluated 14 patients with idiopathic sudden sensorineural hearing loss treated with Radicava IV (foreign formulation; dose not specified).[11] These patients were compared with a control group of 14 patients with similar prognostic factors who had been treated with hyperbaric oxygenation therapy. No significant differences were observed between the Radicava IV group and the control group.

6. **Stroke.** Radicava IV is not FDA-approved for the treatment of patients who have experienced stroke.[1] Radicava IV has been approved in other countries for this indication and there are some foreign data supporting its use.[12] There are no US-based studies of Radicava IV for stroke at this time. A systematic review assessed available efficacy data from three clinical trials (n = 496) of Radicava IV for acute ischemic stroke.[13] These trials compared Radicava IV 30 mg twice daily for 14 days + another treatment vs. the other treatment alone within 72 hours of stroke symptom onset. One trial did not find significantly reduced mortality with Radicava IV vs. the control group; the other two studies did not report this endpoint. Overall, there was a significantly higher proportion of patients who had neurologic improvement in the Radicava IV group vs. control.

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/19/2023
Annual Revision	No criteria changes.	05/15/2024

APPENDIX*

El Escorial criteria for the diagnosis of ALS were initially developed by the World Federation of Neurology (WFN) in 1990. In 1998, the WFN held a workshop for the Research Committee on Motor Neuron Diseases at the Airlie Conference Center in Virginia, which resulted in a revision of the guidelines in 2000. The pivotal study of Radicava IV references the El Escorial criteria updated by the WFN in 2000 (Airlie House). According to these guidelines, the diagnosis of ALS requires:

The presence of:

- Evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiological or neuropathologic examination; AND
- Evidence of upper motor neuron (UMN) degeneration by clinical examination; AND
- Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination.

Together with the absence of:

- Electrophysiological or pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration; AND
- Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.

Without pathological confirmation, the diagnosis of ALS may be categorized into levels of certainty using clinical assessment. The following terms are used to describe the categories of diagnostic certainty.

- **Clinically Definite ALS:** defined on clinical evidence alone by the presence of UMN, as well as LMN signs, in the bulbar region and at least two spinal regions or the presence of UMN and LMN signs in three spinal regions.
- **Clinically Probable ALS:** defined on clinical evidence alone by UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs.
- **Clinically Probable ALS – Laboratory-supported:** defined when clinical signs of UMN and LMN dysfunction are in only one region, or when UMN signs alone are present in one region, and LMN signs defined by EMG criteria are present in at least two regions, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.
- **Clinically Possible ALS:** defined when clinical signs of UMN and LMN dysfunction are found together in only one region or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs and the diagnosis of Clinically Probable ALS – Laboratory supported cannot be proven by evidence on clinical grounds in conjunction with electrodiagnostic, neurophysiologic, neuroimaging or clinical laboratory studies. Other diagnoses must have been excluded to accept a diagnosis of Clinically Possible ALS.

*** This appendix is for reference; it is NOT intended that patients meet the above criteria for approval of Radicava IV.**

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Neurology – Rystiggo Utilization Management Medical Policy
- Rystiggo® (rozanolixizumab-noli subcutaneous infusion – UCB)

REVIEW DATE: 07/05/2023; selected revision 10/18/2023, 02/28/2024

OVERVIEW

Rystiggo, a neonatal Fc receptor blocker, is indicated for the treatment of **generalized myasthenia gravis** in adults who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody-positive.[1]

Disease Overview

Myasthenia gravis is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs.[2] Myasthenia gravis is caused by the production of pathogenic immunoglobulin G (IgG) autoantibodies against neuromuscular junction components (AChR, MuSK, and low density lipoprotein receptor-related protein 4 [LRP4]).[3] Approximately 85% of patients with myasthenia gravis are anti-AChR antibody-positive and approximately 5% to 8% of patients are anti-MuSK antibody-positive.[4] The result of the antibodies at the junction is unsuccessful nerve transmission and deficiency or weakness of muscle contractions.[3] The hallmark of myasthenia gravis is muscle weakness that worsens after periods of activity and improves after periods of rest.[2] Certain muscles such as those that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are often involved in the disorder; however, the muscles that control breathing and neck and limb movements may also be affected.

Clinical Efficacy

The efficacy of Rystiggo was evaluated in an 18-week, multicenter, randomized, double-blind, placebo-controlled trial in adults with anti-AChR or anti-MuSK antibody-positive generalized myasthenia gravis (n = 200).[1,5] Two doses of Rystiggo were studied: 7 mg/kg and 10 mg/kg. Among other criteria, patients in the study had a Myasthenia Gravis Foundation of America classification of II to IVa and a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 3, with at least 3 points from non-ocular symptoms. MG-ADL assesses the impact of generalized myasthenia gravis on daily functions of eight signs or symptoms that are typically impacted by this disease. Each sign or symptom is assessed on a 4-point scale; a higher score indicates greater impairment. At baseline, over 83% of patients received acetylcholinesterase inhibitors, over 50% of patients received oral steroids, and approximately 50% received non-steroidal immunosuppressant therapies, at stable doses. The primary endpoint was the change from baseline to Day 43 in the MG-ADL total score. Statistically significantly greater improvement in the MD-ADL score was observed in both Rystiggo 7 mg/kg and Rystiggo 10 mg/kg groups vs. placebo: -3.4 points in the Rystiggo-treated group at either dose vs. -0.8 points in the placebo group ($P < 0.001$). Statistically significant improvements in the secondary efficacy endpoints were also observed in the Rystiggo groups vs. placebo.

Dosing Information

Rystiggo is administered as a subcutaneous (SC) infusion, at a rate of up to 20 mL/h; infusions are given once weekly by a healthcare professional.[1] For patients weighing < 50 kg, the recommended dose is 420 mg; for patients 50 kg to < 100 kg, the recommended dose is 560 mg; and for patients ≥ 100 kg, the recommended dose is 840 mg. Each treatment cycle is 6 injections (6 weeks). Administer subsequent treatment cycles based on clinical evaluation. The safety of initiating subsequent cycles sooner than 63 days from the start of the previous treatment cycle has not been established.

Guidelines

An international consensus guidance for the management of myasthenia gravis was published in 2016.[6] The guidelines recommend pyridostigmine for the initial treatment in most patients with myasthenia gravis. The ability to discontinue pyridostigmine can indicate that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or immunosuppressant therapy should be used in all patients with myasthenia gravis who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal immunosuppressant agents include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Plasma exchange and intravenous immunoglobulin can be used as short-term treatments in certain patients. A 2020 update to these guidelines provides new recommendations for methotrexate, rituximab, and Soliris® (eculizumab intravenous infusion).[7] All recommendations should be considered extensions or additions to recommendations made in the initial international consensus guidance (2016). Oral methotrexate may be considered as a steroid-sparing agent in patients with generalized myasthenia gravis who have not tolerated or responded to steroid-sparing agents. Rituximab should be considered as an early therapeutic option in patients with anti-MuSK antibody-positive myasthenia gravis who have an unsatisfactory response to initial immunotherapy. Soliris should be considered in the treatment of severe, refractory, anti-AChR antibody-positive generalized myasthenia gravis.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Rystiggo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rystiggo as well as the monitoring required for adverse events and long-term efficacy, approval requires Rystiggo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rystiggo is recommended in those who meet the following criteria:

FDA-Approved Indication

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i. Generalized Myasthenia Gravis. Approve if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets ONE of the following (a or b):

a) Patient has confirmed anti-acetylcholine receptor antibody-positive generalized myasthenia gravis; OR

b) Patient has confirmed anti-muscle-specific tyrosine kinase antibody-positive generalized myasthenia gravis; AND

iii. Patient meets BOTH of the following (a and b):

a) Myasthenia Gravis Foundation of America class of II to IV; AND

b) Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 3 for non-ocular symptoms; AND

iv. Patient meets ONE of the following (a or b):
- **a)** Patient received or is currently receiving pyridostigmine; OR
- **b)** Patient has had inadequate efficacy, a contraindication, or significant intolerance to pyridostigmine; AND

v. Patient has evidence of unresolved symptoms of generalized myasthenia gravis; AND
Note: Examples of unresolved symptoms include difficulty swallowing, difficulty breathing, or a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility).

vi. Treatment cycles are no more frequent than every 63 days from the start of the previous treatment cycle; AND

vii. The medication is being prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Rystiggo. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient is continuing to derive benefit from Rystiggo, according to the prescriber; AND
Note: Examples of derived benefit include reductions in exacerbations of myasthenia gravis; improvements in speech, swallowing, mobility, and respiratory function.

iii. Treatment cycles are no more frequent than every 63 days from the start of the previous treatment cycle; AND

iv. The medication is being prescribed by or in consultation with a neurologist.

Dosing. Approve if the patient meets BOTH of the following (A and B):

A) Patient meets ONE of the following (i, ii, or iii):

i. Patient < 50 kg: The dose is 420 mg administered by subcutaneous infusion once weekly for 6 weeks; OR

ii. Patient is 50 kg to < 100 kg: The dose is 560 mg administered by subcutaneous infusion once weekly for 6 weeks; OR

iii. Patient ≥ 100 kg: The dose is 840 mg administered by subcutaneous infusion once weekly for 6 weeks; AND

B) Treatment cycles are no more frequent than every 63 days from the start of the previous treatment cycle.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rystiggo is not recommended in the following situations:

1. **Concomitant Use with Another Neonatal Fc Receptor Blocker, a Complement Inhibitor, or a Rituximab Product.** There is no evidence to support concomitant use of Rystiggo with another neonatal Fc receptor blocker, a complement inhibitor, or a rituximab product.
   Note: Examples of neonatal Fc receptor blockers are Vyvgart (efgartigimod alfa-fcab intravenous infusion) and Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection).
   Note: Examples of complement inhibitors are Soliris (eculizumab intravenous infusion), Ultomiris (ravulizumab-cwvz intravenous infusion or subcutaneous injection), and Zilbrysq (zilucoplan subcutaneous injection).

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/05/2023
Selected Revision	**Conditions Not Recommended for Approval:** Added "Concomitant Use with Another Neonatal Fc Receptor Blocker, a Complement Inhibitor, or a Rituximab Product". Examples of Neonatal Fc Receptor Blockers and Complement Inhibitors are listed as Notes.	10/18/2023
Selected Revision	**Generalized Myasthenia Gravis:** "Treatment cycles are no more frequent than every 63 days from the start of the previous treatment cycle" was added to the Dosing section.	02/28/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Neurology – Vyvgart Hytrulo Utilization Management Medical Policy
- Vyvgart® Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection – Argenx/Halozyme)

REVIEW DATE: 07/05/2023; selected revision 10/18/2023, 02/28/2024

OVERVIEW

Vyvgart Hytrulo, a neonatal Fc receptor blocker, is indicated for the treatment of **generalized myasthenia gravis** in adults who are anti-acetylcholine receptor antibody positive.

Disease Overview

Myasthenia gravis is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs.[2] The hallmark of myasthenia gravis is muscle weakness that worsens after periods of activity and improves after periods of rest. Certain muscles such as those that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are often involved in the disorder; however, the muscles that control breathing and neck and limb movements may also be affected. Acquired myasthenia gravis results from the binding of autoantibodies to components of the neuromuscular junction, most commonly the acetylcholine receptor.[3]

Clinical Efficacy

Non-inferiority of Vyvgart Hytrulo to Vyvgart Intravenous was demonstrated in the ADAPT-SC study, where patients were randomized to either Vyvgart Hytrulo or Vyvgart Intravenous (n = 110).[4]

The efficacy of Vyvgart Intravenous was evaluated in a 26-week, multicenter, randomized, double-blind, placebo-controlled trial in adults with myasthenia gravis (n = 167).[5] Among other criteria, patients were on stable doses of myasthenia gravis therapy prior to screening (e.g., acetylcholinesterase inhibitors, steroids, or non-steroidal immunosuppressive therapies), either in combination or alone. In addition, patients had a Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV and a Myasthenia Gravis Activities of Daily Living (MG-ADL) total score of ≥ 5. MG-ADL assesses the impact of generalized myasthenia gravis on daily functions of eight signs or symptoms that are typically impacted by this disease. Each sign or symptom is assessed on a 4-point scale; a higher score indicates greater impairment. Patients were randomized to receive Vyvgart Intravenous or placebo. At baseline, most patients had stable doses of acetylcholinesterase inhibitors (> 80%), steroids (> 70%), and/or non-steroidal immunosuppressive therapies (about 60%). The primary efficacy endpoint was comparison of the percentage of MG-ADL responders during the first treatment cycle between treatment groups in the anti-acetylcholine receptor antibody-positive population. An MG-ADL responder was defined as a patient with a 2-point or greater reduction in the total MG-ADL score compared to the treatment cycle baseline for at least 4 consecutive weeks, with the first reduction occurring no later than 1 week after the last infusion of the cycle. Overall, 67.7% of patients who received Vyvgart Intravenous compared with 29.7% of patients who received placebo were considered MG-ADL responders (P < 0.0001).

Dosing Information

The recommended dose is one vial (1,008 mg efgartigimod alfa and 11,200 units hyaluronidase) administered as a subcutaneous injection over 30 to 90 seconds once weekly.[1] Each treatment cycle is four injections (4 weeks). Administer subsequent treatment cycles based on clinical evaluation. The safety of

initiating subsequent cycles sooner than 50 days from the start of the previous treatment cycle has not been established. Vyvgart Hytrulo should be administered by a healthcare professional.

Guidelines

An international consensus guidance for the management of myasthenia gravis was published in 2016.[3] The guidelines recommend pyridostigmine for the initial treatment in most patients with myasthenia gravis. The ability to discontinue pyridostigmine can indicate that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or immunosuppressant therapy should be used in all patients with myasthenia gravis who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal immunosuppressant agents include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Plasma exchange and intravenous immunoglobulin can be used as short-term treatments in certain patients. A 2020 update to these guidelines provides new recommendations for methotrexate, rituximab, and Soliris® (eculizumab intravenous infusion).[6] All recommendations should be considered extensions or additions to recommendations made in the initial international consensus guidance. Oral methotrexate may be considered as a steroid-sparing agent in patients with generalized myasthenia gravis who have not tolerated or responded to steroid-sparing agents. Rituximab should be considered as an early therapeutic option in patients with anti-muscle specific kinase antibody positive myasthenia gravis who have an unsatisfactory response to initial immunotherapy. Soliris should be considered in the treatment of severe, refractory, anti-acetylcholine receptor antibody positive generalized myasthenia gravis.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Vyvgart Hytrulo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vyvgart Hytrulo as well as the monitoring required for adverse events and long-term efficacy, approval requires Vyvgart Hytrulo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vyvgart Hytrulo is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. **Generalized Myasthenia Gravis.** Approve if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has confirmed anti-acetylcholine receptor antibody positive generalized myasthenia gravis; AND
     - **iii.** Patient meets BOTH of the following (a and b):
       - **a)** Myasthenia Gravis Foundation of America classification of II to IV; AND

b) Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 5; AND

iv. Patient meets ONE of the following (a or b):
- **a)** Patient received or is currently receiving pyridostigmine; OR
- **b)** Patient has had inadequate efficacy, a contraindication, or significant intolerance to pyridostigmine; AND

v. Patient has evidence of unresolved symptoms of generalized myasthenia gravis; AND
Note: Examples of unresolved symptoms include difficulty swallowing, difficulty breathing, or a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility); AND

vi. Treatment cycles are no more frequent than every 50 days from the start of the previous treatment cycle; AND

vii. The medication is being prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Vyvgart Hytrulo (or Vyvgart Intravenous [efgartigimod alfa-fcab intravenous infusion]). Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient is continuing to derive benefit from Vyvgart Hytrulo (or Vyvgart Intravenous), according to the prescriber; AND
  Note: Examples of derived benefit include reductions in exacerbations of myasthenia gravis; improvements in speech, swallowing, mobility, and respiratory function.
- **iii.** Treatment cycles are no more frequent than every 50 days from the start of the previous treatment cycle; AND
- **iv.** The medication is being prescribed by or in consultation with a neurologist.

Dosing. Approve the following dosing regimen (A and B):

A) One vial (1,008 mg efgartigimod alfa and 11,200 units hyaluronidase) administered as a subcutaneous injection once weekly for 4 weeks; AND.

B) Treatment cycles are no more frequent than every 50 days from the start of the previous treatment cycle.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vyvgart Hytrulo is not recommended in the following situations:

1. **Concomitant Use with Another Neonatal Fc Receptor Blocker, a Complement Inhibitor, or a Rituximab Product.** There is no evidence to support concomitant use of Vyvgart Hytrulo with another neonatal Fc receptor blocker, a complement inhibitor, or a rituximab product.
   Note: Examples of neonatal Fc receptor blockers are Rystiggo (rozanolixizumab-noli subcutaneous infusion) and Vyvgart (efgartigimod alfa-fcab intravenous infusion).
   Note: Examples of complement inhibitors are Soliris (eculizumab intravenous infusion), Ultomiris (ravulizumab-cwvz intravenous infusion or subcutaneous injection), and Zilbrysq (zilucoplan subcutaneous injection).

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Vyvgart® Hytrulo subcutaneous injection. Boston, MA and San Diego, CA: Argenx and Halozyme; June 2023.
2. National Institute of Neurological Disorders and Stroke (NINDS). Myasthenia Gravis Fact Sheet. National Institutes of Health (NIH) Publication No. 17-768. Publication last updated: March 2020. Available at: https://www.ninds.nih.gov/sites/default/files/migrate-documents/myasthenia_gravis_e_march_2020_508c.pdf Accessed on June 12, 2023.
3. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. *Neurology*. 2016;87:419–425.
4. Data on File. ADAPT-SC – Argenx. Received June 13, 2023.
5. Vyvgart® intravenous infusion [prescribing information]. Boston, MA: Argenx; May 2022.
6. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. *Neurology*. 2021;96(3):114-122.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/05/2023
Selected Revision	**Conditions Not Recommended for Approval:** Added "Concomitant Use with Another Neonatal Fc Receptor Blocker, a Complement Inhibitor, or a Rituximab Product". Examples of neonatal Fc receptor blockers and complement inhibitors were listed as Notes.	10/18/2023
Selected Revision	**Generalized Myasthenia Gravis:** "Treatment cycles are no more frequent than every 50 days from the start of the previous treatment cycle" was added to the Dosing section.	02/28/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Neurology – Vyvgart Intravenous Utilization Management Medical Policy
- Vyvgart® (efgartigimod alfa-fcab intravenous infusion – Argenx)

REVIEW DATE: 07/05/2023; selected revision 10/18/2023, 02/28/2024

OVERVIEW

Vyvgart Intravenous, a neonatal Fc receptor blocker, is indicated for the treatment of **generalized myasthenia gravis** in adults who are anti-acetylcholine receptor antibody positive.[1]

Disease Overview

Myasthenia gravis is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs.[2] The hallmark of myasthenia gravis is muscle weakness that worsens after periods of activity and improves after periods of rest. Certain muscles such as those that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are often involved in the disorder; however, the muscles that control breathing, and neck and limb movements may also be affected. Acquired myasthenia gravis results from the binding of autoantibodies to components of the neuromuscular junction, most commonly the acetylcholine receptor.[3]

Clinical Efficacy

The efficacy of Vyvgart Intravenous was evaluated in a 26-week, multicenter, randomized, double-blind, placebo-controlled trial in adults with myasthenia gravis (n = 167).[5] Among other criteria, patients were on stable doses of myasthenia gravis therapy prior to screening (e.g., acetylcholinesterase inhibitors, steroids, or non-steroidal immunosuppressive therapies), either in combination or alone. In addition, patients had a Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV and a Myasthenia Gravis Activities of Daily Living (MG-ADL) total score of ≥ 5. MG-ADL assesses the impact of generalized myasthenia gravis on daily functions of eight signs or symptoms that are typically impacted by this disease. Each sign or symptom is assessed on a 4-point scale; a higher score indicates greater impairment. Patients were randomized to receive Vyvgart Intravenous or placebo. At baseline, most patients had stable doses of acetylcholinesterase inhibitors (> 80%), steroids (> 70%), and/or non-steroidal immunosuppressive therapies (about 60%). The primary efficacy endpoint was comparison of the percentage of MG-ADL responders during the first treatment cycle between treatment groups in the anti-acetylcholine receptor antibody-positive population. An MG-ADL responder was defined as a patient with a 2-point or greater reduction in the total MG-ADL score compared to the treatment cycle baseline for at least 4 consecutive weeks, with the first reduction occurring no later than 1 week after the last infusion of the cycle. Overall, 67.7% of patients who received Vyvgart Intravenous compared with 29.7% of patients who received placebo were considered MG-ADL responders ($P < 0.0001$).

Non-inferiority of Vyvgart® Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection) to Vyvgart Intravenous was demonstrated in the ADAPT-SC study, where patients were randomized to either Vyvgart Hytrulo or Vyvgart Intravenous (n = 110).[4]

Dosing Information

For patients weighing < 120 kg, the recommended dose is 10 mg/kg administered as an intravenous infusion over one hour once weekly for 4 weeks.[1] For patients weighing ≥ 120 kg, the recommended dose is 1200 mg per infusion. Administer subsequent treatment cycles based on clinical evaluation. The safety of

initiating subsequent cycles sooner than 50 days from the start of the previous treatment cycle has not been established.

Guidelines

An international consensus guidance for the management of myasthenia gravis was published in 2016.[3] The guidelines recommend pyridostigmine for the initial treatment in most patients with myasthenia gravis. The ability to discontinue pyridostigmine can indicate that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or immunosuppressant therapy should be used in all patients with myasthenia gravis who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal immunosuppressant agents include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Plasma exchange and intravenous immunoglobulin can be used as short-term treatments in certain patients. A 2020 update to these guidelines provides new recommendations for methotrexate, rituximab, and Soliris® (eculizumab intravenous infusion).[5] All recommendations should be considered extensions or additions to recommendations made in the initial international consensus guidance. Oral methotrexate may be considered as a steroid-sparing agent in patients with generalized myasthenia gravis who have not tolerated or responded to steroid-sparing agents. Rituximab should be considered as an early therapeutic option in patients with anti-muscle specific tyrosine kinase antibody-positive myasthenia gravis who have an unsatisfactory response to initial immunotherapy. Soliris should be considered in the treatment of severe, refractory, anti-acetylcholine receptor antibody-positive generalized myasthenia gravis.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Vyvgart Intravenous. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vyvgart Intravenous as well as the monitoring required for adverse events and long-term efficacy, approval requires Vyvgart Intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vyvgart Intravenous is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. **Generalized Myasthenia Gravis.** Approve if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has confirmed anti-acetylcholine receptor antibody positive generalized myasthenia gravis; AND
     - **iii.** Patient meets BOTH of the following (a and b):
       - **a)** Myasthenia Gravis Foundation of America classification of II to IV; AND

b) Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 5; AND

iv. Patient meets ONE of the following (a or b):
- **a)** Patient received or is currently receiving pyridostigmine; OR
- **b)** Patient has had inadequate efficacy, a contraindication, or significant intolerance to pyridostigmine; AND

v. Patient has evidence of unresolved symptoms of generalized myasthenia gravis; AND
Note: Examples of unresolved symptoms include difficulty swallowing, difficulty breathing, or a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility); AND

vi. Treatment cycles are no more frequent than every 50 days from the start of the previous treatment cycle; AND

vii. The medication is being prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Vyvgart Intravenous (or Vyvgart Hytrulo [efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection]). Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient is continuing to derive benefit from Vyvgart Intravenous (or Vyvgart Hytrulo), according to the prescriber; AND
  Note: Examples of derived benefit include reductions in exacerbations of myasthenia gravis; improvements in speech, swallowing, mobility, and respiratory function.
- **iii.** Treatment cycles are no more frequent than every 50 days from the start of the previous treatment cycle; AND
- **iv.** The medication is being prescribed by or in consultation with a neurologist.

Dosing. Approve if the patient meets BOTH of the following dosing regimens (A and B):

A) Patient meets ONE of the following (i or ii):
- **i.** Patient < 120 kg: The dose is 10 mg/kg administered by intravenous infusion once weekly for 4 weeks; OR
- **ii.** Patient ≥ 120 kg: The dose is 1,200 mg administered by intravenous infusion once weekly for 4 weeks; AND.

B) Treatment cycles are no more frequent than every 50 days from the start of the previous treatment cycle.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vyvgart Intravenous is not recommended in the following situations:

1. **Concomitant Use with Another Neonatal Fc Receptor Blocker, a Complement Inhibitor, or a Rituximab Product.** There is no evidence to support concomitant use of Vyvgart Intravenous with another neonatal Fc receptor blocker, a complement inhibitor, or a rituximab product.
   Note: Examples of neonatal Fc receptor blockers are Rystiggo (rozanolixizumab-noli subcutaneous infusion) and Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection).
   Note: Examples of complement inhibitors are Soliris (eculizumab intravenous infusion), Ultomiris (ravulizumab-cwvz intravenou infusion or subcutaneous injection), and Zilbrysq (zilucoplan subcutaneous injection).

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Vyvgart® intravenous infusion [prescribing information]. Boston, MA: Argenx; May 2022.
2. National Institute of Neurological Disorders and Stroke (NINDS). Myasthenia Gravis Fact Sheet. National Institutes of Health (NIH) Publication No. 17-768. Publication last updated: March 2020. Available at: https://www.ninds.nih.gov/sites/default/files/migrate-documents/myasthenia_gravis_e_march_2020_508c.pdf. Accessed on June 12, 2023.
3. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. *Neurology*. 2016;87:419–425.
4. Vyvgart® Hytrulo subcutaneous injection. Boston, MA and San Diego, CA: Argenx and Halozyme; June 2023.
5. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. *Neurology*. 2021 Jan 19;96(3):114-122.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Generalized Myasthenia Gravis:** A requirement for treatment cycles to be no more frequent than every 50 days from the start of the previous cycle was added to criteria. The frequency for cycles was removed from the dosing section.	11/16/2022
Early Annual Revision	**Generalized Myasthenia Gravis,** Criteria for "Patient is Currently Receiving Vyvgart": Added Vyvgart Hytrulo to the criterion as the criteria will apply to a patient who is currently receiving Vyvgart or Vyvgart Hytrulo. Criterion "Patient is continuing to derive benefit from Vyvgart, according to the prescriber": Added Vyvgart Hytrulo. Criterion regarding evidence of unresolved symptoms of generalized myasthenia gravis: examples are moved to a Note. Policy renamed from Neurology – Vyvgart to Neurology – Vyvgart Intravenous.	07/05/2023
Selected Revision	**Conditions Not Recommended for Approval:** Added "Concomitant Use with Another Neonatal Fc Receptor Blocker, a Complement Inhibitor, or a Rituximab Product". Examples of Neonatal Fc Receptor Blockers and Complement Inhibitors are listed as Notes.	10/18/2023
Selected Revision	**Generalized Myasthenia Gravis:** "Treatment cycles are no more frequent than every 50 days from the start of the previous treatment cycle" was added to the Dosing section.	02/28/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – Durysta Utilization Management Medical Policy
- Durysta® (bimatoprost implant, for intracameral administration – Allergan)

REVIEW DATE: 02/21/2024

OVERVIEW
Durysta, a prostaglandin analog, is indicated for the reduction of intraocular pressure (IOP) in patients with **open-angle glaucoma** or **ocular hypertension**.[1]

Disease Overview
Glaucoma, a disease that damages the eye's optic nerve, is the leading cause of blindness in people > 60 years of age.[2] Reduction of IOP, regardless of the pretreatment IOP, reduces the risk of disease progression.[3] In addition, IOP reduction may prevent the onset of early glaucoma in patients with ocular hypertension.

Ophthalmic prostaglandins (e.g., bimatoprost, latanoprost), beta-blockers (e.g., levobunolol, timolol), alpha-agonist (brimonidine), carbonic anhydrase inhibitors (brizolamide, dorzolamide), rho kinase inhibitor (netarsudil), and fixed combination products are used to treat glaucoma.[3,4] The choice of product is influenced by potential cost, adverse event profile, dosing schedule, and the degree of pressure lowering needed.[3]

Dosing Considerations
Durysta, a biodegradable implant, is given as a single intracameral administration.[1] Durysta should not be re-administered to an eye that was previously treated with Durysta.

POLICY STATEMENT
Prior Authorization is recommended for medical benefit coverage of Durysta. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for one implant per treated eye (i.e., one implant per treated eye; maximum of two implants per patient). Note that a 1-month (30 days) approval duration is applied to allow for the one-time treatment of one or both eye(s). Because of the specialized skills required for evaluation and diagnosis of patients treated with Durysta as well as the monitoring required for adverse events and long-term efficacy, approval requires Durysta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Durysta is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Ocular Hypertension.** Approve for a one-time use in each treated eye (i.e., one implant per treated eye; a total of two implants per patient) if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient is not receiving re-treatment of eye(s) previously treated with Durysta; AND
   - **C)** Patient meets BOTH of the following (i and ii):
     - **i.** Patient has tried at least two ophthalmic prostaglandins (either as monotherapy or as concomitant therapy) for the treatment of open-angle glaucoma or ocular hypertension; AND
       Note: Examples of ophthalmic prostaglandins include bimatoprost 0.03% ophthalmic solution, latanoprost 0.005% ophthalmic solution, travoprost 0.004% ophthalmic solution; Lumigan (bimatoprost 0.01% ophthalmic solution), Vyzulta (latanoprostene bunod 0.024% ophthalmic solution), Xelpros (latanoprost 0.005% ophthalmic emulsion), tafluprost 0.0015% ophthalmic solution, Iyuzeh (latanoprost 0.005% ophthalmic solution), and Omlonti (omidenepag isopropyl 0.002% ophthalmic solution).
     - **ii.** Patient has tried at least two other ophthalmic products (either as monotherapy or as concomitant therapy) from two different pharmacological classes for the treatment of open-angle glaucoma or ocular hypertension; AND
       Note: Examples of pharmacological classes of ophthalmic products for the treatment of open-angle glaucoma or ocular hypertension include beta-blockers, alpha-agonist (brimonidine), carbonic anhydrase inhibitors, and rho kinase inhibitor (netarsudil).
   - **D)** For each of the ophthalmic medications that were tried, the patient meets ONE of the following (i or ii):
     - **i.** Patient has had inadequate efficacy to the previously tried ophthalmic products, according to the prescriber; OR
     - **ii.** Patient has experienced adverse event(s) severe enough to warrant discontinuation of the previously tried ophthalmic products, according to the prescriber; AND
   - **E)** The medication is administered by or under the supervision of an ophthalmologist.

   Dosing. Approve up to one Durysta implant per treated eye(s) [two implants per patient].

2. **Open-Angle Glaucoma.** Approve for a one-time use in each treated eye (i.e., one implant per treated eye; a total of two implants per patient) if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient is not receiving re-treatment of eye(s) previously treated with Durysta; AND
   - **C)** Patient meets BOTH of the following (i and ii):
     - **i.** Patient has tried at least two ophthalmic prostaglandins (either as monotherapy or as concomitant therapy) for the treatment of open-angle glaucoma or ocular hypertension; AND
       Note: Examples of ophthalmic prostaglandins include bimatoprost 0.03% ophthalmic solution, latanoprost 0.005% ophthalmic solution, travoprost 0.004% ophthalmic solution; Lumigan (bimatoprost 0.01% ophthalmic solution), Vyzulta (latanoprostene bunod 0.024% ophthalmic solution), Xelpros (latanoprost 0.005% ophthalmic emulsion), tafluprost 0.0015% ophthalmic solution, Iyuzeh (latanoprost 0.005% ophthalmic solution), and Omlonti (omidenepag isopropyl 0.002% ophthalmic solution).
     - **ii.** Patient has tried at least two other ophthalmic products (either as monotherapy or as concomitant therapy) from two different pharmacological classes for the treatment of open-angle glaucoma or ocular hypertension; AND

Note: Examples of pharmacological classes of ophthalmic products for the treatment of open-angle glaucoma or ocular hypertension include beta-blockers, alpha-agonist (brimonidine), carbonic anhydrase inhibitors, and rho kinase inhibitor (netarsudil).

D) For each of the ophthalmic medications that were tried, the patient meets ONE of the following criteria (i or ii):
- **i.** Patient has had inadequate efficacy to the previously tried ophthalmic products, according to the prescriber; OR
- **ii.** Patient has experienced adverse event(s) severe enough to warrant discontinuation of the previously tried ophthalmic products, according to the prescriber; AND

E) The medication is administered by or under the supervision of an ophthalmologist.

Dosing. Approve up to one Durysta implant per treated eye(s) [two implants per patient].

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Durysta is not recommended in the following situations:

1. **Re-Treatment of Previously-Treated Eye(s).** Durysta is approved for a one-time use in each treated eye. Repeat administration in previously treated eye(s) is not approvable.

2. **Concurrent use of Durysta with iDose TR (travoprost intracameral implant).** iDose TR is another intracameral implant and should not be used with Durysta.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Durysta® [prescribing information]. Madison, NJ: Allergan; November 2020.
2. Boyd K. Glaucoma. Available at: https://www.aao.org/eye-health/diseases/what-is-glaucoma. Last reviewed, December 6, 2022. Accessed on February 15, 2024.
3. Gedde SJ, Vinod K, Wright MW, et al. Primary open-angle glaucoma Preferred Practice Pattern® guidelines. The American Academy of Ophthalmology. 2020. Available at: at: https://www.aao.org/education/preferred-practice-pattern/primary-open-angle-glaucoma-ppp. Accessed on February 15, 2024.
4. Facts and Comparisons® Online. Wolters Kluwer Health, Inc.; 2024. Available at: https://fco.factsandcomparisons.com/lco/action/home. Accessed on February 15, 2024. Search terms: ophthalmic beta blockers, alpha agonists, prostaglandins, netarsudil.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Ocular Hypertension.** The Note for examples of ophthalmic prostaglandins was revised to include Iyuzeh (latanoprost 0.005% ophthalmic solution) and Omlonti (omidenepag isopropyl 0.002% ophthalmic solution). **Open-Angle Glaucoma.** The Note for examples of ophthalmic prostaglandins was revised to include Iyuzeh (latanoprost 0.005% ophthalmic solution) and Omlonti (omidenepag isopropyl 0.002% ophthalmic solution).	04/19/2023
Early Annual Revision	**Ocular Hypertension:** The specialty requirement was changed from "The medication is prescribed by or in consultation with an ophthalmologist" to "The medication is administered by or under the supervision of an ophthalmologist". **Open-Angle Glaucoma:** The specialty requirement was changed from "The medication is prescribed by or in consultation with an ophthalmologist" to "The medication is administered by or under the supervision of an ophthalmologist". **Conditions Not Recommended for Approval:** Added new condition that Durysta cannot be used concurrently with iDose TR (travoprost intracameral implant).	02/21/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – Gene Therapy – Luxturna Utilization Management Medical Policy
- Luxturna® (voretigene neparvovec-rzyl subretinal injection – Spark Therapeutics)

REVIEW DATE: 02/28/2024

OVERVIEW

Luxturna, an adeno-associated virus vector-based gene therapy, is indicated for the treatment of confirmed **biallelic human retinal pigment epithelial 65 kDa protein (RPE65) mutation-associated retinal dystrophy**.[1] Patients must have viable retinal cells as determined by the treating physician(s).

Luxturna is made up of a live, non-replicating adeno-associated virus serotype 2 which has been genetically modified to express the human RPE65 gene.[1] Luxturna is designed to deliver a normal copy of the gene encoding RPE65 to cells of the retina in patients with reduced or absent levels of biologically active RPE65. Treatment with Luxturna is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation, and Luxturna would potentially be diluted or lost during cell proliferation. The safety and effectiveness of Luxturna have not been established in geriatric patients. Clinical studies of Luxturna for this indication did not include patients ≥ 65 years of age.

Disease Overview

Inherited retinal dystrophies are a broad group of genetic retinal disorders that are associated with progressive visual dysfunction.[2] RPE65 mutation-associated retinal dystrophy is associated with numerous discrete gene mutations and affects 1,000 to 2,000 patients in the US. Mutations in the RPE65 gene lead to reduced or absent levels of RPE65 isomerohydrolase activity.[1] The absence of RPE65 leads to the accumulation of toxic precursors, damage to RPE-producing cells, and, over time, damage to photoreceptors, progressing to near total blindness in most patients.

Dosing Information

The recommended dose of Luxturna for each eye is 1.5×10^{11} vector genomes (vg) administered once per eye by subretinal injection.[1] After completing a vitrectomy (removal of the vitreous gel that fills the eye cavity) and under direct visualization, a small amount of Luxturna is injected slowly until an initial subretinal bleb is observed; the remaining volume is then injected slowly until the total 0.3 mL is delivered. Luxturna should be injected into each eye on separate days within a close interval, but no fewer than 6 days apart.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Luxturna. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Luxturna as well as the specialized training required for administration of Luxturna, approval requires Luxturna to be administered by a retinal specialist. All approvals are provided for one injection per eye. Note: A 1-month (30 days) approval duration is applied to allow for the one-time treatment of both eyes.

All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with eviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc

Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

Documentation: Documentation is required for use of Luxturna as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Luxturna is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Biallelic Human Retinal Pigment Epithelial 65 kDa Protein (RPE65) Mutation-Associated Retinal Dystrophy.** Approve for a one-time treatment course (i.e., a total of two injections, one injection in each eye) if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient has a genetically confirmed diagnosis of biallelic RPE65 mutation-associated retinal dystrophy **[documentation required]**; AND
   - **B)** Patient is ≥ 12 months of age and < 65 years of age **[documentation required]**; AND
   - **C)** Luxturna is administered by a retinal specialist **[documentation required]**; AND
   - **D)** Patient must have viable retinal cells as determined by the treating physician **[documentation required]**; AND
   - **E)** Patient is not receiving retreatment of eye(s) previously treated with Luxturna **[documentation required]**.

   Dosing. Approve the following dosing regimen (A and B):
   - **A)** One 1.5 x 10^{11} vector genomes (vg) injection administered by subretinal injection into each eye; AND
   - **B)** The doses for the first eye and the second eye are separated by at least 6 days (i.e., injection of the second eye occurs 6 or more days after injection of the first eye).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Luxturna is not recommended in the following situations:

1. **Retreatment of previously treated eye(s)**. Luxturna is for one-time use in each eye. Repeat dosing in previously treated eye(s) is not approvable.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Luxturna® subretinal injection [prescribing information]. Philadelphia, PA: Spark Therapeutics; May 2022.
2. FDA news release. FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss. Published on: December 19, 2017. Page last updated: March 16, 2018. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-novel-gene-therapy-treat-patients-rare-form-inherited-vision-loss. Accessed on February 22, 2024.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Policy Name Change:** The designation "Gene Therapy" was added to the policy title: Ophthalmology – Gene Therapy – Luxturna UM Medical Policy. No criteria changes.	02/22/2023
Annual Revision	No criteria changes.	02/28/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – iDose TR Utilization Management Medical Policy
- iDose® TR (travoprost implant, for intracameral administration – Glaukos)

REVIEW DATE: 02/14/2024

OVERVIEW
iDose TR, a prostaglandin analog, is indicated for the reduction of intraocular pressure (IOP) in **open-angle glaucoma** or **ocular hypertension**.[1]

Disease Overview
Glaucoma, a disease that damages the eye's optic nerve, is the leading cause of blindness in people > 60 years of age.[2] Reduction of IOP, regardless of the pretreatment IOP, reduces the risk of disease progression.[3] In addition, IOP reduction may prevent the onset of early glaucoma in patients with ocular hypertension.

Ophthalmic prostaglandins, beta-blockers, alpha-agonist (brimonidine), carbonic anhydrase inhibitors, rho kinase inhibitor (netarsudil), and fixed combination products are used to treat glaucoma.[3,4] The choice of product is influenced by potential cost, adverse event profile, dosing schedule, and the degree of pressure lowering needed.[3]

Dosing Considerations
iDose TR, an intracameral implant, is given as a single intracameral administration.[1] iDose TR should not be re-administered to an eye that was previously treated with iDose TR.

POLICY STATEMENT
Prior Authorization is recommended for medical benefit coverage of iDose TR. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for one implant per treated eye (i.e., one implant per treated eye; maximum of two implants per patient). Note that a 1-month (30 days) approval duration is applied to allow for the one-time treatment of one or both eye(s). Because of the specialized skills required for evaluation and diagnosis of patients treated with iDose TR as well as the monitoring required for adverse events and long-term efficacy, approval requires iDose TR to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of iDose TR is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Ocular Hypertension.** Approve for a one-time use in each treated eye (i.e., one implant per treated eye; a total of two implants per patient) if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient is not receiving re-treatment of eye(s) previously treated with iDose TR; AND
   - **C)** Patient meets BOTH of the following criteria (i and ii):
     - **i.** Patient has tried at least two ophthalmic prostaglandins (either as monotherapy or as concomitant therapy) for the treatment of open-angle glaucoma or ocular hypertension; AND
       Note: Examples of ophthalmic prostaglandins include bimatoprost 0.03% ophthalmic solution, latanoprost 0.005% ophthalmic solution, travoprost 0.004% ophthalmic solution; Lumigan (bimatoprost 0.01% ophthalmic solution), Vyzulta (latanoprostene bunod 0.024% ophthalmic solution), Xelpros (latanoprost 0.005% ophthalmic emulsion), tafluprost 0.0015% ophthalmic solution, Iyuzeh (latanoprost 0.005% ophthalmic solution), and Omlonti (omidenepag isopropyl 0.002% ophthalmic solution).
     - **ii.** Patient has tried at least two other ophthalmic products (either as monotherapy or as concomitant therapy) from two different pharmacological classes for the treatment of open-angle glaucoma or ocular hypertension; AND
       Note: Examples of pharmacological classes of ophthalmic products for the treatment of open-angle glaucoma or ocular hypertension include beta-blockers, alpha-agonist (brimonidine), carbonic anhydrase inhibitors, and rho kinase inhibitor (netarsudil).
   - **D)** For each of the ophthalmic medications that were tried, the patient meets ONE of the following criteria (i or ii):
     - **i.** Patient has had inadequate efficacy to the previously tried ophthalmic products, according to the prescriber; OR
     - **ii.** Patient has experienced adverse event(s) severe enough to warrant discontinuation of the previously tried ophthalmic products, according to the prescriber; AND
   - **E)** The medication is administered by or under the supervision of an ophthalmologist.

   Dosing. Approve up to one iDose TR implant per treated eye(s) [two implants per patient].

2. **Open-Angle Glaucoma.** Approve for a one-time use in each treated eye (i.e., one implant per treated eye; a total of two implants per patient) if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient is not receiving re-treatment of eye(s) previously treated with iDose TR; AND
   - **C)** Patient meets BOTH of the following criteria (i and ii):
     - **i.** Patient has tried at least two ophthalmic prostaglandins (either as monotherapy or as concomitant therapy) for the treatment of open-angle glaucoma or ocular hypertension; AND
       Note: Examples of ophthalmic prostaglandins include bimatoprost 0.03% ophthalmic solution, latanoprost 0.005% ophthalmic solution, travoprost 0.004% ophthalmic solution; Lumigan (bimatoprost 0.01% ophthalmic solution), Vyzulta (latanoprostene bunod 0.024% ophthalmic solution), Xelpros (latanoprost 0.005% ophthalmic emulsion), tafluprost 0.0015% ophthalmic solution, Iyuzeh (latanoprost 0.005% ophthalmic solution), and Omlonti (omidenepag isopropyl 0.002% ophthalmic solution).
     - **ii.** Patient has tried at least two other ophthalmic products (either as monotherapy or as concomitant therapy) from two different pharmacological classes for the treatment of open-angle glaucoma or ocular hypertension; AND

Note: Examples of pharmacological classes of ophthalmic products for the treatment of open-angle glaucoma or ocular hypertension include beta-blockers, alpha-agonist (brimonidine), carbonic anhydrase inhibitors, and rho kinase inhibitor (netarsudil).

D) For each of the ophthalmic medications that were tried, the patient meets ONE of the following criteria (i or ii):
- **i.** Patient has had inadequate efficacy to the previously tried ophthalmic products, according to the prescriber; OR
- **ii.** Patient has experienced adverse event(s) severe enough to warrant discontinuation of the previously tried ophthalmic products, according to the prescriber; AND

E) The medication is administered by or under the supervision of an ophthalmologist.

Dosing. Approve up to one iDose TR implant per treated eye(s) [two implants per patient].

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of iDose TR is not recommended in the following situations:

1. **Re-Treatment of Previously-Treated Eye(s).** iDose TR is approved for a one-time use in each treated eye. Repeat administration in previously treated eye(s) is not approvable.

2. **Concurrent use of iDose TR with Durysta (bimatoprost intracameral implant).** Durysta is another intracameral implant and should not be used with iDose TR.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. iDose® TR intracameral implant [prescribing information]. San Clemente, CA: Glaukos; December 2023
2. Boyd K. Glaucoma. Available at: https://www.aao.org/eye-health/diseases/what-is-glaucoma. Last reviewed, December 4, 2023. Accessed on February 14, 2024.
3. Gedde SJ, Vinod K, Wright MW, et al. Primary open-angle glaucoma Preferred Practice Pattern® guidelines. The American Academy of Ophthalmology. 2020. Available at: at: https://www.aao.org/education/preferred-practice-pattern/primary-open-angle-glaucoma-ppp. Accessed on February 14, 2024.
4. Facts and Comparisons® Online. Wolters Kluwer Health, Inc.; 2024. Available at: https://fco.factsandcomparisons.com/lco/action/home. Accessed on February 14, 2024. Search terms: ophthalmic beta blockers, alpha agonists, prostaglandins, netarsudil.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy		02/14/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – Izervay Utilization Management Medical Policy
- Izervay™ (avacincaptad pegol intravitreal injection – Iveric)

REVIEW DATE: 08/16/2023

OVERVIEW

Izervay, a complement C5 inhibitor, is indicated for the treatment of **geographic atrophy (GA) secondary to age-related macular degeneration (AMD)**.[1] The recommended dose for Izervay is 2 mg administered by intravitreal injection to each affected eye once a month (approximately every 28 ± 7 days) for up to 12 months.

Disease Overview

AMD, a chronic, multifactorial, progressive central retinal disease, is the leading cause of irreversible blindness in the elderly population.[2-4] GA is a chronic progressive degeneration of the macula and is an advanced stage of AMD.[4,5] Approximately 20% of individuals with AMD will develop GA. GA is characterized by localized atrophy of the outer retinal tissue and irreversible loss of photoreceptors, retinal pigment epithelium, and choriocapillaris.[4-6] Initially, the GA lesions appear in the perifoveal macula but over time, the lesions often expand and coalesce to include the fovea. As the atrophic area expands, visual function and/or acuity decreases. In the clinical studies, patients had GA secondary to AMD with a best-corrected visual acuity (BCVA) between 20/25 and 20/320.[7,8]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Izervay. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Izervay as well as the monitoring required for adverse events and long-term efficacy, approval requires Izervay to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Izervay is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Geographic Atrophy.** Approve for 1 year if the patient meets the following (A, B, and C):
   - **A)** Patient has geographic atrophy secondary to age-related macular degeneration; AND
   - **B)** Patient has a best corrected visual acuity (BCVA) in the affected eye of between 20/25 and 20/320 letters; AND
   - **C)** The medication is administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both criteria (A and B):

A) The dose is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection for each eye being treated; AND

B) The dosing interval is not more frequent than once every 21 days for each eye being treated.
Note: The dosing interval is once monthly (approximately every 28 ± 7 days).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Izervay is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Izervay™ intravitreal injection [prescribing information]. Parsippany, NJ: Iveric; August 2023.
2. Kawa M, Machalinska A, Roginska D, Machalinski R. Complement system in pathogenesis of AMD: dual player in degeneration and protection of retinal tissue. *J Immunol Res.* 2014;483960.
3. Rein DB, Wittenborn JS, Burke-Conte Z, et al. Prevalence of age-related macular degeneration in the US in 2019. *JAMA Ophthalmol*. 2022;140:1202-1208.
4. Nabbioso M, Lambiase A, Cerini A, et al. Therapeutic approaches with intravitreal injections in geographic atrophy secondary to age-related macular degeneration: current drugs and potential molecules. *Int J Molec Sciences*. 2019;20(7):169.
5. Shae YS, Krogh Nielsen M, Do DV, et al. Geographic atrophy. Available at: https://eyewiki.aao.org/Geographic_Atrophy#:~:text=Geographic%20atrophy%20(GA)%20is%20a,retinal%20pigment%20epithelium%20and%20choriocapillaris. Accessed on August 7, 2023.
6. Fleckenstein M, Mitchel P, Freud KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125:369-390.
7. Jaffe GJ, Westby K, Csaky KG, et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: a randomized pivotal Phase 2/3 trial. *Ophthalmology*. 2021;128:576-586.
8. Data on file. Izervay – GATHER2 study. Iveric; received on August 7, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/16/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – Syfovre Utilization Management Medical Policy
- Syfovre™ (pegcetacoplan intravitreal injection – Apellis)

REVIEW DATE: 03/13/2024

OVERVIEW

Syfovre, a complement 3 inhibitor, is indicated for the treatment of **geographic atrophy (GA) secondary to age-related macular degeneration (AMD)**.[1] The recommended dose for Syfovre is 15 mg (0.1 mL of 150 mg/mL solution) administered by intravitreal injection to each affected eye once every 25 to 60 days.

In the pivotal studies (OAKS and DERBY), all eligible patients had a best corrected visual acuity (BCVA) of 24 letters or better on Early Treatment Diabetic Retinopathy Study (ETDRS) charts (Snellen chart equivalent of 20/320 or better).[2]

Disease Overview

AMD, a chronic, multifactorial, progressive central retinal disease, is the leading cause of irreversible blindness in the elderly population.[3,4] There are two types of AMD: exudative or neovascular ("wet") and nonexudative or ("dry"). GA, a chronic progressive degeneration of the macula, is an advanced stage of dry AMD.[4,5] GA is characterized by localized atrophy of the outer retinal tissue and irreversible loss of photoreceptors, retinal pigment epithelium, and choriocapillaris.[4-6] Initially, the GA lesions appear in the perifoveal macula but over time, the lesions often expand and coalesce to include the fovea.[6,7] Area of the lesions is associated with a corresponding loss of visual function.[7]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Syfovre. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Syfovre as well as the monitoring required for adverse events and long-term efficacy, approval requires Syfovre to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Syfovre is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Geographic Atrophy.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient has geographic atrophy secondary to age-related macular degeneration; AND
   - **B)** Patient meets ONE of the following (i or ii):

i. Patient has a best corrected visual acuity (BCVA) of 24 letters or better using Early Treatment Diabetic Retinopathy Study (ETDRS) charts; OR
ii. Patient has a best corrected visual acuity (BCVA) of 20/320 or better using the Snellen chart; AND

C) The medication is administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets BOTH criteria (A and B):
A) The dose is 15 mg (0.1 mL of 150 mg/mL solution) administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Syfovre is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Syfovre™ intravitreal injection [prescribing information]. Waltham, MA: Apellis; November 2023.
2. Heier JS, Lad EM, Holz FG, et al. Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): two multicentre, randomised, double-masked, sham-controlled, phase 3 trials. *Lancet*. 2023 Oct 21;402(10411):1434-1448.
3. Rein DB, Wittenborn JS, Burke-Conte Z, et al. Prevalence of age-related macular degeneration in the US in 2019. *JAMA Ophthalmol*. 2022;140:1202-1208.
4. Nabbioso M, Lambiase A, Cerini A, et al. Therapeutic approaches with intravitreal injections in geographic atrophy secondary to age-related macular degeneration: current drugs and potential molecules. *Int J Molec Sciences*. 2019;20(7):1693.
5. Shae YS, Krogh Nielsen M, Do DV, et al. Geographic atrophy. Available at: https://eyewiki.aao.org/Geographic_Atrophy#:~:text=Geographic%20atrophy%20(GA)%20is%20a,retinal%20pigment%20epithelium%20and%20choriocapillaris. Accessed on March 4, 2024.
6. Fleckenstein M, Mitchel P, Freud KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125:369-390.
7. Pfau M, Schmitz-Valckenberg S, Ribeiro R, et al. Association of complement C3 inhibitor pegcetacoplan with reduced photoreceptor degeneration beyond areas of geographic atrophy. *Sci Rep*. 2022;12:17870.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/01/2023
Annual Revision	**Geographic Atrophy**. Previously, the criterion regarding best-corrected visual acuity (BCVA) used the threshold "24 letters or better using Early Treatment Diabetic Retinopathy Study (ETDRS) charts" and the Snellen equivalent to BCVA of 24 letters or better using ETDRS charts (20/320) was listed in a Note. The criterion was revised such that the required BCVA can be the patient has "24 letters or better using Early Treatment Diabetic Retinopathy Study (ETDRS) charts OR 20/320 or better using the Snellen chart". The Note regarding the Snellen equivalent of ETDRS was removed.	03/13/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – Tepezza Utilization Management Medical Policy
- Tepezza™ (teprotumumab intravenous infusion – Horizon)

REVIEW DATE: 02/07/2024

OVERVIEW

Tepezza, an insulin-like growth factor-1 receptor (IGF-1R) antagonist, is indicated for the treatment of **thyroid eye disease**, regardless of thyroid eye disease activity or duration.[1]

Dosing Information

The recommended dose is 10 mg/kg administered by intravenous (IV) infusion for the initial dose, followed by 20 mg/kg administered IV once every 3 weeks for seven additional doses.[1]

Disease Overview

Thyroid eye disease, a rare, serious, debilitating and painful autoimmune disease, is also known as thyroid-associated ophthalmopathy, Graves' ophthalmopathy, or Graves' orbitopathy.[2] Thyroid eye disease is most commonly related to Graves' disease; however, it can also develop in patients with other thyroid diseases (e.g., Hashimoto's thyroiditis). The prevalence is higher in females than males (16 per 100,000 vs. 3 per 100,000, respectively).[3] Risk factors include female gender, middle age, and smoking.[2]

Most patients with thyroid eye disease develop eye disease while being treated for hyperthyroidism under the care of an endocrinologist.[4] Thyroid eye disease is characterized by endomysial interstitial edema, expansion, and proliferation of cells within the fibrofatty compartment, resulting in clinical manifestations of periorbital edema, lid retraction, proptosis, diplopia, corneal breakdown and in rare cases, optic nerve compression. This disease is associated with major comorbidities that can lead to blindness.

Consensus Statement

The American Thyroid Association and the European Thyroid Association issued a consensus statement in 2022 for the management of thyroid eye disease.[4] The Task Force notes "active" thyroid eye disease as disease with a clinical activity score (CAS) of ≥ 3 or if the patient has history or documentation of progression of thyroid eye disease based on subjective or objective worsening of vision, soft tissue inflammation, motility, or proptosis. CAS assesses seven items (spontaneous retrobulbar pain, pain on attempted up or lateral gaze, redness of the eyelids, redness of the conjunctiva, swelling of the eyelids, inflammation of the caruncle and/or plica, and conjunctival edema); each item is given one point if present. The severity of disease is divided into three groups: mild (features of disease have a minor impact on daily life insufficient to justify treatment), moderate (patient does not have sight-threatening disease but disease has sufficient impact on daily life to justify the risks of medical or surgical intervention), or sight-threatening (patient with dysthyroid optic neuropathy and/or corneal breakdown and/or globe subluxation). Pharmacologic treatment includes oral or IV glucocorticoids; mycophenolate, rituximab, Tepezza, and Actemra (tocilizumab IV infusion). Tepezza is noted as a preferred treatment with the following goals: disease inactivation and diplopia; reduction of proptosis; and improvement of eye motility. It is an acceptable treatment for disease inactivation and reduction of soft tissue involvement.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Tepezza. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tepezza as well as the monitoring required for adverse events and long-term efficacy, approval requires Tepezza to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tepezza is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. Thyroid Eye Disease. Approve for 6 months if the patient meets the following (A, B, C, and D):
Note: Thyroid Eye Disease is also recognized as Graves' ophthalmopathy, Graves' orbitopathy, thyroid-associated ophthalmopathy, and thyroid orbitopathy.

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has been assessed as having least moderate severity level of disease based on signs and symptoms, according to the prescriber; AND
  Note: Examples of signs and symptoms of disease of at least moderate severity include the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, proptosis ≥ 3 mm above normal for race and sex, and diplopia (Gorman score 2 to 3).
- **C)** Patient has not received 8 doses (total) of Tepezza; AND
  Note: The maximum recommended treatment is for 8 doses. For a patient who has started therapy but has not completed 8 doses, approve the number of doses required for the patient to receive a total of 8 doses.
- **D)** The medication is prescribed by or in consultation with an ophthalmologist, endocrinologist, or a physician who specializes in thyroid eye disease.

Dosing. Approve up to 20 mg/kg per dose administered by intravenous infusion no more frequently than every 3 weeks for 8 doses.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tepezza is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Tepezza intravenous infusion [prescribing information]. Lake Forest, IL: Horizon; July 2023.
2. Horizon Therapeutics. Teprotumumab for injection. Briefing document for the Food and Drug Administration Dermatologic and Ophthalmic Drugs Advisory Committee. Meeting Date: December 13, 2019. Available at:

https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-public-participation-information-december-13-2019-meeting-dermatologic-and-ophthalmic-drugs#event-information. Accessed on January 18, 2024.
3. Bartley GB, Fatourechi V, Kadrmas EF, et al. Clinical features of Graves' ophthalmopathy in an incidence cohort. *Am J Ophthalmol.* 1996;121(3):284-290.
4. Burch HB, Perros P, Bednarczuk T, et al. Management of thyroid eye disease: a consensus statement by the American Thyroid Association and the European Thyroid Association. *Thyroid*. 2022;32(12):1439-1470. doi: 10.1089/thy.2022.0251. Epub 2022 Dec 8.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	01/18/2023
Update	05/24/2023: Tepezza prescribing information was revised in April 2023. FDA-approved indication was revised from "Treatment of thyroid eye disease" to "Treatment of thyroid eye disease, regardless of thyroid eye disease or duration". Criteria were not changed.	--
Annual Revision	**Thyroid Eye Disease**: The criterion that the patient has active disease of at least moderate severity based on signs and symptoms, according to the prescriber was changed to remove the word "active". The new criterion requires that the patient has at least moderate severity level of disease based on signs and symptoms, according to the prescriber. The Note was revised to read: Examples of signs and symptoms of disease of at least moderate severity include the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, proptosis ≥ 3 mm above normal for race and sex, and diplopia (Gorman score 2 to 3).	02/07/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Beovu Utilization Management Medical Policy
- Beovu® (brolucizumab intravitreal injection – Novartis)

REVIEW DATE: 11/15/2023

OVERVIEW

Beovu, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the following uses:[1]
- **Diabetic macular edema** (DME).
- **Neovascular (wet) age-related macular degeneration** (nAMD).

The recommended dosing for each indication is as follows[1]:
- **DME:** 6 mg administered by intravitreal injection every 6 weeks (approximately every 39 to 45 days) for the first five doses, followed by 6 mg administered by intravitreal injection once every 8 to 12 weeks.
- **nAMD:** 6 mg administered by intravitreal injection once a month (approximately every 25 to 31 days) for the first three doses, followed by 6 mg administered by intravitreal injection once every 8 to 12 weeks.

Other Uses with Supportive Evidence

Overproduction of VEGF may lead to other eye conditions, including neovascular glaucoma, retinopathy of prematurity, and other retinal and choroidal neovascular conditions affecting the eye.[2,3] The VEGF inhibitors have the potential to be used off-label to reduce or slow visual impairment or vision loss associated with other eye conditions related to increased VEGF production.[2,4,5] The use of anti-VEGF agents have been shown to stop the angiogenic process and maintain visual acuity and improve vision in patients with certain neovascular ophthalmic conditions; therefore, research is rapidly evolving on the use of VEGF inhibitors in other neovascular ophthalmic conditions which threaten vision.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Beovu. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Beovu as well as the monitoring required for adverse events and long-term efficacy, approval requires Beovu to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Beovu is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Diabetic Macular Edema.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

   Dosing. Approve if the requested dosing meets the following (A and B):
   A) The dose is 6 mg administered by intravitreal injection for each eye being treated; AND
   B) The dosing interval is not more frequent than once every 39 days for five doses, followed by not more frequently than once every 8 weeks for each eye being treated.

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2. **Neovascular (Wet) Age-Related Macular Degeneration.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

   Dosing. Approve if the requested dosing meets the following (A and B):
   A) The dose is 6 mg administered by intravitreal injection for each eye being treated; AND
   B) The dosing interval is not more frequent than once every 25 days for three doses, followed by not more frequently than once every 8 weeks for each eye being treated.

Other Uses with Supportive Evidence

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3. **Other Neovascular Diseases of the Eye.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.
   Note: Examples of other neovascular diseases of the eye include neovascular glaucoma, retinopathy of prematurity, sickle cell neovascularization, choroidal neovascular conditions.

   Dosing. Approve if the requested dosing meets the following (A and B):
   A) The dose is 6 mg administered by intravitreal injection for each eye being treated; AND
   B) The dosing interval is not more frequent than once every 25 days for three doses, followed by not more frequently than once every 8 weeks for each eye being treated.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Beovu is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Beovu® intravitreal injection [prescribing information]. Hanover, NJ: Novartis; September 2023.
2. Barakat MR, Kaiser PK. VEGF inhibitors for the treatment of neovascular age-related macular degeneration. *Expert Opin Investig Drugs*. 2009;18(5):637-646.
3. Tolentino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv Ophthalmol*. 2011;56(2):95-113.
4. Kinnunen K, Ylä-Herttuala S. Vascular endothelial growth factors in retinal and choroidal neovascular diseases. *Ann Med*. 2012;44(1):1-17.

5. Horsley MB, Kahook MY. Anti-VEGF therapy for glaucoma. *Curr Opin Ophthalmol*. 2010;21(2):112-117.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/16/2022
Annual Revision	No criteria changes.	11/15/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Eylea and Eylea HD Utilization Management Medical Policy
- Eylea® (aflibercept intravitreal injection – Regeneron)
- Eylea® HD (aflibercept intravitreal injection – Regeneron)

REVIEW DATE: 11/15/2023

OVERVIEW

Eylea, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the following uses:[1]
- **Diabetic macular edema**.
- **Diabetic retinopathy**.
- **Macular edema following retinal vein occlusion**.
- **Neovascular (wet) age-related macular degeneration**.
- **Retinopathy of Prematurity**.

Eylea HD, a high dose VEGF inhibitor, is indicated for the following uses:[6]
- **Diabetic macular edema**.
- **Diabetic retinopathy**.
- **Neovascular (wet) age-related macular degeneration**.

Dosing Information:

Eylea: For all of the indications, except retinopathy of prematurity, the recommended dose for Eylea is 2 mg administered by intravitreal injection.[1] The frequency of dosing depends on the indication and patient response. Some patients require every 4 week dosing (approximately every 25 days, monthly). The dose for retinopathy of prematurity is 0.4 mg administered by intravitreal injection; repeat injections may be given and the treatment interval between doses injected into the same eye should be at least 10 days.

Eylea HD: For all indications, the recommended dose for Eylea HD is 8mg administered by intravitreal injection.[6] For diabetic macular edema and neovascular (wet) age-related macular degeneration, the dosing regimen for Eylea HD is once every 4 weeks (approximately every 28 days +/- 7 day) for the first three doses, followed by one dose every 8 to 16 weeks, +/- 1 week. For diabetic retinopathy, the dosing is every 4 weeks (approximately every 28 days +/- 7 day) for the first three doses, followed by one dose every 8 to 12 weeks, +/- 1 week.

Other Uses with Supportive Evidence for Eylea

Overproduction of VEGF may lead to other eye conditions, including neovascular glaucoma and other retinal and choroidal neovascular conditions affecting the eye.[2,3] The VEGF inhibitors have the potential to be used off-label to reduce or slow visual impairment or vision loss associated with other eye conditions related to increased VEGF production.[2,4,5] The use of anti-VEGF agents have been shown to stop the angiogenic process and maintain visual acuity and improve vision in patients with certain neovascular ophthalmic conditions; therefore, research is rapidly evolving on the use of VEGF inhibitors in other neovascular ophthalmic conditions which threaten vision.[4,5]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Eylea and Eylea HD. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Eylea and Eylea HD as well as the monitoring required for adverse events and long-term efficacy, approval requires Eylea and Eylea HD to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Eylea is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. Diabetic Macular Edema. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 2 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

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2. Diabetic Retinopathy. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 2 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

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3. Macular Edema Following Retinal Vein Occlusion. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 2 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

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4. Neovascular (Wet) Age-Related Macular Degeneration. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 2 mg administered by intravitreal injection for each eye being treated; AND

B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

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5. Retinopathy of Prematurity. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 0.4 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 10 days for each eye being treated.

Other Uses with Supportive Evidence

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6. Other Neovascular Diseases of the Eye. Approve for 1 year if administered by or under the supervision of an ophthalmologist.
Note: Examples of other neovascular diseases of the eye include neovascular glaucoma, sickle cell neovascularization, and choroidal neovascular conditions.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 2 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

II. Coverage of Eylea HD is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. Diabetic Macular Edema. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 8 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 21 days for three doses, followed by not more frequent than once every 7 weeks for each eye being treated.
Note: The recommended dose is once every 4 weeks (approximately every 28 days +/- 7 day) for the first three doses, followed by one dose every 8 to 16 weeks, +/- 1 week.

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2. Diabetic Retinopathy. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 8 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 21 days for three doses, followed by not more frequent than once every 7 weeks for each eye being treated.
Note: The recommended dose is once every 4 weeks (approximately every 28 days +/- 7 day) for the first three doses, followed by one dose every 8 to 12 weeks, +/- 1 week.

3. Neovascular (Wet) Age-Related Macular Degeneration. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 8 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 21 days for three doses, followed by not more frequent than once every 7 weeks for each eye being treated.
Note: The recommended dose is once every 4 weeks (approximately every 28 days +/- 7 day) for the first three doses, followed by one dose every 8 to 16 weeks, +/- 1 week.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Eylea and Eylea HD is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Eylea® intravitreal injection [prescribing information]. Tarrytown, NY: Regeneron; August 2023.
2. Barakat MR, Kaiser PK. VEGF inhibitors for the treatment of neovascular age-related macular degeneration. *Expert Opin Investig Drugs*. 2009;18(5):637-646.
3. Tolentino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv Ophthalmol*. 2011;56(2):95-113.
4. Kinnunen K, Ylä-Herttuala S. Vascular endothelial growth factors in retinal and choroidal neovascular diseases. *Ann Med*. 2012;44(1):1-17.
5. Horsley MB, Kahook MY. Anti-VEGF therapy for glaucoma. *Curr Opin Ophthalmol*. 2010;21(2):112-117.
6. Eylea® HD intravitreal injection [prescribing information]. Tarrytown, NY: Regeneron; August 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/16/2022
Selected Revision	**Retinopathy of Prematurity:** This condition was moved to the FDA-Approved Indications; previously, it was included in the Note of examples of Other Neovascular Diseases of the Eye, under "Other Uses with Supportive Evidence". For this indication, the dosing was changed to be 0.4 mg administered per injection, with the dosing interval changed to be not more frequent than once every 10 days for each eye being treated (previously, it was the same as Other Neovascular Diseases of the Eye, which was 2 mg per treated eye, with a dosing interval of at least 25 days between doses).	02/22/2023
Selected Revision	**Eylea HD:** Eylea HD was added to the policy; conditions and criteria for approval were added to the policy.	08/30/2023
Annual Revision	No criteria changes.	11/15/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Ranibizumab Products Utilization Management Medical Policy
- Byooviz™ (ranibizumab-nuna intravitreal injection – Biogen)
- Cimerli™ (ranibizumab-eqrn intravitreal injection – Coherus)
- Lucentis® (ranibizumab intravitreal injection – Genentech)

REVIEW DATE: 11/15/2023

OVERVIEW

Lucentis and Cimerli (interchangeable biosimilar to Lucentis) are vascular endothelial growth factor (VEGF) inhibitors indicated for the following uses:[1,7]
- **Diabetic macular edema**.
- **Diabetic retinopathy**.
- **Macular edema following retinal vein occlusion**.
- **Myopic choroidal neovascularization**.
- **Neovascular (wet) age-related macular degeneration**.

Byooviz (interchangeable biosimilar to Lucentis) is indicated for the following uses:[6]
- **Macular edema following retinal vein occlusion**.
- **Myopic choroidal neovascularization**.
- **Neovascular (wet) age-related macular degeneration**.

The recommended dosing for each of the indication is as follows:[1,6,7]
- **Diabetic macular edema, diabetic retinopathy:** 0.3 mg administered by intravitreal injection once every month (approximately 28 days) [Cimerli and Lucentis]
- **Macular edema following retinal vein occlusion, neovascular (wet) age-related macular degeneration:** 0.5 mg administered by intravitreal injection once every month (approximately 28 days).
- **Myopic choroidal neovascularization:** 0.5 mg administered by intravitreal injection once every month (approximately 28 days) for up to 3 months; patients may be retreated if needed.

Other Uses with Supportive Evidence

Overproduction of VEGF may lead to other eye conditions, including neovascular glaucoma, retinopathy of prematurity, and other retinal and choroidal neovascular conditions affecting the eye.[2,3] The VEGF inhibitors have the potential to be used off-label to reduce or slow visual impairment or vision loss associated with other eye conditions related to increased VEGF production.[2,4,5] The use of anti-VEGF agents have been shown to stop the angiogenic process and maintain visual acuity and improve vision in patients with certain neovascular ophthalmic conditions; therefore, research is rapidly evolving on the use of VEGF inhibitors in other neovascular ophthalmic conditions which threaten vision.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of ranibizumab products. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with ranibizumab products as well as the monitoring required for adverse events and long-term efficacy, approval requires ranibizumab products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of ranibizumab products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. **Diabetic Macular Edema.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

   Dosing. Approve if the dose meets both criteria (A and B):
   A) The dose is 0.3 mg administered by intravitreal injection for each eye being treated; AND
   B) The dosing interval is not more frequent than once every 28 days for each eye being treated.

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2. **Diabetic Retinopathy.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

   Dosing. Approve if the dose meets both criteria (A and B):
   A) The dose is 0.3 mg administered by intravitreal injection for each eye being treated; AND
   B) The dosing interval is not more frequent than once every 28 days for each eye being treated.

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3. **Macular Edema Following Retinal Vein Occlusion.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

   Dosing. Approve if the dose meets both criteria (A and B):
   A) The dose is 0.5 mg administered by intravitreal injection for each eye being treated; AND
   B) The dosing interval is not more frequent than once every 28 days for each eye being treated.

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4. **Myopic Choroidal Neovascularization.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

   Dosing. Approve if the dose meets both criteria (A and B):
   A) The dose is 0.5 mg administered by intravitreal injection for each eye being treated; AND

B) The dosing interval is not more frequent than once every 28 days for each eye being treated.

5. Neovascular (Wet) Age-Related Macular Degeneration. Approve for 1 year if administered by or under the supervision of an ophthalmologist.
Dosing. Approve if the dose meets both criteria (A and B):
A) The dose is 0.5 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 28 days for each eye being treated.

Other Uses with Supportive Evidence

6. Other Neovascular Diseases of the Eye. Approve for 1 year if administered by or under the supervision of an ophthalmologist.
Note: Examples of other neovascular diseases of the eye include neovascular glaucoma, retinopathy of prematurity, sickle cell neovascularization, choroidal neovascular conditions.

Dosing. Approve if the dose meets both criteria (A and B):
A) The dose is 0.5 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 28 days for each eye being treated.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of ranibizumab products is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Lucentis® intravitreal injection [prescribing information]. South San Francisco, CA: Genentech; August 2023.
2. Barakat MR, Kaiser PK. VEGF inhibitors for the treatment of neovascular age-related macular degeneration. *Expert Opin Investig Drugs*. 2009;18(5):637-646.
3. Tolentino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv Ophthalmol*. 2011;56(2):95-113.
4. Kinnunen K, Ylä-Herttuala S. Vascular endothelial growth factors in retinal and choroidal neovascular diseases. *Ann Med*. 2012;44(1):1-17.
5. Horsley MB, Kahook MY. Anti-VEGF therapy for glaucoma. *Curr Opin Ophthalmol*. 2010;21(2):112-117.
6. Byooviz™ intravitreal injection [prescribing information]. Cambridge, MA: Biogen; October 2023.
7. Cimerli™ intravitreal injection [prescribing information]. Redwood City, CA: Coherus; August 2022.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/16/2022
Annual Revision	For all indications/uses, the dosing interval was changed from "not more frequent than once every 25 days for each eye being treated" to "not more frequent than once every 28 days for each eye being treated"; the 28 days aligns with the prescribing information.	11/15/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Susvimo Utilization Management Medical Policy
- Susvimo™ (ranibizumab intravitreal injection via ocular implant – Genentech)

REVIEW DATE: 11/15/2023

OVERVIEW

Susvimo, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of patients with **neovascular** (wet) **age-related macular degeneration** (nAMD) who have previously responded to at least two intravitreal injections of a VEGF inhibitor.[1] In contrast to the other VEGF inhibitor products which are administered as intravitreal injections, Susvimo is an intravitreal implant.

Safety

Susvimo has a Boxed Warning regarding endophthalmitis, which occurred at a 3-fold higher rate with Susvimo vs. Lucentis (1.7% vs. 0.5% in active-controlled trials).[1] Additional Warnings associated with the implant and/or implant-related procedures unique to Susvimo include rhegmatogenous retinal detachment, implant dislocation, vitreous hemorrhage, conjunctival erosion or retraction, conjunctival bleb, postoperative decrease in visual acuity, air bubbles causing improper filling of the implant, and deflection of the implant. These Warnings/Precautions are unique to Susvimo (among the injectable VEGF inhibitor class) and in general, many of these Warnings/Precautions are associated with the Susvimo implant and/or other implant-related procedures.

POLICY STATEMENT

Due to the safety concerns, **approval is not recommended** for Susvimo. There are significant risks associated with use based on the Boxed Warning regarding endophthalmitis.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Susvimo is not recommended in the following situations:

1. **Neovascular (Wet) Age-Related Macular Degeneration.** Due to the safety data, approval is not recommended for Susvimo. In the pivotal trial, Susvimo demonstrated non-inferiority compared with Lucentis.[1-3] However, ocular adverse events were more frequent with Susvimo vs. Lucentis; patients treated with Susvimo require regular monitoring to evaluate for presence of these adverse events. Notably, Susvimo labeling includes a unique Boxed Warning regarding endophthalmitis, which was three times more frequent with Susvimo vs. Lucentis.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Susvimo™ intravitreal injection via ocular implant [prescribing information]. South San Francisco, CA: Genentech; April 2022.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/16/2022
Annual Revision	No criteria changes.	11/15/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Vabysmo Utilization Management Medical Policy
- Vabysmo® (faricimab-svoa intravitreal injection – Genentech)

REVIEW DATE: 11/15/2023

OVERVIEW

Vabysmo, a vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2) inhibitor, is indicated for the following uses:[1]

- **Diabetic macular edema** (DME).
- **Macular edema following retinal vein occlusion** (RVO).
- **Neovascular (wet) age-related macular degeneration** (nAMD).

For the indication of macular edema following RVO, Vabysmo is recommended for use for 6 months.[1] The prescribing information does not note a duration of treatment for DME or nAMD.

Dosing Information

The recommended dosing for each indication is as follows[1]:

- DME: There are two recommended dosage regimens: 1) 6 mg administered by intravitreal injection every 4 weeks (approximately every 28 ± 7 days) for at least four doses and then depending on clinical evaluation, dosing interval may be modified by extensions of up to 4 week interval increments or reductions of up to 8 week interval increments; or 2) 6 mg administered by intravitreal injection every 4 weeks (approximately every 28 ± 7 days) for the first six doses and then the dosing frequency is every 8 weeks (2 months); some patients may require dosing every 4 weeks after the first four doses.
- Macular edema following RVO: The recommended dose is 6 mg administered by intravitreal injection every 4 weeks (approximately every 28 ± 7 days) for 6 months.
- nAMD: The recommended dose is 6 mg administered by intravitreal injection every 4 weeks (approximately every 28 ± 7 days) for the first four doses. Thereafter, depending on clinical evaluation, dosing frequency can range from every 4 weeks to every 16 weeks.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Vabysmo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vabysmo as well as the monitoring required for adverse events and long-term efficacy, approval requires Vabysmo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vabysmo is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. Diabetic Macular Edema. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the requested dosing meets the following (A and B):
A) The dose is 6 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 4 weeks for each eye being treated.

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2. Macular Edema Following Retinal Vein Occlusion. Approve for 6 months if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the requested dosing meets the following (A and B):
A) The dose is 6 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 4 weeks for each eye being treated.

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3. Neovascular (Wet) Age-Related Macular Degeneration. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the requested dosing meets the following (A and B):
A) The dose is 6 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 4 weeks for each eye being treated.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vabysmo is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Vabysmo™ intravitreal injection [prescribing information]. South San Francisco, CA: Genentech; October 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Neovascular (Wet) Age-Related Macular Degeneration:** The dosing interval was changed to not more frequent than once every 4 weeks.	11/16/2022
Annual Revision	**Macular Edema Following Retinal Vein Occlusion:** This condition and criteria for approval was added to the policy.	11/15/2023

CARECONTINUUM™

MEDICAL STEP MANAGEMENT POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors Medical Step Management Policy

- Repackaged ophthalmic bevacizumab injection
- Beovu® (brolucizumab-dbll intravitreal injection – Novartis)
- Byooviz™ (ranibizumab-nuna intravitreal injection – Biogen)
- Cimerli™ (ranibizumab-eqrn intravitreal injection – Coherus)
- Eylea® (aflibercept intravitreal injection – Regeneron)
- Eylea® HD (aflibercept intravitreal injection – Regeneron)
- Lucentis® (ranibizumab intravitreal injection – Genentech)
- Vabysmo™ (faricimab-svoa intravitreal injection – Genentech/Roche)

REVIEW DATE: 07/26/2023; selected revision 10/04/2023

OVERVIEW

All of the intravitreal vascular endothelial growth factor (VEGF) inhibitors are indicated for various neovascular conditions of the eye.[1-6,9] Refer to Table 1 for specific FDA approved ophthalmic conditions.

Table 1. Intravitreal Vascular Endothelial Growth Factor Inhibitors: FDA-Approved Indications.[1-6,9]

	Beovu	Byooviz	Cimerli	Eylea	Eylea HD	Lucentis	Vabysmo
Diabetic macular edema	X		X	X	X	X	X
Diabetic retinopathy			X	X	X	X	
Macular edema following retinal vein occlusion		X	X	X		X	
Myopic choroidal neovascularization		X	X			X	
Neovascular (wet) age-related macular degeneration	X	X	X	X	X	X	X
Retinopathy of prematurity				X			

Bevacizumab intravenous infusion (Avastin®, biosimilars) is a VEGF inhibitor that is repackaged and administered by intravitreal injection for off-label use in age-related macular degeneration, diabetic macular edema (including patients with diabetic retinopathy), and other neovascular conditions of the eye.[7,8]

POLICY STATEMENT

This Medical Step Management program has been developed to encourage the use of the Preferred Product. For all Non-Preferred Products, the patient is required to meet the respective standard *Utilization Management Medical Policy* criteria. The program also directs the patient to try the Preferred Product prior to the approval of a Non-Preferred Product. For ophthalmic conditions, Prior Authorization is not required for medical benefit coverage of repackaged ophthalmic bevacizumab injection. Requests for Non-Preferred Products will also be reviewed using the exception criteria (below). All approvals are provided for durations noted below.

Documentation: Documentation is required for use of Non-Preferred Products as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

Automation: None.

Preferred Products: Repackaged ophthalmic bevacizumab injection
Non-Preferred Products: Beovu, Byooviz, Cimerli, Eylea, Eylea HD, Lucentis, Vabysmo

RECOMMENDED EXCEPTION CRITERIA

Non-Preferred Products	Exception Criteria
Beovu	**1.** Approve for 1 year if the patient meets the following (A and B): **A)** Patient meets the standard *Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Beovu Utilization Management Medical Policy* criteria; AND **B)** Patient meets ONE of the following (i or ii): **i.** Patient is currently receiving therapy with Beovu **[documentation required]**; OR **ii.** Patient meets ONE of the following (a or b): **a)** Patient meets both of the following [(1) and (2)]: **(1)** Patient has previously tried repackaged bevacizumab **[documentation required]**; AND **(2)** Either inadequate efficacy or intolerability was demonstrated **[documentation required]**; OR **b)** If, in the professional opinion of the prescriber, the safety of using the repackaged bevacizumab or the supplier of the repackaged bevacizumab is of significant concern.
Eylea, Eylea HD	**1.** Approve for 1 year if the patient meets the following (A and B): **A)** Patient meets the standard *Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Eylea and Eylea HD Utilization Management Medical Policy* criteria; AND **B)** Patient meets ONE of the following (i or ii): **i.** Patient is currently receiving therapy with Eylea or Eylea HD **[documentation required]**; OR **ii.** Patient meets ONE of the following (a, b, c, d, or e): **a)** Patient meets both of the following [(1) and (2)]: **(1)** Patient has previously tried repackaged bevacizumab **[documentation required]**; AND **(2)** Either inadequate efficacy or intolerability was demonstrated **[documentation required]**; OR **b)** Patient has diabetic macular edema and has a baseline visual acuity worse than 20/40 according to the prescriber; OR **c)** Patient has diabetic macular edema with significant retinal thickening according to the prescriber; OR **d)** Patient has diabetic retinopathy (without diabetic macular edema); OR

	e) If, in the professional opinion of the prescriber, the safety of using the repackaged bevacizumab or the supplier of the repackaged bevacizumab is of significant concern.
Byooviz, Cimerli, Lucentis	**1.** Approve for 1 year if the patient meets the following (A and B): **A)** Patient meets the standard *Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Ranibizumab Products Utilization Management Medical Policy* criteria; AND **B)** Patient meets ONE of the following (i or ii): **i.** Patient is currently receiving therapy with Byooviz, Cimerli, or Lucentis **[documentation required]**; OR **ii.** Patient meets ONE of the following (a, b, or c): **a)** Patient meets both of the following [(1) and (2)]: **(1)** Patient has previously tried repackaged bevacizumab **[documentation required]**; AND **(2)** Either inadequate efficacy or intolerability was demonstrated **[documentation required]**; OR **b)** Patient has diabetic retinopathy (without diabetic macular edema); OR **c)** If, in the professional opinion of the prescriber, the safety of using the repackaged bevacizumab or the supplier of the repackaged bevacizumab is of significant concern.
Vabysmo	**1.** Approve for 1 year if the patient meets the following (A and B): **A)** Patient meets the standard *Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Vabysmo Utilization Management Medical Policy* criteria; AND **B)** Patient meets ONE of the following (i or ii): **i.** Patient is currently receiving therapy with Vabysmo **[documentation required]**; OR **ii.** Patient meets ONE of the following (a or b): **a)** Patient meets both of the following [(1) and (2)]: **(1)** Patient has previously tried repackaged bevacizumab **[documentation required]**; AND **(2)** Either inadequate efficacy or intolerability was demonstrated **[documentation required]**; OR **b)** If, in the professional opinion of the prescriber, the safety of using the repackaged bevacizumab or the supplier of the repackaged bevacizumab is of significant concern.

REFERENCES

1. Beovu® intravitreal injection [prescribing information]. Hanover, NJ: Novartis; December 2022.
2. Eylea® intravitreal injection [prescribing information]. Tarrytown, NY: Regeneron; February 2023.
3. Lucentis® intravitreal injection [prescribing information]. South San Francisco, CA: Genentech; October 2020.
4. Byooviz™ intravitreal injection [prescribing information]. Cambridge, MA: Biogen; June 2023.
5. Vabysmo™ intravitreal injection [prescribing information]. South San Francisco, CA: Genentech; January 2023.
6. Cimerli™ intravitreal injection [prescribing information]. Redwood City, CA: Coherus; November 2022.
7. American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern® Guidelines. Age-related macular degeneration. San Francisco, CA: American Academy of Ophthalmology; 2019. Available at: https://www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp. Accessed on July 21, 2023.

8. American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern® Guidelines. Diabetic retinopathy. San Francisco, CA: American Academy of Ophthalmology; 2019. Available at: https://www.aao.org/preferred-practice-pattern/diabetic-retinopathy-ppp. Accessed on July 21, 2023.
9. Eylea™ HD intravitreal injection [prescribing information]. Tarrytown, NY: Regeneron; August 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	06/29/2022
Selected Revision	**Vabysmo:** This product was added as a Non-Preferred Product; criteria for approval were added. **Byooviz:** This product was added as Non-Preferred Product; the criteria for Byooviz are the same as those previously developed for Lucentis.	07/27/2022
Selected Revision	**Cimerli:** This product was added as Non-Preferred Product; the criteria for Cimerli are the same as those previously developed for Lucentis.	10/05/2022
Annual Revision	No criteria changes.	07/26/2023
Selected Revision	**Eylea HD:** This product was added as a Non-Preferred Product; the criteria for Eylea HD are the same as those previously developed for Eylea.	10/04/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Pompe Disease – Enzyme Replacement Therapy – Lumizyme Utilization Management Medical Policy

- Lumizyme® (alglucosidase intravenous infusion – Genzyme)

REVIEW DATE: 05/08/2024

OVERVIEW

Lumizyme, a human hydrolytic lysosomal glycogen-specific enzyme (acid α-glucosidase), is indicated for patients with **Pompe disease** (acid α-glucosidase deficiency).[1] It is produced in a Chinese hamster ovary cell line via recombinant DNA technology. After administration of Lumizyme, it is internalized into cells and transported to lysosomes where it catalyzes the breakdown of glycogen to glucose.

Disease Overview

Pompe disease (glycogen storage disease type II, or acid maltase deficiency), is a rare lysosomal storage disorder characterized by a deficiency in acid α-glucosidase activity leading to the accumulation of glycogen, particularly in muscle.[2,3] The onset, progression, and severity of Pompe disease is variable. Infantile-onset Pompe disease usually manifests in the first few months of life and death often occurs in the first year of life, if left untreated.[2] Clinical manifestations of infantile-onset Pompe disease includes hypotonia, difficulty feeding, and cardiopulmonary failure.[4] Late-onset Pompe disease a has more variable clinical course, can manifest any time after 12 months of age, and patients typically present with progressive muscle weakness which can progress to respiratory insufficiency.[3,4] The diagnosis of Pompe disease is established by demonstrating decreased acid α-glucosidase activity in blood, fibroblasts, or muscle tissue; or by genetic testing.[3,4] Definitive treatment of Pompe disease consists of enzyme replacement therapy with Lumizyme.[2-4]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Lumizyme. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lumizyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Lumizyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lumizyme is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Acid Alpha-Glucosidase Deficiency (Pompe Disease).** Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** The diagnosis is established by ONE of the following (i or ii):
     - **i.** Patient has a laboratory test demonstrating deficient acid alpha-glucosidase activity in blood, fibroblasts, or muscle tissue; OR
     - **ii.** Patient has a molecular genetic test demonstrating biallelic pathogenic or likely pathogenic acid alpha-glucosidase (GAA) gene variants; AND
   - **B)** Lumizyme is prescribed by or in consultation with a geneticist, neurologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

   Dosing. Each dose must not exceed 20 mg/kg administered intravenously no more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lumizyme is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Lumizyme® intravenous infusion [prescribing information]. Cambridge, MA: Genzyme; March 2024.
2. Chien YH, Hwu WL, Lee NC. Pompe disease: Early diagnosis and early treatment make a difference. *Pediatr Neonatol*. 2013;54:219-227.
3. Llerena Junior JC, Nascimento OJM, Oliveira ASB, et al. Guidelines for the diagnosis, treatment and clinical monitoring of patients with juvenile and adult Pompe disease. *Arq Neuropsiquiatr*. 2016;74:166-176.
4. Cupler EJ, Berger KI, Leshner RT, et al. Consensus treatment recommendations for late-onset Pompe disease. *Muscle Nerve*. 2012;45:319-333.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/12/2023
Update	10/04/2023: No criteria changes. Policy name changed from Enzyme Replacement Therapy – Lumizyme to Pompe Disease – Enzyme Replacement Therapy – Lumizyme.	NA
Annual Revision	**Acid Alpha-Glucosidase Deficiency (Pompe Disease):** Confirmation of a genetic mutation in the acid alpha-glucosidase gene was rephrased to more specifically state, "genetic test demonstrating biallelic pathogenic or likely pathogenic acid alpha-glucosidase gene variants".	05/08/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Pompe Disease – Enzyme Replacement Therapy – Nexviazyme Utilization Management Medical Policy
- Nexviazyme® (avalglucosidase alfa-ngpt intravenous infusion – Genzyme)

REVIEW DATE: 05/08/2024

OVERVIEW

Nexviazyme, a hydrolytic lysosomal glycogen-specific recombinant human α-glucosidase enzyme, is indicated for **late-onset Pompe disease** (lysosomal acid α-glucosidase deficiency) in patients ≥ 1 year of age.[1]

Disease Overview

Pompe disease (glycogen storage disease type II, or acid maltase deficiency), is a rare lysosomal storage disorder characterized by a deficiency in acid α-glucosidase activity leading to the accumulation of glycogen, particularly in muscle.[2,3] The onset, progression, and severity of Pompe disease is variable. Infantile-onset Pompe disease usually manifests in the first few months of life and death often occurs in the first year of life, if left untreated.[2] Clinical manifestations of infantile-onset Pompe disease includes hypotonia, difficulty feeding, and cardiopulmonary failure.[4] Late-onset Pompe disease has a more variable clinical course and can manifest any time after 12 months of age.[3,4] Patients typically present with progressive muscle weakness which can progress to respiratory insufficiency. The diagnosis of Pompe disease is established by demonstrating decreased acid α-glucosidase activity in blood, fibroblasts, or muscle tissue; or by genetic testing.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Nexviazyme. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nexviazyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Nexviazyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nexviazyme is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Acid Alpha-Glucosidase Deficiency (Pompe Disease).** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   A) Patient is ≥ 1 year of age; AND

B) Patient has late-onset acid alpha-glucosidase deficiency (late-onset Pompe disease); AND
C) The diagnosis is established by ONE of the following (i or ii):
  i. Patient has a laboratory test demonstrating deficient acid alpha-glucosidase activity in blood, fibroblasts, or muscle tissue; OR
  ii. Patient has a molecular genetic test demonstrating biallelic pathogenic or likely pathogenic acid alpha-glucosidase (GAA) gene variants; AND
D) The medication is prescribed by or in consultation with a geneticist, neurologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) Patient ≥ 30 kg: Dose is 20 mg/kg administered by intravenous infusion once every 2 weeks; OR
B) Patient < 30 kg: Dose is 40 mg/kg administered by intravenous infusion once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nexviazyme is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Nexviazyme ® intravenous infusion [prescribing information]. Cambridge, MA: Genzyme; April 2023.
2. Chien YH, Hwu WL, Lee NC. Pompe disease: Early diagnosis and early treatment make a difference. *Pediatr Neonatol*. 2013;54:219-227.
3. Llerena Junior JC, Nascimento OJM, Oliveira ASB, et al. Guidelines for the diagnosis, treatment and clinical monitoring of patients with juvenile and adult Pompe disease. *Arq Neuropsiquiatr*. 2016;74:166-176.
4. Cupler EJ, Berger KI, Leshner RT, et al. Consensus treatment recommendations for late-onset Pompe disease. *Muscle Nerve*. 2012;45:319-333.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/23/2023
Update	10/04/2023: No criteria changes. Policy name changed from Enzyme Replacement Therapy – Nexviazyme to Pompe Disease – Enzyme Replacement Therapy – Nexviazyme.	NA
Early Annual Revision	**Acid Alpha-Glucosidase Deficiency (Pompe Disease):** Confirmation of a genetic mutation in the acid alpha-glucosidase gene was rephrased to more specifically state, "genetic test demonstrating biallelic pathogenic or likely pathogenic acid alpha-glucosidase gene variants".	05/08/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Pompe Disease – Enzyme Replacement Therapy – Pombiliti Utilization Management Medical Policy
- Pombiliti® (cipaglucosidase alfa-atga intravenous infusion – Amicus)

REVIEW DATE: 05/08/2024

OVERVIEW

Pombiliti, a hydrolytic lysosomal glycogen-specific recombinant human α-glucosidase enzyme, is indicated in combination with Opfolda® (miglustat capsules), an enzyme stabilizer, for **late-onset Pompe disease** (lysosomal acid α-glucosidase deficiency) in adults weighing ≥ 40 kg and who are not improving on their current enzyme replacement therapy.[1]

Disease Overview

Pompe disease (glycogen storage disease type II, or acid maltase deficiency), is a rare lysosomal storage disorder characterized by a deficiency in acid α-glucosidase activity leading to the accumulation of glycogen, particularly in muscle.[2,3] The onset, progression, and severity of Pompe disease is variable. Infantile-onset Pompe disease usually manifests in the first few months of life and death often occurs in the first year of life, if left untreated.[2] Clinical manifestations of infantile-onset Pompe disease includes hypotonia, difficulty feeding, and cardiopulmonary failure.[4] Late-onset Pompe disease has a more variable clinical course and can manifest any time after 12 months of age.[3,4] Patients typically present with progressive muscle weakness which can progress to respiratory insufficiency. The diagnosis of Pompe disease is established by demonstrating decreased acid α-glucosidase activity in blood, fibroblasts, or muscle tissue; or by genetic testing.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Pombiliti. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Pombiliti as well as the monitoring required for adverse events and long-term efficacy, approval requires Pombiliti to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Pombiliti is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Acid Alpha-Glucosidase Deficiency (Pompe Disease).** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, and F):
   A) Patient is ≥ 18 year of age; AND

B) Patient weighs ≥ 40 kg; AND
C) The medication will be used in combination with Opfolda (miglustat capsules); AND
D) Patient has not demonstrated an improvement in objective measures after receiving ONE of the following for at least one year (i or ii):
Note: Examples of objective measures include forced vital capacity (FVC) and six-minute walk test (6MWT).
  i. Lumizyme (alglucosidase alfa intravenous infusion); OR
  ii. Nexviazyme (avalglucosidase alfa-ngpt intravenous infusion); AND
E) Patient has late-onset acid alpha-glucosidase deficiency (late-onset Pompe disease) with diagnosis established by ONE of the following (i or ii):
  i. Patient has a laboratory test demonstrating deficient acid alpha-glucosidase activity in blood, fibroblasts, or muscle tissue; OR
  ii. Patient has a molecular genetic test demonstrating biallelic pathogenic or likely pathogenic acid alpha-glucosidase (GAA) gene variants; AND
F) The medication is prescribed by or in consultation with a geneticist, neurologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

Dosing. Each dose must not exceed 20 mg/kg administered intravenously no more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Pombiliti is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Pombiliti ® intravenous infusion [prescribing information]. Philadelphia, PA: Amicus; September 2023.
2. Chien YH, Hwu WL, Lee NC. Pompe disease: Early diagnosis and early treatment make a difference. *Pediatr Neonatol*. 2013;54:219-227.
3. Llerena Junior JC, Nascimento OJM, Oliveira ASB, et al. Guidelines for the diagnosis, treatment and clinical monitoring of patients with juvenile and adult Pompe disease. *Arq Neuropsiquiatr*. 2016;74:166-176.
4. Cupler EJ, Berger KI, Leshner RT, et al. Consensus treatment recommendations for late-onset Pompe disease. *Muscle Nerve*. 2012;45:319-333.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	-	10/04/2023
Early Annual Revision	**Acid Alpha-Glucosidase Deficiency (Pompe Disease):** Confirmation of a genetic mutation in the acid alpha-glucosidase gene was rephrased to more specifically state, "genetic test demonstrating biallelic pathogenic or likely pathogenic acid alpha-glucosidase gene variants".	05/08/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Proprotein Convertase Subtilisin Kexin Type 9 Related Products – Leqvio Utilization Management Medical Policy
- Leqvio® (inclisiran subcutaneous injection – Novartis)

REVIEW DATE: 05/08/2024

OVERVIEW

Leqvio, a small interfering ribonucleic acid (RNA) directed to proprotein convertase subtilisin kexin type 9 (PCSK9) messenger RNA, is indicated as an adjunct to diet and statin therapy for the treatment of adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce low-density lipoprotein cholesterol (LDL-C).[1] The safety and effectiveness have not been established in pediatric patients.

Repatha® (evolocumab subcutaneous injection) and Praluent® (alirocumab subcutaneous injection) are PCSK9 inhibitor products.[2,3]

Dosing Information

Leqvio is given as a subcutaneous injection and should be administered by a healthcare professional.[1] The dose is 284 mg given as a single subcutaneous injection initially, again at 3 months, and then once every 6 months.

Guidelines

Many guidelines are available regarding the treatment of patients with dyslipidemia which include the management of HeFH and atherosclerotic cardiovascular disease (ASCVD).[4-9] For patients with elevated LDL-C, statins are the cornerstone of therapy and recommended first-line to be used at maximally tolerated doses due to the established benefits regarding the reduction of cardiovascular (CV) risks. Atorvastatin 40 mg to 80 mg once daily (QD) and rosuvastatin 20 mg to 40 mg QD are considered high-intensity statins as they achieve LDL-C lowering of ≥ 50%.

- The **American College of Cardiology (ACC) Expert Consensus Decision Pathway on the Role of Non-Statin Therapies** for LDL-Cholesterol Lowering in the Management of Atherosclerotic cardiovascular disease (ASCVD) Risk (2022) make several recommendations regarding PCSK9 inhibitors.[4] For adults with clinical ASCVD at very high risk (e.g., patients with major ASCVD events, HeFH, diabetes) who are on statin therapy for secondary prevention, the general goal is ≥ 50% LDL-C reduction and an LDL-C < 55 mg/dL with maximally tolerated statin therapy. If the above goals are not achieved, the initial non-statin agents recommended include ezetimibe and/or a PCSK9 monoclonal antibody (i.e., Repatha or Praluent). Leqvio may be considered. For adults without clinical ASCVD or diabetes or LDL-C ≥ 190 mg/dL who have undergone subclinical atherosclerosis imaging, if the coronary artery calcium score is ≥ 1,000 Agatston units, PCSK9 monoclonal antibodies (i.e., Repatha or Praluent) may be non-statin agents to consider following high-intensity statin therapy and ezetimibe to achieve the goal of a ≥ 50% LDL-C reduction (and LDL-C threshold < 70 mg/dL).
- The **American Heart Association (AHA)/ACC guidelines on the management of blood cholesterol** (updated 2018) defines ASCVD as an acute coronary syndrome, those with a history of myocardial infarction, stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack, or peripheral arterial disease.[5,6] Although LDL-C thresholds are not always recognized, in general, an LDL-C < 70 mg/dL is recommended for most patients with

ASCVD to reduce CV risk. Use of a PCSK9 as an adjunct is justified if this goal is not met with maximally tolerated statins.[5,6] Additionally, reviews have recognized that patients with an elevated coronary artery calcium or calcification score (e.g., ≥ 300 Agatston units) are at an increased risk of CV events.[11-14]

- The **American Diabetes Association Standards of Care for Diabetes** discuss CV disease and risk management (2024).[7] For patients with diabetes who are 40 to 75 years of age at higher CV risk (including those with one or more ASCVD risk factors) it is recommended to use high-intensity statin therapy to reduce LDL-C by ≥ 50% of baseline and to target an LDL-C of < 70 mg/dL. Also, for patients with diabetes who are 40 to 75 years of age at higher CV risk, especially those with multiple ASCVD risk factors and an LDL-C ≥ 70 mg/dL, it may be reasonable to add ezetimibe or a PCSK9 inhibitor to a maximum tolerated statin.
- Guidelines for **Chronic Coronary Disease from the AHA and ACC** (along with other organizations) [2023] state in such patients who are judged to be at very high risk and on maximally tolerated statin therapy and an LDL-C ≥ 70 mg/dL, ezetimibe can be beneficial to further reduce the risk of a major adverse coronary event.[8] Patients with chronic coronary disease who are considered to be at very high risk who have and LDL-C ≥ 70 mg/dL who are receiving maximally tolerated statins and ezetimibe, a PCSK9 monoclonal antibody can be beneficial to further reduce the risk of a major adverse coronary event.
- A **Scientific Statement from the AHA on Familial Hypercholesterolemia** (2015),[9] as well as other information,[10] provide additional guidance on diagnosing familial hypercholesterolemia (e.g., HeFH). For HeFH, Dutch Lipid Network criteria scoring is used, as well the Simon Broome criteria.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Leqvio. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. A patient who has previously met Initial Therapy criteria for Leqvio for the requested indication under the Coverage Review Department and is currently receiving Leqvio is only required to meet continuation of therapy criteria (i.e., currently receiving therapy). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Leqvio, or is restarting Leqvio, Initial Therapy criteria must be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Leqvio is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Heterozygous Familial Hypercholesterolemia (HeFH).*** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient meets ONE of the following (a, b, or c):

a) Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR

b) Patient has phenotypic confirmation of heterozygous familial hypercholesterolemia; OR
Note: Examples include pathogenic variants at the low-density lipoprotein receptor (LDLR), apolipoprotein B (apo B), proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene.

c) Patient has been diagnosed with heterozygous familial hypercholesterolemia meeting ONE of the following diagnostic criteria thresholds [(1) or (2)]:
(1) Prescriber confirms that the Dutch Lipid Network criteria score was > 5; OR
(2) Prescriber confirms that Simon Broome criteria met the threshold for "definite" or "possible (or probable)" familial hypercholesterolemia; AND

iii. Patient meets ONE of the following (a or b):

a) Patient meets ALL of the following [(1), (2), and (3)]:
(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single entity or as a combination product]); AND
(2) Patient has tried one high-intensity statin along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND
(3) LDL-C level after this treatment regimen remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting ONE of the following [(1) or (2)]:
(1) Patient experienced statin-related rhabdomyolysis; OR
Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).
(2) Patient meets ALL of the following [(a), (b), and (c)]:
(a) Patient experienced skeletal-related muscle symptoms; AND
Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND
(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); OR
Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

B) Patient Currently Receiving Leqvio. Approve if according to the prescriber, the patient has experienced a response to therapy.
Note: Examples of a response to therapy include decreasing LDL-C, total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Leqvio for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Leqvio, Initial Therapy criteria must be met.

Dosing. Approve ONE of the following dosage regimens (A or B):

A) Initial dose is 284 mg given as a single subcutaneous injection, again at 3 months, and then once every 6 months; OR

B) Maintenance dose is 284 mg given as a subcutaneous injection once every 6 months.

2. Primary Hyperlipidemia.* Approve for 1 year if the patient meets ONE of the following (A or B):
Note: This is not associated with established cardiovascular disease or heterozygous familial hypercholesterolemia (HeFH) and may be referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated low-density lipoprotein cholesterol (LDL-C) levels.

A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient meets ONE of the following (a or b):
  - **a)** Patient has a coronary artery calcium or calcification score ≥ 300 Agatston units; OR
  - **b)** Patient has diabetes; AND
- **iii.** Patient meets ONE of the following (a or b):
  - **a)** Patient meets ALL of the following [(1]), (2), and (3)]:
    - **(1)** Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]); AND
    - **(2)** Patient has tried the one high-intensity statin therapy above along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND
    - **(3)** LDL-C level after this treatment regimen remains ≥ 70 mg/dL; OR
  - **b)** Patient has been determined to be statin intolerant by meeting ONE of the following [(1) or (2)]:
    - **(1)** Patient experienced statin-related rhabdomyolysis; OR
      Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).
    - **(2)** Patient meets ALL of the following [(a), (b), and (c)]:
      - **(a)** Patient experienced skeletal-related muscle symptoms; AND
        Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
      - **(b)** The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND
      - **(c)** When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); OR
        Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

B) Patient Currently Receiving Leqvio. Approve if according to the prescriber, the patient has experienced a response to therapy.
Note: Examples of a response to therapy include decreasing LDL-C, total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Leqvio for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Leqvio, Initial Therapy criteria must be met.

Dosing. Approve ONE of the following dosage regimens (A or B):

A) Initial dose is 284 mg given as a single subcutaneous injection, again at 3 months, and then once every 6 months; OR

B) Maintenance dose is 284 mg given as a subcutaneous injection once every 6 months.

Other Uses with Supportive Evidence

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3. Established Cardiovascular Disease.* Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient has had one of the following conditions or diagnoses (a, b, c, d, e, or f):

a) A previous myocardial infarction or a history of an acute coronary syndrome; OR

b) Angina (stable or unstable); OR

c) A past history of stroke or transient ischemic attack; OR

d) Coronary artery disease; OR

e) Peripheral arterial disease; OR

f) Patient has undergone a coronary or other arterial revascularization procedure in the past; AND

Note: Examples include coronary artery bypass graft surgery, percutaneous coronary intervention, angioplasty, and coronary stent procedures.

iii. Patient meets ONE of the following (a or b):

a) Patient meets all of the following [(1), (2), and (3)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single entity or as a combination product]); AND

(2) Patient has tried one high-intensity statin along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND

(3) Low-density lipoprotein cholesterol (LDL-C) level after this treatment regimen remains ≥ 55 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting ONE of the following [(1) or (2)]:

(1) Patient experienced statin-related rhabdomyolysis; OR

Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).

(2) Patient meets ALL of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND

Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND

(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); OR

Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

B) Patient Currently Receiving Leqvio. Approve if according to the prescriber, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing LDL-C, total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Leqvio for this specific

indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Leqvio, Initial Therapy criteria must be met.

Dosing. Approve ONE of the following dosage regimens (A or B):

A) Initial dose is 284 mg given as a single subcutaneous injection, again at 3 months, and then once every 6 months; OR

B) Maintenance dose is 284 mg given as a subcutaneous injection once every 6 months.

Note:

* A patient may have a diagnosis that pertains to more than one indication, therefore, consider review under different approval conditions, if applicable (e.g., a patient with heterozygous familial hypercholesterolemia may have established cardiovascular disease, a patient with primary hyperlipidemia may have heterozygous familial hypercholesterolemia).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Leqvio is not recommended in the following situations:

1. **Concurrent use of Leqvio with Repatha (evolocumab subcutaneous injection) or Praluent (alirocumab subcutaneous injection).** Repatha and Praluent are PCSK9 inhibitors and should not be used with Leqvio due to a similar mechanism of action.[1] Patients receiving PCSK9 inhibitors were excluded from the pivotal trials with Leqvio.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	It was added to the Policy Statement that a patient who has previously met initial therapy criteria for Leqvio for the requested indication under the Coverage Review Department and is currently receiving Leqvio is only required to meet continuation of therapy criteria (i.e., currently receiving therapy). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Leqvio, or is restarting Leqvio, initial criteria must be met. In addition, the following changes were made: **Atherosclerotic Cardiovascular Disease:** Requirements were divided to distinguish between initial therapy and patient currently receiving Leqvio (previously there was only one criteria set). For a patient who is currently receiving Leqvio and has previously met initial therapy criteria for the requested indication under the Coverage Review Department, only the continuation of therapy criteria has to be met. The continuation of therapy criteria states that according to the prescribing physician, the patient has experienced a response to therapy with examples provided in a Note. **Heterozygous Familial Hypercholesterolemia:** Requirements were divided to distinguish between initial therapy and patient currently receiving Leqvio (previously there was only one criteria set). The criteria to confirm the diagnosis of heterozygous familial hypercholesterolemia were reworded regarding the use of the Dutch Lipid Network criteria and the Simon Broome criteria; also, the phrase "prescriber used" was changed to "the prescribing physician confirms". For a patient who is currently receiving Leqvio and has previously met initial therapy criteria for the requested indication under the Coverage Review Department, only the continuation of therapy criteria has to be met. The continuation of therapy criteria states that according to the prescribing physician, the patient has experienced a response to therapy with examples provided in a Note.	04/26/2023
Selected Revision	**Atherosclerotic Cardiovascular Disease:** The condition was moved from FDA-Approved Indications to Other Uses with Supportive Evidence. Also, coronary artery disease was added as a condition or diagnosis that represents this indication of use in this related requirement. A Note was added that a patient may have a diagnoses that pertains to more than one indication, therefore, consider review under different approval conditions, if applicable. **Heterozygous Familial Hypercholesterolemia:** A Note was added that a patient may have a diagnoses that pertains to more than one indication, therefore, consider review under different approval conditions, if applicable. **Primary Hyperlipidemia:** This was added as a new FDA-approved indication.	08/30/2023

HISTORY (CONTINUED)

Type of Revision	Summary of Changes	Review Date
Annual Revision	It was removed from the Policy Statement that the agent is prescribing by or in consultation with a physician who specializes in the condition being treated. In addition, the following changes were made: **Established Cardiovascular Disease:** The name of the indication was changed to as stated (previously "Atherosclerotic Cardiovascular Disease"). For Initial Therapy, the requirement that the medication is prescribed by, or in consultation with a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders was removed. The requirement that the low-density lipoprotein cholesterol level after treatment with one high-intensity statin therapy and ezetimibe be ≥ 70 mg/dL was changed to ≥ 55 mg/dL. For a Patient Currently Receiving the Medication, the requirement that the "prescribing physician" notes that the patient has experienced a response to therapy was changed to "prescriber". **Heterozygous Familial Hypercholesterolemia:** For Initial Therapy, the requirement that the medication is prescribed by, or in consultation with a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders was removed. The requirement that the patient has had genetic confirmation of heterozygous familial hypercholesterolemia by mutations in the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9, or low-density lipoprotein receptor adaptor protein 1 gene was changed to state that the patient has had phenotypic confirmation of heterozygous familial hypercholesterolemia with the above examples moved to a Note. Regarding the diagnosis of heterozygous familial hypercholesterolemia by meeting the Dutch Lipid Network criteria score or the Simon Broome criteria, the requirement that this be confirmed by the "prescribing physician" was changed to "prescriber". For a Patient Currently Receiving the Medication, the requirement that the "prescribing physician" notes that the patient has experienced a response to therapy was changed to "prescriber". **Primary Hyperlipidemia:** For Initial Therapy, the requirement that the medication is prescribed by, or in consultation with a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders was removed. A patient with diabetes now qualifies for this indication (if requirements are met); previously, high risk was only defined by a patient who had a "coronary artery calcium or calcification score ≥ 300 Agatston units". The requirement that the low-density lipoprotein cholesterol level after treatment with one high-intensity statin therapy, along with ezetimibe, be ≥ 100 mg/dL was changed to ≥ 70 mg/dL. For a Patient Currently Receiving the Medication, the requirement that the "prescribing physician" notes that the patient has experienced a response to therapy was changed to "prescriber".	05/08/2024

APPENDIX A

Simon Broome Register Diagnostic Criteria.[9,10]

Definite Familial Hypercholesterolemia
Raised cholesterol
--Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a patient < 16 years of age; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in a patient > 16 years of age;
AND
--Tendon xanthomas in the patient or in a first (parent, sibling, or child) or second-degree relative (grandparent, aunt, or uncle);
OR
DNA-based evidence of LDL-receptor, familial defective APOB, or PCSK9 mutation.
Possible (or Probable) Familial Hypercholesterolemia
Raised cholesterol
--Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a patient < 16 years of age; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in a patient > 16 years of age;
AND
Family history of premature myocardial infarction younger than 50 years of age in second-degree relative or younger than 60 years of age in first-degree relative;
OR
Raised cholesterol
--Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a patient < 16 years of age; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in a patient > 16 years of age;
AND
Family history of raised cholesterol > 7.5 mmol (290 mg/dL) in adult first-degree or second-degree relative or > 6.7 mmol/L (260 mg/dL) in child or sibling aged < 16 years.

LDL-C – Low-density lipoprotein cholesterol; LDL – Low-density lipoprotein; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

APPENDIX B.

Dutch Lipid Network Criteria.[9,10]

Criteria	Score
Family History	
First-degree relative with known premature coronary and/or vascular disease (men < 55 years, women < 60 years)	1
First degree relative with known LDL-C > 95th percentile for age and sex	1
First-degree relative with tendon xanthomata and/or arcus cornealis, OR	2
Patient is < 18 years of age with LDL-C > 95th percentile for age and sex	2
Clinical History	
Patient with premature CAD (age as above)	2
Patient with premature cerebral or peripheral vascular disease (age as above)	1
Physical Examination	
Tendon xanthomas	6
Arcus cornealis at age < 45 years	4
LDL-C	
LDL-C ≥ 8.5 mmol/L (330 mg/dL)	8
LDL-C 6.5 to 8.4 mmol/L (250 to 329 mg/dL)	5
LDL-C 5.0 to 6.4 mmol/L (190 to 249 mg/dL)	3
LDL-C 4.0 to 4.9 mg/dL (155 to 189 mg/dL)	1
DNA Analysis	
Functional mutation LDLR, APOB or PCSK9 gene	8
Stratification	**Total score**
Definite familial hypercholesterolemia	> 8
Probable familial hypercholesterolemia	6 to 8
Possible familial hypercholesterolemia	3 to 5
Unlikely familial hypercholesterolemia	< 3

LDL-C – Low-density lipoprotein cholesterol; CAD – Coronary artery disease; LDLR – Low-density lipoprotein receptor; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Psychiatry – Spravato Utilization Management Medical Policy
- Spravato® (esketamine nasal spray – Janssen)

REVIEW DATE: 05/22/2024

OVERVIEW

Spravato, a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist, is indicated in conjunction with an oral antidepressant for the treatment of:[1]

- Depressive symptoms in adults with **major depressive disorder (MDD) with acute suicidal ideation or behavior**.
- **Treatment-resistant depression** (TRD) in adults.

Limitation of Use: The effectiveness of Spravato in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of Spravato does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of Spravato. Spravato is not approved as an anesthetic agent. The safety and effectiveness of Spravato as an anesthetic agent have not been established.

Spravato should be administered in conjunction with an oral antidepressant.[1] For MDD with acute suicidal ideation or behavior, the recommended dosage is 84 mg twice weekly for 4 weeks. The dosage may be reduced to 56 mg twice weekly based on tolerability. After 4 weeks of treatment, evidence of therapeutic benefit should be evaluated to determine the need for continued treatment. The use of Spravato, in conjunction with an oral antidepressant, beyond 4 weeks has not been systematically evaluated in the treatment of depressive symptoms in patients with MDD with acute suicidal ideation or behavior. For treatment-resistant depression, the recommended dose is 56 mg intranasally on Day 1, followed by 56 mg or 84 mg intranasally twice weekly for Weeks 1 through 4. On Weeks 5 to 8, Spravato should be administered once weekly at a dose of 56 mg or 84 mg intranasally. On Week 9 and thereafter, the dosing frequency should be individualized to the least frequent dosing to maintain remission/response (either every 2 weeks or once weekly) at a dose of 56 mg or 84 mg. Spravato must be administered under the direct supervision of a healthcare provider.

Disease Overview

Major depressive disorder is a serious, life-threatening condition with high rates of morbidity and a chronic disease course.[2] Major depressive disorder is considered the leading cause of disability worldwide and is also associated with increased mortality rates.[3,4] About 30% to 40% of patients with major depressive disorder fail to respond to first-line treatments including oral antidepressant medications of all classes (e.g., selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants [TCAs], bupropion) and/or psychotherapy.[2,5] In addition, the onset of treatment response for these modalities, even when effective, often takes ≥ 4 weeks, leading to greater suffering, expense, and risk. For regulatory purposes, the FDA considers patients to have treatment-resistant depression if they have MDD and they have not responded to treatment despite trials of at least two antidepressants given at adequate doses for an adequate duration in the current episode.[2]

The available treatments for treatment-resistant depression are limited.[2] Prior to the approval of Spravato, only one medication was FDA-approved for treatment-resistant depression, Symbyax® (olanzapine and fluoxetine capsules). Symbyax is indicated for treatment-resistant depression (major depressive disorder

in patients who do not respond to two separate trials of different antidepressants of adequate dose and duration in the current episode) and acute depressive episodes in bipolar I disorder.[6]

Guidelines

In 2022, the U.S. Department of Veterans Affairs (VA) and U.S. Department of Defense (DoD) published a guideline for the management of MDD.[7] The guideline divides treatment into uncomplicated MDD and MDD that is severe or has a partial or limited response to initial treatment. For uncomplicated MDD, the guideline recommends that MDD be treated with either psychotherapy (i.e., acceptance and commitment therapy, behavioral therapy/behavioral activation, cognitive behavioral therapy, interpersonal therapy, mindfulness-based cognitive therapy, problem-solving therapy, or short-term psychodynamic psychotherapy) or pharmacotherapy (i.e., bupropion, mirtazapine, selective serotonin reuptake inhibitors [SSRIs], serotonin–norepinephrine reuptake inhibitors [SNRIs], trazodone, vilazodone, or vortioxetine) as monotherapy, based on patient preference. Factors including treatment response, severity, and chronicity may lead to other treatment strategies, such as augmentation, combination treatment, switching of treatments, or use of non-first-line treatments. When choosing an initial pharmacotherapy, the guideline suggests against using esketamine, ketamine, monoamine oxidase inhibitors (MAOIs), nefazodone, or tricyclic antidepressants (TCAs). For the treatment of MDD that is severe or has a partial or limited response to initial treatment, the guideline recommends offering a combination of pharmacotherapy and evidence-based psychotherapy for MDD characterized as severe (e.g., nine-item patient health questionnaire [PHQ-9] score > 20), persistent (duration > 2 years), or recurrent (≥ two episodes). For patients with MDD who have shown partial or no response to an adequate trial of initial pharmacotherapy, the guideline suggests switching to another antidepressant, switching to psychotherapy, augmenting with psychotherapy, or augmenting with a second-generation antipsychotic. For patients who have shown partial or no response to ≥ two adequate pharmacologic treatment trials, the guideline suggests offering repetitive transcranial magnetic stimulation for treatment. For patients with MDD who have not responded to several adequate pharmacologic trials, the guideline suggests ketamine or esketamine for augmentation. For patients with MDD who achieve remission with antidepressants, the guideline recommends continuation of antidepressants at the therapeutic dose for ≥ 6 months to decrease risk for relapse. For patients with MDD at high risk for relapse or recurrence (e.g., ≥ two prior episodes, unstable remission status), the guideline suggests offering a course of cognitive behavioral therapy, interpersonal therapy, or mindfulness-based cognitive therapy during the continuation phase of treatment (i.e., after remission is achieved).

Abuse and Misuse

Spravato contains esketamine, a Schedule III controlled substance (CIII), which may be subject to abuse and diversion.[1] Assess each patient's risk for abuse or misuse prior to prescribing Spravato. All patients receiving Spravato should be monitored for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy. Patients with a history of drug abuse or dependence are at greater risk. Careful consideration should be given prior to prescribing Spravato to individuals with a history of substance use disorder.

Safety

Spravato labeling includes a Boxed Warning regarding sedation, dissociation, respiratory depression, abuse and misuse, and suicidal thoughts and behaviors in pediatric and young adult patients.[1] The most common psychological effects of Spravato were dissociative or perceptual changes (including distortion of time, space and illusions), derealization and depersonalization (61% to 84% of patients treated with Spravato developed dissociative or perceptual changes based on the Clinician-Administered Dissociative States Scale). Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering Spravato; treatment should be initiated only if the benefit outweighs the risk.

Because of the risks of serious adverse outcomes resulting from sedation, dissociation, respiratory depression, and abuse and misuse, Spravato is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) program.[1] Healthcare settings must be certified in the program and ensure that Spravato is only dispensed in healthcare settings and administered to patients who are enrolled in the program, administered by patients under the direct observation of a healthcare provider, and that patients are monitored by a healthcare provider for at least 2 hours after administration of Spravato. Pharmacies must be certified in the REMS and must only dispense Spravato to healthcare settings that are certified in the program.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Spravato. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Spravato as well as the monitoring required for adverse events and efficacy, approval requires Spravato to be prescribed by a physician who specializes in the condition being treated.

A 2-month approval duration is applied for the indication of MDD with Acute Suicidal Ideation or Behavior to allow time for the scheduling and administration of a 4-week course of therapy at a certified healthcare setting. If after completing the 4-week course of therapy for MDD with Acute Suicidal Ideation or Behavior, another request for Spravato is submitted and the patient meets the approval criteria, then another 4-week course of treatment (with a 2-month approval duration to complete the course of therapy) could be approved.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Spravato is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Major Depressive Disorder with Acute Suicidal Ideation or Behavior.** Approve for 2 months if the patient meets the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has major depressive disorder that is considered to be severe, according to the prescriber; AND
   - **C)** Patient is concomitantly receiving at least one oral antidepressant; AND
     Note: Antidepressants may include, but are not limited to, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), mirtazapine, and bupropion.
   - **D)** Patient has one of the following (i or ii):
     - **i.** No history of psychosis; OR
     - **ii.** History of psychosis and the prescriber believes that the benefits of Spravato outweigh the risks; AND

E) The medication is prescribed by a psychiatrist.

Dosing. Approve the following dosing regimen (A and B):
A) Maximum single dose: 84 mg intranasally; AND
B) Twice weekly dosing for 4 weeks.

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2. Treatment-Resistant Depression. Approve for 6 months if the patient meets the following (A, B, C, D, E, and F):
A) Patient is ≥ 18 years of age; AND
B) Patient meets both of the following (i and ii):
i. Patient has demonstrated nonresponse (≤ 25% improvement in depression symptoms or scores) to at least two different antidepressants, each from a different pharmacologic class; AND
Note: Different pharmacologic classes of antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), bupropion, mirtazapine, etc.
ii. Each antidepressant was used at therapeutic dosages for at least 6 weeks in the current episode of depression, according to the prescriber; AND
C) Patient is concomitantly receiving at least one oral antidepressant; AND
Note: Antidepressants may include, but are not limited to, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), mirtazapine, and bupropion.
D) Patient has one of the following (i or ii):
i. No history of psychosis; OR
ii. History of psychosis and the prescriber believes that the benefits of Spravato outweigh the risks; AND
E) The patient's history of controlled substance prescriptions has been checked using the state prescription drug monitoring program (PDMP), according to the prescriber; AND
F) The medication is prescribed by a psychiatrist.

Dosing. Approve the following dosing regimen (A, B, and C):
A) Maximum single dose: 84 mg intranasally; AND
B) Induction phase (Weeks 1 through 4): twice weekly dosing; AND
C) Maintenance phase (Weeks 5 and after): up to once weekly dosing.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Spravato is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Treatment-Resistant Depression:** Removed "unless unavailable in the state" from criterion requiring the "patient's history of controlled substance prescriptions has been checked using the state prescription drug monitoring program (PDMP)." Removed Note regarding Missouri not having a statewide PDMP (legislation was enacted in 2021). **Policy Statement:** A Note was added to the Policy Statement to clarify that a 2-month approval duration is applied for the indication of MDD with Acute Suicidal Ideation or Behavior to allow time for the scheduling and administration of a 4-week course of therapy at a certified healthcare setting. Additionally, if after completing the 4-week course of therapy for MDD with Acute Suicidal Ideation or Behavior, another request for Spravato is submitted and the patient meets the approval criteria, then another 4-week course of treatment (with a 2-month approval duration to complete the course of therapy) could be approved.	05/31/2023
Annual Revision	No criteria changes.	05/22/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Pulmonary Arterial Hypertension – Epoprostenol Products Utilization Management Medical Policy
- Flolan® (epoprostenol intravenous infusion – GlaxoSmithKline, generic)
- Veletri® (epoprostenol intravenous infusion – Actelion)

REVIEW DATE: 10/04/2023

OVERVIEW

Epoprostenol intravenous infusion, a prostacyclin vasodilator, is indicated for the treatment of pulmonary arterial hypertension (PAH) [World Health Organization {WHO} Group 1] to improve exercise capacity.[1-3]

Epoprostenol intravenous infusion has been used with varying results in patients with chronic thromboembolic pulmonary hypertension (CTEPH).[4-6] It is sometimes used as a bridge prior to surgery. Limited options are available for patients with CTEPH.

Disease Overview

PAH is a serious but rare condition impacting fewer than 20,000 patients in the US.[7,8] The estimated incidence of PAH is 2 cases per 1 million per year with a prevalence of 10.6 cases per 1 million adults.[7] It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized.[7,8] In this progressive disorder, the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment. In time, right-sided heart failure and/or death may occur. Common PAH symptoms include shortness of breath, fatigue, chest pain, dizziness, and fainting, along with impairment in activity tolerance. It is more prevalent in women. Patients of all ages may develop the disease; however, the mean age of diagnosis typically happens between 36 to 50 years. Children may also have PAH. The condition may occur due to various underlying medical conditions or as a disease (e.g., connective tissue disease, HIV) that uniquely impacts the pulmonary circulation; both genetic and environmental factors may be involved. PAH is defined as a mean pulmonary artery pressure (mPAP) > 20 mmHg (at rest) with a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and a pulmonary vascular resistance > 2 Wood units measured by cardiac catheterization.[13] The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved. Lung transplantation may be recommended if pharmacological or medical therapies fail, based upon patient status. The WHO categorizes PAH into stages, which is also referred to as the functional class (Class I to IV) and is an adaptation of the New York Heart Association system to evaluate activity tolerance.

CTEPH is a persistent obstruction of pulmonary arteries and is often a complication of pulmonary embolism.[9,10] It is classified within Group 4 pulmonary hypertension. Symptoms include progressive dyspnea on exertion, as well as fatigue, syncope, hemoptysis, and signs of right heart failure. Pulmonary endarterectomy is the treatment of choice for most patients with CTEPH. However, around 40% of patients are deemed inoperable for various reasons. Medication therapy may also be recommended. Anticoagulant therapy is also given.

Guidelines

Several guidelines address intravenous epoprostenol products in the management of pulmonary hypertension.[8,11]

- **Pulmonary Arterial Hypertension:** The CHEST guidelines and Expert Panel Report regarding therapy for PAH in adults (2019) cites the many medications that have utility for this condition.[8] In the absence of contraindications, patients with PAH should undergo acute vasoreactivity testing utilizing a short-acting agent (e.g., calcium channel blockers). For patients in Functional Class II, oral therapies are recommended such as endothelin receptor antagonists (ambrisentan, bosentan, Opsumit® [macitentan tablets]), phosphodiesterase type 5 inhibitors (tadalafil, sildenafil), and Adempas® (riociguat tablets). It is suggested that parenteral or inhaled prostanoids not be chosen as initial therapy for treatment naïve-patients with PAH with WHO Functional Class II symptoms or as second-line agents for patients with PAH with WHO Functional Class II who have not met their treatment goals. Parenteral prostanoids are recommended for patients with PAH in Functional Class III and IV.[8] The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines regarding the treatment of pulmonary hypertension (2022) also recognize intravenous epoprostenol as having a prominent role in the management of this condition, usually in later therapy stages and after other therapies.[11]
- **Chronic Thromboembolic Pulmonary Hypertension:** Guidelines from the ESC/ERS regarding the treatment of pulmonary hypertension (2022) recommended to consider parenteral prostacyclin analogs for patients with inoperable CTEPH.[11]

Safety

Epoprostenol should not be abruptly discontinued or have the dose rapidly decreased as rebound pulmonary hypertension may occur.[1-3]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of epoprostenol. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for 1 year in duration unless otherwise noted below. Specifically, approvals will remain up to 14 days for patients currently receiving the agent for the indication of PAH (WHO Group 1) with inadequate information or if the criteria are not met. These cases are reviewed by a nurse or pharmacist. Because of the specialized skills required for evaluation and diagnosis of patients treated with epoprostenol injection as well as the monitoring required for adverse events and long-term efficacy, approval requires epoprostenol injection to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: In the *Pulmonary Arterial Hypertension – Epoprostenol Utilization Management Medical Policy*, documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Epoprostenol Utilization Management Medical Policy* is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of epoprostenol injection is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1].** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, iv, and v):
     - **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
     - **ii.** Patient meets the following (a and b):
       - **a)** Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND
       - **b)** Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
     - **iii.** Patient meets ONE of the following (a or b):
       - **a)** Patient is in Functional Class III or IV; OR
       - **b)** Patient is in Functional Class II and meets ONE of the following [(1) or (2)]:
         - **(1)** Patient has tried or is currently receiving one oral agent for PAH; OR
           Note: Examples of oral agents for PAH include bosentan, ambrisentan, Opsumit (macitentan tablets), sildenafil, tadalafil, Adempas (riociguat tablets), Orenitram (treprostinil extended-release tablets), Alyq (tadalafil tablets), Tadliq (tadalafil oral suspension), and Uptravi (selexipag tablets).
         - **(2)** Patient has tried one inhaled or parenteral prostacyclin product for PAH; AND
           Note: Examples of inhaled and parenteral prostacyclin products for PAH include Tyvaso (treprostinil inhalation solution), Tyvaso DPI (treprostinil oral inhalation powder), Ventavis (iloprost inhalation solution), treprostinil injection, and epoprostenol injection.
     - **iv.** Patient with idiopathic PAH must meet one of the following (a, b, c, d, or e):
       - **a)** Patient meets both of the following [(1) and (2)]:
         - **(1)** According to the prescriber, the patient has had an acute response to vasodilator testing that occurred during the right heart catheterization; AND
           Note: An example of a response can be defined as a decrease in mean pulmonary artery pressure of at least 10 mm Hg to an absolute mean pulmonary artery pressure of less than 40 mm Hg without a decrease in cardiac output.
         - **(2)** Patient has tried one calcium channel blocker (CCB) therapy; OR
           Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets.
       - **b)** According to the prescriber, the patient did not have an acute response to vasodilator testing; OR
       - **c)** According the prescriber, the patient cannot undergo a vasodilator test; OR
       - **d)** Patient cannot take CCB therapy; OR
         Note: Examples of reasons a patient cannot take CCB therapy include right heart failure or decreased cardiac output.
       - **e)** Patient has tried one CCB; AND
         Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets.
     - **v.** Medication is prescribed by or in consultation with a cardiologist or a pulmonologist; OR
   - **B)** Patient Currently Receiving Epoprostenol. Approve for the duration noted below if the patient meets one of the following (i or ii):
     - **i.** Approve for 1 year if the patient meets ALL of the following (a and b):
       - **a)** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
       - **b)** Patient meets the following [(1) and (2)]:

(1) Patient has had a right heart catheterization; AND
(2) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

c) Medication is prescribed by or in consultation with a cardiologist or a pulmonologist; OR

ii. Approve a short-term supply of epoprostenol for up to 14 days if the patient does not meet the criteria in 1Bi above or if there is insufficient information available. All approvals are reviewed by a nurse or pharmacist.
Note: A 14-day supply should be sufficient to address coverage issues. However, multiple short-term approvals are allowed if a coverage determination cannot be made. Abrupt discontinuation of epoprostenol therapy may have severe adverse consequences.

Dosing. Approve up to 100 ng/kg/minute intravenously.

Other Uses with Supportive Evidence

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2. Chronic Thromboembolic Pulmonary Hypertension (CTEPH). Approve for 1 year if the agent is prescribed by or in consultation with a pulmonologist or a cardiologist.

Dosing. Approve up to 45 ng/kg/minute intravenously.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of epoprostenol injection is not recommended in the following situations:

1. **Chronic Obstructive Pulmonary Disease (COPD) in a Patient Without PAH (WHO Group 1).** COPD is classified as Group 3 Pulmonary Hypertension (pulmonary hypertension associated with lung diseases and/or hypoxia). Pulmonary hypertension may develop late in the course of COPD, but medications used for the treatment of PAH (WHO Group 1) are not recommended therapies.[12]

2. **Concurrent Use with Parenteral Treprostinil Products, Oral Prostacyclin Products, or Inhaled Prostacyclin Agents Used for Pulmonary Hypertension.**
Note: Examples of medications include Orenitram (treprostinil extended-release tablets), Uptravi (selexipag tablets and intravenous infusion), Tyvaso (treprostinil inhalation solution), Tyvaso DPI (treprostinil oral inhalation powder), Ventavis (iloprost inhalation solution), and treprostinil injection (Remodulin, generic).

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Flolan® intravenous infusion [prescribing information]: Research Triangle Park: NC; GlaxoSmithKline; August 2021.
2. Epoprostenol sodium intravenous infusion [prescribing information]. Cranbury, NJ: Sun; January 2021.
3. Veletri® intravenous infusion [prescribing information]. South San Francisco, CA: Actelion/Janssen; July 2022.
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13. Maron B. Revised definition of pulmonary hypertension and approach to management: a clinical primer. *J Am Heart Assoc*. 2023 April 7. [epub ahead of print].

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Pulmonary Arterial Hypertension (World Health Organization Group 1):** Tyvaso DPI was added as an example of a prostacyclin product used for pulmonary arterial hypertension. Tadliq was added as an example of an oral agent used for pulmonary arterial hypertension. **Conditions Not Recommended for Approval:** It was added that concurrent use with parenteral treprostinil products, oral prostacyclin products, or inhaled prostacyclin agents used for pulmonary hypertension is not permitted. Examples of medications were provided in a Note.	10/05/2022
Annual Revision	No criteria changes.	10/04/2023

CARECONTINUUM™

MEDICAL STEP MANAGEMENT POLICY

POLICY: Pulmonary Arterial Hypertension – Treprostinil Injection Medical Step Management Policy

- Remodulin® (treprostinil subcutaneous or intravenous infusion – United Therapeutics, generic)

REVIEW DATE: 03/06/2024

OVERVIEW

Treprostinil injection, a prostacyclin vasodilator, is indicated for the treatment of **pulmonary arterial hypertension** (World Health Organization Group 1) to diminish symptoms associated with exercise and reduce the rate of clinical deterioration for patients who require transition from epoprostenol.[1,2]

POLICY STATEMENT

This Medical Step Management program has been developed to encourage the use of the Preferred Product. For all medications (Preferred and Non-Preferred), the patient is required to meet the *Pulmonary Arterial Hypertension – Treprostinil Injection Utilization Management Medical Policy* criteria. The program also directs the patient to try the Preferred Product prior to the approval of a Non-Preferred Product. Requests for Non-Preferred Products will also be reviewed using the exception criteria (below). If the patient meets the standard *Pulmonary Arterial Hypertension – Treprostinil Injection Utilization Management Medical Policy* criteria, but has not tried a Preferred Product, approval for a Preferred Product will be authorized. All approvals are provided for 1 year in duration, unless otherwise noted below.

Documentation: Documentation is required for use of Remodulin as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, claims records, and other information. For certain criteria, verification is an option as noted by **[verification required]**.

Automation: None.

Preferred Products: generic treprostinil injection
Non-Preferred Products: Remodulin

RECOMMENDED EXCEPTION CRITERIA

Non-Preferred Product	Exception Criteria
Remodulin	**1.** Approve for 1 year if the patient meets BOTH of the following (A and B): **A)** Patient meets the standard *Pulmonary Arterial Hypertension – Treprostinil Injection Utilization Management Medical Policy* criteria; AND **B)** Patient meets ONE of the following (i or ii): **i.** If the request is for Remodulin for subcutaneous continuous infusion, the patient meets ONE of the following (a or b): **a)** For Initial Therapy or Patient is Currently Receiving Remodulin for < 90 Days, patient meets ONE of the following [(1) or (2)]: **(1)** Patient meets BOTH of the following [(a) and (b)]: **(a)** Patient has tried generic treprostinil for subcutaneous continuous infusion **[documentation required]**; AND **(b)** Patient cannot take generic treprostinil for subcutaneous continuous infusion due to a formulation difference in the inactive ingredients(s) [e.g., differences in stabilizing agent, buffering agent, and/or surfactant] which, according to the prescriber, would result in a significant allergy or serious adverse reaction **[documentation required]**; OR **(2)** Patient cannot take generic treprostinil because appropriate durable medical equipment is not available such as the patient does not have or cannot obtain a compatible pump that allows generic treprostinil to be administered; OR **b)** For a Patient Currently Receiving Remodulin for ≥ 90 days, patient meets ONE of the following [(1) or (2)]: **(1)** Patient meets BOTH of the following [(a) and (b)]: **(a)** Patient has been started on therapy for ≥ 90 days **[documentation required]**; AND **(b)** Patient has a history of medical or prescription pharmacy paid claims **[documentation or verification required]**; OR **(2)** Patient cannot take generic treprostinil because appropriate durable medical equipment is not available such as the patient does not have or cannot obtain a compatible pump that allows generic treprostinil to be administered; OR **ii.** If the request is for Remodulin for intravenous continuous infusion, patient meets ONE of the following (a or b): **a)** For Initial Therapy or Patient is Currently Receiving Remodulin for < 90 Days, patient meets BOTH of the following [(1) and (2)]: **(1)** Patient has tried generic treprostinil for intravenous continuous infusion **[documentation required]**; AND **(2)** Patient cannot take generic treprostinil for intravenous continuous infusion due to a formulation difference in the inactive ingredients(s) [e.g., differences in stabilizing agent, buffering agent, and/or surfactant] which, according to the prescriber, would result in a significant allergy or serious adverse reaction **[documentation required]**; OR **b)** For a Patient Currently Receiving Remodulin for ≥ 90 days patient meets BOTH of the following [(1) and (2)]:

	(1) Patient has been started on therapy for ≥ 90 days **[documentation required]**; AND **(2)** Patient has a history of medical or prescription pharmacy paid claims **[documentation or verification required]**. **2.** If the patient has met the standard *Pulmonary Arterial Hypertension – Treprostinil Injection Utilization Management Medical Policy* criteria (1A), but has not met exception criteria (Bi) or (Bii) for brand Remodulin, approve generic treprostinil injection.

REFERENCES

1. Remodulin® subcutaneous or intravenous infusion [prescribing information]: Research Triangle Park, NC: United Therapeutics; October 2023.
2. Treprostinil subcutaneous or intravenous infusion [prescribing information]. North Wales, PA: Teva; May 2022.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	03/08/2023
Annual Revision	No criteria changes.	03/06/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Pulmonary Arterial Hypertension – Treprostinil Injection Utilization Management Medical Policy

- Remodulin® (treprostinil subcutaneous or intravenous infusion – United Therapeutics, generic)

REVIEW DATE: 10/04/2023

OVERVIEW

Treprostinil injection, a prostacyclin vasodilator, is indicated for the treatment of pulmonary arterial hypertension (PAH) [World Health Organization {WHO} Group 1] to:[1,2]

- **Diminish symptoms associated** with exercise.
- **Reduce the rate of clinical deterioration** for patients who require transition from epoprostenol.

Treprostinil injection has been used with varying results in patients with chronic thromboembolic pulmonary hypertension (CTEPH).[3-7] Benefits noted include improvement in functional class, six-minute walk distance, and in hemodynamic parameters. Treprostinil injection is sometimes used as a bridge prior to surgery. Limited options are available for patients with CTEPH.

Disease Overview

PAH is a serious but rare condition impacting fewer than 20,000 patients in the US.[8,9] The estimated incidence of PAH is 2 cases per 1 million per year with a prevalence of 10.6 cases per 1 million adults.[8] It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized.[8,9] In this progressive disorder the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment. In time, right-sided heart failure and/or death may occur. Common PAH symptoms include shortness of breath, fatigue, chest pain, dizziness, and fainting, along with impairment in activity tolerance. It is more prevalent in women. Patients of all ages may develop the disease; however, the mean age of diagnosis typically happens between 36 to 50 years. Children may also have PAH. The condition may occur due to various underlying medical conditions or as a disease (e.g., connective tissue disease, HIV) that uniquely impacts the pulmonary circulation; both genetic and environmental factors may be involved. PAH is defined as a mean pulmonary artery pressure (mPAP) > 20 mmHg (at rest) with a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and a pulmonary vascular resistance > 2 Wood units measured by cardiac catheterization.[14] The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved. Lung transplantation may be recommended if pharmacological or medical therapies fail, based upon patient status. The WHO categorizes PAH into stages, which is also referred to as the functional class (Class I to IV) and is an adaptation of the New York Heart Association system to evaluate activity tolerance.

CTEPH is a persistent obstruction of pulmonary arteries and is often a complication of pulmonary embolism.[10,11] It is classified within Group 4 pulmonary hypertension. Symptoms include progressive dyspnea on exertion, as well as fatigue, syncope, hemoptysis, and signs of right heart failure. Pulmonary endarterectomy is the treatment of choice for most patients with CTEPH. However, around 40% of patients are deemed inoperable for various reasons. Medication therapy may also be recommended. Anticoagulant therapy is also given.

Guidelines

Several guidelines address treprostinil injection in the management of pulmonary hypertension.[9,12]

- **Pulmonary Arterial Hypertension:** An updated CHEST guideline and Expert Panel Report regarding therapy for PAH in adults (2019) provides the evidence for use of the many medications for this condition.[9] In the absence of contraindications, patients with PAH should undergo acute vasoreactivity testing utilizing a short-acting agent (e.g., calcium channel blockers). For patients in Functional Class II, oral therapies are recommended such as endothelin receptor antagonists (ambrisentan, bosentan, Opsumit® [macitentan tablets]), phosphodiesterase type 5 inhibitors (tadalafil, sildenafil), and Adempas® (riociguat tablets). It is suggested that parenteral or inhaled prostanoids not be chosen as initial therapy for treatment naïve patients with PAH with WHO Functional Class II symptoms or as second-line agents for patients with PAH with WHO Functional Class II who have not met their treatment goals. Prostanoids may be considered in patients who have contraindications or difficulty tolerating phosphodiesterase type 5 inhibitors or endothelin receptor antagonists. Parenteral prostanoids are recommended for patients with PAH in Functional Class III and IV.[9] The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines regarding the treatment of pulmonary hypertension (2022) also recognize parenteral treprostinil as having a prominent role in the management of this condition, usually in later therapy stages and after other therapies.[12]
- **Chronic Thromboembolic Pulmonary Hypertension:** Guidelines from the ESC/ERS regarding the treatment of pulmonary hypertension (2022) recommended to consider parenteral prostacyclin analogs for patients with inoperable CTEPH.[12]

Safety

Treprostinil injection should not be abruptly discontinued or have the dose rapidly decreased as rebound pulmonary hypertension may occur.[1,2]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of treprostinil injection. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for 1 year in duration unless otherwise noted below. Specifically, approvals will remain up to 14 days for patients currently receiving the agent for the indication of PAH (WHO Group 1) with inadequate information or if the criteria are not met. These cases are reviewed by a nurse or pharmacist. Because of the specialized skills required for evaluation and diagnosis of patients treated with treprostinil injection as well as the monitoring required for adverse events and long-term efficacy, approval requires treprostinil injection to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: In the *Pulmonary Arterial Hypertension – Treprostinil Injection Utilization Management Medical Policy*, documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory results. For a patient case in which the documentation requirement of the right heart catheterization upon Prior Authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Treprostinil Injection Utilization Management Medical Policy* is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of treprostinil injection is recommended in those who meet one of the following criteria:

FDA-Approved Indication

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1. **Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1].** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, iv, and v):
     - **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
     - **ii.** Patient meets the following criteria (a and b):
       - **a)** Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND
       - **b)** Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
     - **iii.** Patient meets ONE of the following (a or b):
       - **a)** Patient is in Functional Class III or IV; OR
       - **b)** Patient is in Functional Class II and meets ONE of the following [(1) or (2)]:
         - **(1)** Patient has tried or is currently receiving one oral agent for PAH; OR
           Note: Examples of oral agents for PAH include bosentan, ambrisentan, Opsumit (macitentan tablets), Adempas (riociguat tablets), sildenafil, tadalafil, Alyq (tadalafil tablets), Tadliq (tadalafil oral suspension), Orenitram (treprostinil extended-release tablets), and Uptravi (selexipag tablets).
         - **(2)** Patient has tried one inhaled or parenteral prostacyclin product for PAH; AND
           Note: Examples of inhaled and parenteral prostacyclin products for PAH include Ventavis (iloprost inhalation solution), Tyvaso (treprostinil inhalation solution), Tyvaso DPI (treprostinil oral inhalation powder), and epoprostenol intravenous infusion (Flolan, Veletri, generics).
     - **iv.** Patient with idiopathic PAH must meet one of the following (a, b, c, d, or e):
       - **a)** Patient meets both of the following [(1) and (2)]:
         - **(1)** According to the prescriber, the patient has had an acute response to vasodilator testing that occurred during the right heart catheterization; AND
           Note: An example of a response can be defined as a decrease in mean pulmonary artery pressure of at least 10 mm Hg to an absolute mean pulmonary artery pressure of less than 40 mm Hg without a decrease in cardiac output.
         - **(2)** Patient has tried one calcium channel blocker (CCB) therapy; OR
           Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets.
       - **b)** According to the prescriber, the patient did not have an acute response to vasodilator testing; OR
       - **c)** According to the prescriber, the patient cannot undergo a vasodilator test; OR
       - **d)** Patient cannot take CCB therapy; OR
         Note: Examples of reasons patients cannot take CCB therapy include right heart failure or decreased cardiac output.
       - **e)** Patient has tried one CCB; AND
         Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets.
     - **v.** Medication is prescribed by or in consultation with a cardiologist or a pulmonologist; OR

B) Patient Currently Receiving Treprostinil Injection. Approve for the duration noted below if the patient meets ONE of the following (i or ii):
- **i.** Approve for 1 year if the patient meets ALL of the following (a , b, and c):
  - **a)** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
  - **b)** Patient meets both of the following [(1) and (2)]:
    - **(1)** Patient has had a right heart catheterization; AND
    - **(2)** Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
  - **c)** Medication is prescribed by or in consultation with a cardiologist or a pulmonologist; OR
- **ii.** Approve a short-term supply of treprostinil injection for up to 14 days if the patient does not meet the criteria in 1Bi above or if there is insufficient information available. All approvals are reviewed by a nurse or pharmacist.
  Note: A 14-day supply should be sufficient to address coverage issues. However, multiple short-term approvals are allowed if a coverage determination cannot be made. Abrupt discontinuation of treprostinil injection therapy may have severe adverse consequences.

Dosing. Approve up to 100 ng/kg/minute given subcutaneously or intravenously.

Other Uses with Supportive Evidence

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2. Chronic Thromboembolic Pulmonary Hypertension (CTEPH). Approve for 1 year if the agent is prescribed by or in consultation with a pulmonologist or a cardiologist.

Dosing. Approve up to 50 ng/kg/minute subcutaneously or intravenously.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of treprostinil injection is not recommended in the following situations:

1. **Chronic Obstructive Pulmonary Disease (COPD) in a Patient Without PAH (WHO Group 1).** COPD is classified as Group 3 Pulmonary Hypertension (pulmonary hypertension associated with lung diseases and/or hypoxia). Pulmonary hypertension may develop late in the course of COPD, but medications used for the treatment of PAH (WHO Group 1) are not recommended therapies.[12]

2. **Concurrent Use with Parenteral Epoprostenol Products, Oral Prostacyclin Products, or Inhaled Prostacyclin Agents Used for Pulmonary Hypertension.**
   Note: Examples of medications include Orenitram (treprostinil extended-release tablets), Uptravi (selexipag tablets and intravenous infusion), Tyvaso (treprostinil inhalation solution), Tyvaso DPI (treprostinil oral inhalation powder), Ventavis (iloprost inhalation solution), and epoprostenol injection (Flolan, Veletri, generic).

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Remodulin® subcutaneous or intravenous infusion [prescribing information]. Research Triangle Park, NC: United Therapeutic; July 2021.
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14. Maron B. Revised definition of pulmonary hypertension and approach to management: a clinical primer. *J Am Heart Assoc*. 2023 April 7. [epub ahead of print].

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	The word "Remodulin" was removed from the name of the policy. In addition, the following changes were made. **Pulmonary Arterial Hypertension (World Health Organization Group 1):** Tyvaso DPI was added as an example of a prostacyclin product used for pulmonary arterial hypertension. Tadliq was added as an example of an oral agent used for pulmonary arterial hypertension. **Conditions Not Recommended for Approval:** It was added that concurrent use with with parenteral epoprostenol products, oral prostacyclin products, or inhaled prostacyclin agents used for pulmonary hypertension is not permitted. Examples of medications are provided in a Note.	10/05/2022
Annual Revision	No criteria changes.	10/04/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Repository Corticotropin – Acthar Gel Utilization Management Medical Policy
- Acthar® Gel (repository corticotropin intramuscular and subcutaneous injection – Mallinckrodt)

REVIEW DATE: 05/01/2024

OVERVIEW

Acthar, an adrenocorticotropic hormone (ACTH) analog, is indicated for the following uses:[1]
- **Infantile spasms**, treatment of, in infants and children < 2 years of age as monotherapy.
- **Multiple sclerosis, treatment of exacerbations** in adults.

Although data are limited, the prescribing information notes that Acthar may also be used for the following disorders and diseases:[1]
- **Allergic states**, such as serum sickness.
- **Collagen diseases**, during an exacerbation or as a maintenance therapy in selected cases of systemic lupus erythematosus and systemic dermatomyositis (polymyositis).
- **Dermatologic diseases**, such as severe erythema multiforme and Stevens-Johnson syndrome.
- **Edematous state** including to induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus.
- **Respiratory diseases** such as symptomatic sarcoidosis.
- **Rheumatoid disorders**, as an adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in psoriatic arthritis, rheumatoid arthritis (including juvenile rheumatoid arthritis) [selected cases may require low-dose maintenance therapy], and ankylosing spondylitis.
- **Ophthalmic diseases** including severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, and anterior segment inflammation.

The Acthar gel vial is for either intramuscular or subcutaneous injection.[1] Acthar gel single-dose pre-filled SelfJect injector is for subcutaneous administration by adults only (used to administered single doses of 40 units or 80 units only). For infantile spasms, doses must be given intramuscularly using the Acthar gel vial. The recommended dose for this use is 150 units/m^2 divided twice daily into two injections of 75 units/m^2. After 2 weeks of treatment, dosing should be gradually tapered and discontinued over a 2-week period. Acthar gel single-dose prefilled SelfJect injector is not to be used for the treatment of infantile spasms.

Clinical Efficacy

A review regarding repository corticotropin found few randomized controlled trials supporting the clinical benefit of repository corticotropin or ACTH for various conditions (e.g., use in rheumatoid arthritis, ankylosing spondylitis, optic neuritis, systemic lupus erythematosus, and nephrotic syndrome).[2] Most data suggest that repository corticotropin or ACTH was not superior to corticosteroids for treating relapses in patients with multiple sclerosis.

Guidelines

Several guidelines discuss repository corticotropin or ACTH.

- The **American Academy of Neurology** and the **Child Neurology Society** published an evidence-based guideline for the medical treatment of infantile spasms (2012).[3] ACTH is a first-line agent for the short-term treatment of infantile spasms.
- **Infantile Spasms Working Group** published a US consensus report on infantile spasms in 2010.[4] Most patients with this condition (90%) present within the first year of life. ACTH is an effective first-line therapy for infantile spasms.
- **Kidney Disease Improving Global Outcomes** (KDIGO) published clinical practice guidelines for the management of glomerular disease (2021).[5] This includes diagnoses such as nephrotic syndrome, membranous nephropathy, immunoglobulin A nephropathy, minimal change disease, infection-related glomerulonephritis, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and lupus nephritis. ACTH is not prominent in the guidelines and there is a lack of quality evidence regarding ACTH. Updated KDIGO guidelines were published regarding the management of lupus nephritis (2024), as well as for the management of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (2024).[22,23] ACTH is not mentioned in the guidelines.
- The **National Multiple Sclerosis Society** has recommendations regarding corticosteroids in the management of multiple sclerosis relapses or exacerbations.[6] High-dose corticosteroids are the accepted standard of care short-term. The most common regimen is 500 to 1,000 mg of intravenous methylprednisolone given daily for 3 to 5 days, with or without an oral steroid tapering regimen (most often prednisone) for 1 to 3 weeks. ACTH and high-dose intravenous methylprednisolone have been shown to possess similar efficacy in the management of multiple sclerosis relapses.[7]
- The **American College of Rheumatology** has many guidelines regarding use in rheumatoid-type conditions.[8] ACTH does not have a prominent role and is generally not recommended for use in any of the related American College of Rheumatology guidelines.
- The **American College of Rheumatology** has guidelines for the management of gout (2020).[9] For gout flare management, using colchicine, non-steroidal anti-inflammatory drugs, or glucocorticoids (oral, intraarticular, or intramuscular) are appropriate first-line therapy for gout flare over interleukin-1 inhibitors or ACTH.
- The **European Respiratory Society** published guidelines on the treatment of sarcoidosis (2021).[10] Repository corticotropin use should be reserved for patients who have failed prior treatments (e.g., steroids, antimetabolites). Only limited data are available. Repository corticotropin should be considered in a case by case basis only when other therapies are not effective or tolerated.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Acthar Gel. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients with these conditions, as well as monitoring required for adverse events and efficacy, approval requires Acthar Gel to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Acthar Gel is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Infantile Spasms, Treatment.** Approve Acthar Gel multidose vial for 1 month if the patient meets ALL of the following (A, B, and C):
   Note: Acthar Gel single-dose pre-filled SelfJect Injector for subcutaneous use should not be approved.
   A) Child is less than 2 years of age; AND
   B) Acthar is being administered as an intramuscular injection; AND
   C) Medication is prescribed by a physician who has consulted with or specializes in neurology.

   Dosing. Approve up to 150 units/m^2 by intramuscular injection per day for up to 1 month.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Acthar is not recommended in the following situations:

1. **Ankylosing Spondylitis.** The American College of Rheumatology guidelines for the treatment of ankylosing spondylitis do not convey a role for ACTH in this condition.[11,12]

2. **Dermatomyositis or Polymyositis.** British Society for Rheumatology guidelines on the management of pediatric, adolescent, and adult patients with idiopathic inflammatory myopathy (2022) do not cite ACTH as an agent to utilize in patients with such conditions.[13]

3. **Diabetic Nephropathy.** ACTH is not a cited therapy or the standard of care for the management of chronic kidney disease in patients with diabetes.[5,14]

4. **Glomerular Kidney Diseases.**
   Note: Diagnoses can include nephrotic syndrome, membranous nephropathy, immunoglobulin A nephropathy, minimal change disease, infection-related glomerulonephritis, focal segmental glomerulosclerosis, and membranoproliferative glomerulonephritis. ACTH is not prominent in related guidelines from KDIGO (2021) and there is a lack of quality evidence regarding ACTH to support its use.[5] KDIGO guidelines for the management of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (2024) do not mention ACTH.[23]

5. **Gout.** American College of Rheumatology guidelines for gout (2020) recommend other therapies beside ACTH for gout flare management (e.g., colchicine, non-steroidal anti-inflammatory drugs, or glucocorticoids).[9]

6. **Juvenile Idiopathic Arthritis.** Related guidelines from the American College of Rheumatology regarding the treatment of juvenile idiopathic arthritis (2021) do not mention ACTH as having a role for this disease.[15]

7. **Lupus Nephritis.** The KDIGO guidelines for the management of glomerular disease (2021) cite many other agents besides ACTH for the management of this condition.[5] The European League Against Rheumatism-European Renal Association-European Dialysis and Transplantation Association joint recommendations on the management of lupus nephritis do not cite ACTH as a therapy to use in this

condition.[16] Updated KDIGO guidelines were published regarding the management of lupus nephritis (2024) and do not mention ACTH.[22]

8. **Multiple Sclerosis, Acute Exacerbations.** High-dose corticosteroids, usually intravenous methylprednisolone, are the accepted standard of care short-term for acute relapses or exacerbations.[6]

9. **Ophthalmic Conditions.** Only limited data describe the use of ACTH in ophthalmic-related conditions (e.g., acute optic neuritis, keratitis, retinal vasculitis).[2,17-19] Prospective data are needed to more rigorously define the efficacy and safety of ACTH in ocular disease.

10. **Psoriatic Arthritis.** The American College of Rheumatology/National Psoriasis Foundation guidelines for the treatment of psoriatic arthritis (2018) do not mention a role for ACTH in this condition.[20]

11. **Rheumatoid Arthritis.** The American College of Rheumatology guidelines for the treatment of rheumatoid arthritis (2021) do not mention a role for ACTH in this disease state.[21]

12. **Sarcoidosis.** The European Respiratory Society published guidelines on the treatment of sarcoidosis (2021).[10] Repository corticotropin use should be reserved for patients who have failed prior treatments (e.g., steroids, antimetabolites). Only limited data are available. Repository corticotropin should be considered in a case by case basis only when other therapies are not effective or tolerated.

13. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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1. Acthar® Gel injection for subcutaneous and intramuscular use [prescribing information]. Bridgewater, NJ: Mallinckrodt; February 2024.
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14. American Diabetes Association Professional Practice Committee. Chronic Kidney Disease and Risk Management: Standards of Medical Care in Diabetes-2024. *Diabetes Care*. 2024;47(1):S219-S230.
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23. Kidney Disease Improving Global Outcomes ANCA Vasculitis Work Group. KDIGO 2024 clinical practice guideline for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. *Kidney Int*. 2024;105(Suppl 3S):S71-S116.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/19/2023
Annual Revision	**Infantile Spasms, Treatment:** It was added to specify that the formulation of Acthar Gel to be approved for this use is the multidose vial. A Note was added that Acthar Gel single-dose pre-filled SelfJect Injector for subcutaneous use should not be approved. A criterion was added that Acthar is being administered as an intramuscular injection.	05/01/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Repository Corticotropin – Cortrophin Gel Utilization Management Medical Policy
- Purified Cortrophin™ Gel (repository corticotropin subcutaneous and intramuscular injection – ANI)

REVIEW DATE: 05/01/2024

OVERVIEW

Cortrophin Gel, a porcine derived purified corticotrophin (adrenocorticotropic hormone [ACTH] {1-39}) product, is indicated in the following disorders:[1]

- **Allergic states**, such as atopic dermatitis and serum sickness.
- **Collagen diseases**, during an exacerbation or as a maintenance therapy in selected cases of systemic lupus erythematosus and systemic dermatomyositis (polymyositis).
- **Dermatologic diseases**, such as severe erythema multiforme (Stevens-Johnson syndrome) and severe psoriasis.
- **Edematous state** including to induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus.
- **Nervous system**, acute exacerbations of multiple sclerosis.
- **Respiratory diseases** such as symptomatic sarcoidosis.
- **Rheumatoid disorders**, as an adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in psoriatic arthritis, rheumatoid arthritis (including juvenile rheumatoid arthritis) [selected cases may require low-dose maintenance therapy], ankylosing spondylitis, and acute gouty arthritis.
- **Ophthalmic diseases** including severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as allergic conjunctivitis, keratitis, iritis and iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, and anterior segment inflammation.

Clinical Efficacy

A recent review regarding repository corticotropin found few randomized controlled trials supporting the clinical benefit of repository corticotropin or ACTH for various conditions (e.g., use in rheumatoid arthritis, ankylosing spondylitis, optic neuritis, systemic lupus erythematosus, and nephrotic syndrome).[2] Most data suggest that repository corticotropin or ACTH was not superior to corticosteroids for treating relapses in patients with multiple sclerosis.

Guidelines

Several guidelines discuss repository corticotrophin or ACTH.

- **Kidney Disease Improving Global Outcomes** (KDIGO) published clinical practice guidelines for the management of glomerular disease (2021).[3] This includes diagnoses such as nephrotic syndrome, membranous nephropathy, immunoglobulin A nephropathy, minimal change disease, infection-related glomerulonephritis, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and lupus nephritis. ACTH is not prominent in the guidelines and there is a lack of quality evidence regarding ACTH. Updated KDIGO guidelines were published regarding the management of lupus nephritis (2024), as well as for the management of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (2024).[20,21] ACTH is not mentioned in the guidelines.

- The **National Multiple Sclerosis Society** has recommendations regarding corticosteroids in the management of multiple sclerosis relapses or exacerbations.[4] High-dose corticosteroids are the accepted standard of care short-term. The most common regimen is 500 to 1,000 mg of intravenous methylprednisolone given daily for 3 to 5 days, with or without an oral steroid tapering regimen (most often prednisone) for 1 to 3 weeks. ACTH and high-dose intravenous methylprednisolone have been shown to possess similar efficacy in the management of multiple sclerosis relapses.[5]
- The **American College of Rheumatology** has many guidelines regarding use in rheumatoid-type conditions.[6] ACTH does not have a prominent role and is generally not recommended for use in any of the related American College of Rheumatology guidelines.
- The **American College of Rheumatology** has guidelines for the management of gout (2020).[7] For gout flare management, using colchicine, non-steroidal anti-inflammatory drugs, or glucocorticoids (oral, intraarticular, or intramuscular) are appropriate first-line therapy for gout flare over interleukin-1 inhibitors or ACTH.
- The **European Respiratory Society** published guidelines on the treatment of sarcoidosis (2021).[8] Repository corticotropin use should be reserved for patients who have failed prior treatments (e.g., steroids, antimetabolites). Only limited data are available. Repository corticotropin should be considered in a case by case basis only when other therapies are not effective or tolerated.

POLICY STATEMENT

Due to the lack of updated clinical efficacy data and potential safety concerns with long-term use, **approval is not recommended** for Cortrophin Gel. The current Cortrophin Gel efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits beyond those provided by other available therapies.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cortrophin Gel is not recommended in the following situations:

1. **Ankylosing Spondylitis.** The American College of Rheumatology guidelines for the treatment of ankylosing spondylitis do not convey a role for ACTH in this condition.[9,10]

2. **Dermatomyositis or Polymyositis.** British Society for Rheumatology guidelines on the management of pediatric, adolescent, and adult patients with idiopathic inflammatory myopathy (2022) do not cite ACTH as an agent to utilize in patients with such conditions.[11]

3. **Diabetic Nephropathy.** ACTH is not a cited therapy or the standard of care for the management of chronic kidney disease in patients with diabetes.[3,12]

4. **Glomerular Kidney Diseases.**
   Note: Diagnoses can include nephrotic syndrome, membranous nephropathy, immunoglobulin A nephropathy, minimal change disease, infection-related glomerulonephritis, focal segmental glomerulosclerosis, and membranoproliferative glomerulonephritis. ACTH is not prominent in related

guidelines from KDIGO (2021) and there is a lack of quality evidence regarding ACTH to supports its use.[3] KDIGO guidelines for the management of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (2024) do not mention ACTH.[21]

5. **Gout.** American College of Rheumatology guidelines for gout (2020) recommend other therapies beside ACTH for gout flare management (e.g., colchicine, non-steroidal anti-inflammatory drugs, or glucocorticoids).[7]

6. **Infantile Spasms, Treatment.** Purified Cortrophin Gel is not FDA-approved for this use.[1]

7. **Juvenile Idiopathic Arthritis.** Related guidelines from the American College of Rheumatology regarding the treatment of juvenile idiopathic arthritis (2021) do not mention ACTH as having a role for this disease.[13]

8. **Lupus Nephritis.** The KDIGO guidelines for the management of glomerular disease (2021) cite many other agents besides ACTH for the management of this condition.[3] The European League Against Rheumatism-European Renal Association-European Dialysis and Transplantation Association joint recommendations on the management of lupus nephritis do not cite ACTH as a therapy to use in this condition.[14] Updated KDIGO guidelines were published regarding the management of lupus nephritis (2024) and do not mention ACTH.[20]

9. **Multiple Sclerosis, Acute Exacerbations.** High-dose corticosteroids, usually intravenous methylprednisolone, are the accepted standard of care short-term for acute relapses or exacerbations.[4]

10. **Ophthalmic Conditions.** Only limited data describes the use of ACTH in ophthalmic-related conditions (e.g., acute optic neuritis, keratitis, retinal vasculitis).[2,15-17] Prospective data are needed to more rigorously define the efficacy and safety of ACTH in ocular disease.

11. **Psoriatic Arthritis.** The American College of Rheumatology/National Psoriasis Foundation guidelines for the treatment of psoriatic arthritis (2018) do not mention a role for ACTH in this condition.[18]

12. **Rheumatoid Arthritis.** The American College of Rheumatology guidelines for the treatment of rheumatoid arthritis (2021) do not mention a role for ACTH in this disease state.[19]

13. **Sarcoidosis.** The European Respiratory Society published guidelines on the treatment of sarcoidosis (2021).[8] Repository corticotropin use should be reserved for patients who have failed prior treatments (e.g., steroids, antimetabolites). Only limited data are available. Repository corticotropin should be considered in a case by case basis only when other therapies are not effective or tolerated.

14. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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12. American Diabetes Association Professional Practice Committee. Chronic Kidney Disease and Risk Management: Standards of Medical Care in Diabetes-2024. *Diabetes Care*. 2024;47(1):S219-S230.
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21. Kidney Disease Improving Global Outcomes ANCA Vasculitis Work Group. KDIGO 2024 clinical practice guideline for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. *Kidney Int*. 2024;105(Suppl 3S):S71-S116.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/19/2023
Annual Revision	No criteria changes.	05/01/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Rituximab Intravenous Products Utilization Management Medical Policy
- Riabni™ (rituximab-arrx intravenous infusion – Amgen)
- Rituxan® (rituximab intravenous infusion – Genentech)
- Ruxience® (rituximab-pvvr intravenous infusion – Pfizer)
- Truxima® (rituximab-abbs intravenous infusion – Celltrion/Teva)

REVIEW DATE: 08/16/2023

OVERVIEW

Rituximab products are CD20-directed cytolytic antibodies. All approved rituximab intravenous products are indicated for treatment of the following conditions:

- **Chronic lymphocytic leukemia** (CLL), in combination with fludarabine and cyclophosphamide (FC) for the treatment of patients with previously untreated and previously treated CD20-positive disease.
- **Granulomatosis with polyangiitis** (Wegener's granulomatosis) and **microscopic polyangiitis** in adults, in combination with glucocorticoids.
- **Non-Hodgkin lymphoma** (NHL), for the following uses:
  - previously untreated follicular, CD20-positive disease, in combination with first-line chemotherapy, and in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as a single-agent maintenance therapy.
  - for relapsed or refractory, low-grade or follicular, CD20-positive, B-cell disease.
  - for non-progressing (including stable disease) low-grade, CD20-positive, B-cell disease as a single agent after first-line cyclophosphamide/vincristine/prednisone (CVP) chemotherapy.
  - for previously untreated diffuse large B-cell, CD20-positive disease, in combination with cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) or other anthracycline-based chemotherapy regimens.
- **Rheumatoid arthritis**, in adult patients with moderately to severely active disease, in combination with methotrexate for patients who have had an inadequate response to one or more tumor necrosis factor inhibitors (TNFis).

In addition to the above indications, Rituxan intravenous is also indicated for treatment of the following conditions:

- **Granulomatosis with polyangiitis** (Wegener's granulomatosis) and **microscopic polyangiitis** in patients ≥ 2 years of age, in combination with glucocorticoids.
- **Pemphigus vulgaris**, for adults with moderate to severe disease.
- **B-cell lymphoma,** in patients ≥ 6 months of age with previously untreated, advanced stage, CD20-positive diffuse large B-cell lymphoma, Burkitt lymphoma, Burkitt-like lymphoma, or mature B-cell acute leukemia in combination with chemotherapy.

Riabni, Ruxience, and Truxima are approved as biosimilar to Rituxan intravenous, indicating no clinically meaningful differences in safety and effectiveness and the same mechanism of action, route of administration, dosage form, and strength as Rituxan intravenous. However, minor differences in clinically inactive components are allowed. At this time, the biosimilars have only demonstrated biosimilarity, not interchangeability.

Guidelines

The use of rituximab is supported in clinical guidelines in numerous situations, both as first-line therapy and in patients who are refractory or have relapsed following treatment with other therapies.[4-21]

- **Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis:** Guidelines from the American College of Rheumatology (ACR) [2021] list rituximab among the alternatives for induction or maintenance of remission. Various regimens are recommended with a typical maximum of 1,000 mg/infusion. For maintenance dosing, at least 4 months should separate doses. The optimal dose of rituximab for remission maintenance remains uncertain. Although scheduled maintenance is conditionally recommended over use of CD19+ B-cell counts and/or ANCA titers to guide retreatment, there are data to support both approaches.
- **Immune Thrombocytopenia (ITP):** Guidelines from the American Society of Hematology (ASH) for ITP (2019) mention rituximab as an alternative for children and adults with ITP who do not respond to first-line treatment, and for adults who are corticosteroid-dependent.[17]
- **Multiple Sclerosis (MS):** In June 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[18] Rituximab is listed among various options, involving different mechanisms of action and modes of administration, which have shown benefits in patients with MS. The American Academy of Neurology has practice guidelines regarding disease-modifying therapies for adults with MS.[19] The guidelines mention rituximab for use in MS.
- **Neuromyelitis Optica Spectrum Disorders:** A review article lists rituximab as an effective treatment for neuromyelitis optica.[20]
- Oncology indications covered in National Comprehensive Cancer Network (NCCN) guidelines:[6]
  - **Acute Lymphoblastic Leukemia (ALL):** Guidelines (version 2.2023 – July 28, 2023) list rituximab in multiple regimens for Philadelphia chromosome (Ph)-negative disease for patients with CD20-positive disease.[11] In those with Ph-positive disease, rituximab should be considered in addition to chemotherapy for those with CD20-positive disease, especially in those < 60 years of age.
  - **B-Cell Lymphomas:** In the guidelines (version 5.2023 – July 07, 2023), rituximab is included in multiple treatment regimens across the spectrum of disease.[8] Guidelines for pediatric aggressive mature B-cell lymphomas (version 1.2023 – April 04, 2023) include rituximab intravenous as a component of treatment regimens for induction therapy/initial treatment and as subsequent therapy for relapsed or refractory disease.[9] For primary cutaneous lymphomas (version 1.2023 – January 5, 2023), rituximab is a treatment option for patients with primary cutaneous B-cell lymphoma.[10]
  - **CLL/Small Lymphocytic Lymphoma:** Rituximab features prominently in the guidelines (version 3.2023 – June 12, 2023) and is included in multiple treatment regimens across the spectrum of disease.[7]
  - **Graft-Versus-Host Disease (GVHD):** The hematopoietic cell transplantation guidelines (version 1.2023 – March 31, 2023) list rituximab among the agents used for steroid-refractory chronic GVHD.[15]
  - **Hairy Cell Leukemia:** Guidelines (version 1.2023 – August 30, 2022) recommend rituximab as a component in a preferred primary regimen, and in multiple regimens for relapsed/refractory disease (including in patients with progressive disease after relapsed/refractory therapy).[12]
  - **Hodgkin Lymphoma:** Guidelines (version 2.2023 – November 8, 2022) recommend rituximab ± chemotherapy and/or radiation (depending on the clinical presentation) in the first-line setting for nodular lymphocyte-predominant disease.[13] Rituximab is also used for relapsed/refractory disease and for maintenance. Guidelines for pediatric disease (version

2.2023 – March 9, 2023) include rituximab in regimens for primary treatment of nodular lymphocyte-predominant disease.[25]
    - **Primary Central Nervous System Lymphoma:** Guidelines for central nervous system cancers (version 1.2023 – March 24, 2023) recommend rituximab in multiple regimens for induction therapy and relapsed or refractory primary central nervous system lymphoma.[24]
    - **Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma:** Guidelines (version 1.2023 – July 6, 2022) include rituximab in regimens across the spectrum of disease (primary therapy, previously treated disease, and maintenance).[14]
- **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitors:** NCCN (version 2.2023 – May 9, 2023) and the American Society of Clinical Oncology (ASCO) guidelines (2021) recommend rituximab as an option for corticosteroid-refractory dermatologic and hematologic immune mediated adverse events, as well as for immune-mediated encephalitis and myositis.[26,27]
- **Pemphigus Vulgaris:** British guidelines (2017) list rituximab in combination with corticosteroids as a first-line therapy.[23]
- **Rheumatoid Arthritis:** Guidelines from ACR (2021) recommend addition of a biologic or a targeted synthetic DMARD for a patient taking the maximum tolerated dose of methotrexate who is not at target.[16]
- **Systemic Lupus Erythematosus (SLE):** European League Against Rheumatism (EULAR) recommendations for the management of SLE (2019) mention rituximab as a therapeutic option for patients who are refractory to standard immunosuppressive therapies.[21]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of rituximab IV products. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with rituximab products as well as the monitoring required for adverse events and long-term efficacy, initial approval requires rituximab to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

*Indications and/or approval conditions noted with **[eviCore]** are managed by eviCore healthcare for those clients who use eviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to eviCore at www.eviCore.com.*

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of rituximab intravenous products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
    A) Induction Treatment. Approve for 1 month if the patient meets ALL of the following (i, ii, and iii):
        i. Patient has an ANCA-associated vasculotide; AND

Note: Examples of ANCA-associated vasculitis include granulomatosis with polyangiitis (GPA) [Wegener's granulomatosis] or microscopic polyangiitis (MPA).

ii. The medication is being administered in combination with glucocorticoids; AND

iii. The medication is prescribed by or in consultation with a rheumatologist, nephrologist, or immunologist.

B) Follow-Up Treatment of Patients Who Have Received Induction Treatment for ANCA-Associated Vasculitis. Approve for 1 year if the patient meets BOTH of the following (i and ii):
Note: This includes a patient who received induction treatment using a rituximab product or other standard of care immunosuppressants.

i. According to the prescriber, the patient achieved disease control with induction treatment; AND

ii. If the patient previously received a course of therapy, at least 16 weeks will elapse between courses.

Dosing. Approve one of the following (A or B):

A) Initial Therapy: Approve one of the following (i or ii):

i. 375 mg/m^2 per dose administered intravenously for 4 doses separated by at least 7 days; OR

ii. Up to two 1,000 mg intravenous doses separated by at least 2 weeks.

B) Follow-Up Treatment of a Patient Who Has Received Induction Treatment for ANCA-Associated Vasculitis: Approve one of the following (i or ii):

i. ≥ 18 years of age: Up to 1,000 mg administered by intravenous infusion for 6 doses; OR

ii. < 18 Years of age: Up to 250 mg/m^2 administered by intravenous infusion for 2 doses.

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2. B-Cell Lymphoma. *[eviCore]* Approve for 1 year if prescribed by or in consultation with an oncologist.
Note: Examples of B-cell lymphomas include follicular lymphoma, diffuse large B-cell lymphoma, high-grade B-cell lymphoma, acquired immune deficiency (AIDS)-related B-cell lymphoma, Burkitt lymphoma, Castleman's disease, marginal zone lymphoma (e.g., extranodal or MALT [gastric or nongastric], nodal, or splenic marginal zone lymphoma), primary mediastinal large B-cell lymphoma, mantle cell lymphoma, post-transplant lymphoproliferative disorders, gray zone lymphoma, primary cutaneous B-cell lymphoma, pediatric aggressive mature B-cell lymphomas.

Dosing. Approve one of the following regimens (A or B):

A) Approve up to 375 mg/m^2 per dose administered intravenously with doses separated by at least 7 days; OR

B) Approve up to 375 mg/kg^2 on two days of each cycle.

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3. Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. *[eviCore]* Approve for 1 year if prescribed by or in consultation with an oncologist.

Dosing. Approve up to 500 mg/m^2 administered as an intravenous infusion on 1 day of each cycle.

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4. Pemphigus Vulgaris. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Treatment. Approve for 1 month (which is adequate duration to administer one course of therapy) if the patient meets BOTH of the following (i and ii):

i. Therapy is initiated in combination with a corticosteroid unless contraindicated; AND
Note: An example of a corticosteroid is prednisone.
ii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Being Treated for a Relapse or for Maintenance of Pemphigus Vulgaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):
i. Subsequent infusions will be administered no sooner than 16 weeks following the previous infusion of a rituximab product; AND
ii. The medication is prescribed by or in consultation with a dermatologist.

Dosing. Approve one of the following (A or B):
A) Initial Treatment or Treatment of a Relapse. Approve one course of therapy, which consists of up to two 1,000 mg doses administered as an intravenous infusion separated by at least 2 weeks; OR
B) Maintenance Therapy. Approve up to 500 mg per dose administered intravenously.

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5. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 1 month (which is adequate duration to administer one course of therapy) if the patient meets ALL of the following conditions (i, ii, and iii):
i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND
Note: Examples of conventional synthetic DMARDs include methotrexate [oral or injectable], leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient already has a 3-month trial of at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix A for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic is not required to "step back" and try a conventional synthetic DMARD.
ii. The medication will not be used concurrently with another biologic or with a targeted synthetic DMARD; AND
Note: Refer to Appendix A for examples of biologics and targeted synthetic DMARDs.
iii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient has already Received One or More Courses of a Rituximab Product for Rheumatoid Arthritis. Approve for 1 month (which is adequate duration to administer one course of therapy) if the patient meets ALL of the following conditions (i, ii, and iii):
i. 16 weeks or greater will elapse between treatment courses; AND
Note: For example, there will be a minimum of 16 weeks since the first dose of the previous course and the first dose of the next course of a rituximab product.
ii. The medication will not be used concurrently with another biologic or with a targeted synthetic DMARD; AND
Note: Refer to Appendix A for examples of biologics and targeted synthetic DMARDs.
iii. If the patient has already received two or more courses of therapy, the patient meets at least ONE of the following (a or b):
a) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
Note: Examples of standardized and validated measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II,

Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

Dosing. Approve one course of therapy, which consists of up to two 1,000mg intravenous doses separated by at least 2 weeks.

Other Uses with Supportive Evidence

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6. Acute Lymphoblastic Leukemia. ***[eviCore]*** Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient has CD20-positive disease; AND

B) The medication is prescribed by or in consultation with an oncologist.

Dosing: Approve up to 375 mg/m^2 administered intravenously with doses separated by at least 7 days.

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7. Graft-Versus-Host Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month if the patient meets the following (i and ii):

i. Patient has tried at least one conventional systemic treatment for graft versus host disease; AND

Note: Examples include systemic corticosteroids (methylprednisolone, prednisone), cyclosporine, tacrolimus, mycophenolate mofetil, Imbruvica (ibrutinib capsules and tablets), imatinib, antithymocyte globulin, Nipent (pentostatin infusion), or an infliximab product.

ii. The medication is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center.

B) Patient has Already Received a Course of a Rituximab Product for Graft-Versus-Host Disease. Approve for 1 year if the patient meets at least ONE of the following (i or ii):

i. When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating a rituximab product); OR

Note: An example of objective measures is normalization of liver function tests, red blood cell count, or platelet count, or resolution of fever or rash.

ii. Compared with baseline (prior to initiating a rituximab product), patient experienced an improvement in at least one symptom, such as improvement in skin, oral mucosal, ocular, or gastrointestinal symptoms (e.g., nausea, vomiting, anorexia).

Dosing. Approve up to 375 mg/m^2 administered intravenously with doses separated by at least 7 days.

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8. Hairy Cell Leukemia. ***[eviCore]*** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 375 mg/m^2 administered intravenously with doses separated by at least 7 days.

9. Hodgkin Lymphoma. *[eviCore]* Approve for 1 year if the patient meets BOTH of the following (A and B):
- **A)** Patient has nodular lymphocyte-predominant disease; AND
- **B)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 375 mg/m^2 administered intravenously with doses separated by at least 7 days.

10. Immune Thrombocytopenia (ITP). Approve if the patient meets ONE of the following (A or B):
- **A)** Initial Therapy. Approve for 1 month if the patient meets BOTH of the following (i and ii):
  - **i.** Patient has tried one other therapy; AND
    Note: Examples of therapies for ITP include intravenous immunoglobulin (IVIG), anti-D (RHO) immunoglobulin, corticosteroids, and splenectomy.
  - **ii.** The agent is prescribed by or in consultation with a hematologist.
- **B)** Patient has Already Received a Course of a Rituximab Product for ITP. Approve for 1 month if the patient meets ALL of the following (i, ii, and iii):
  - **i.** At least 6 months will elapse between treatment courses; AND
    Note: For example, there will be a minimum of 6 months separating the first dose of the previous course and the first dose of the requested course of a rituximab product.
  - **ii.** Patient responded to therapy as determined by the prescriber; AND
    Note: Examples of a response include a platelet count increase from baseline following treatment with a rituximab product.
  - **iii.** The prescriber has determined that the patient has relapsed.
    Note: Examples of a relapse include the patient experiences thrombocytopenia after achievement of a remission.

Dosing. Approve up to 375 mg/m^2 administered intravenously with doses separated by at least 7 days.

11. Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitors. Approve for the duration noted if the patient meets the following (A or B):
Note: Examples of checkpoint inhibitors are Keytruda (pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), Yervoy (ipilimumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion), Bavencio (avelumab intravenous infusion), Imfinzi (durvalumab intravenous infusion), and Libtayo (cemiplimab-rwlc intravenous infusion).
- **A)** Initial Therapy. Approve for 1 month if the patient meets BOTH of the following (i and ii):
  - **i.** Patient is symptomatic despite a trial of at least ONE systemic corticosteroid; AND
    Note: Examples of a corticosteroid include methylprednisolone and prednisone.
  - **ii.** The medication is prescribed by or in consultation with an oncologist, neurologist, rheumatologist, or dermatologist.
- **B)** Patient has Already Received a Course of a Rituximab Product. Approve for 1 month if prescribed by or in consultation with an oncologist, neurologist, rheumatologist, or dermatologist.

Dosing. Approve dosing that meets the following (A or B):
- **A)** Approve up to 500 mg/m^2 administered intravenously for 2 doses separated by at least 14 days; OR
- **B)** Approve up to 375 mg/m^2 administered intravenously for 4 doses separated by at least 7 days.

12. Multiple Sclerosis. Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets ALL the following (i, ii, iii, and iv):

i. According to the prescriber, the patient has experienced inadequate efficacy or significant intolerance to at least TWO other disease-modifying agent for multiple sclerosis; AND
Note: See Appendix B for examples of disease-modifying agents used for multiple sclerosis.

ii. Medication will not be used concurrently with another disease-modifying agent used for multiple sclerosis; AND
Note: See Appendix B for examples of disease-modifying agents used for multiple sclerosis.

iii. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; AND

iv. At least 6 months will elapse between treatment courses.
Note: For example, if the patient has already received a course of therapy there will be a minimum of 6 months separating the first dose of the previous course and the first dose of the requested course of therapy.

B) Patient is Currently Receiving Rituximab. Approve if the patient meets one of the following (i or ii):

i. Patient has been receiving Rituximab for < 1 year. Approve if the patient meets ALL of the following (a, b, and c):

a) Medication will not be used concurrently with another disease-modifying agent used for multiple sclerosis; AND
Note: See Appendix B for examples of disease-modifying agents used for multiple sclerosis.

b) At least 6 months will elapse between treatment courses; AND
Note: For example, if the patient has already received a course of therapy there will be a minimum of 6 months separating the first dose of the previous course and the first dose of the requested course of therapy.

c) Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR

ii. Patient has been receiving Rituximab for 1 year or more. Approve for 1 year if the patient meets ALL of the following (a, b, c, and d):

a) Medication will not be used concurrently with another disease-modifying agent used for multiple sclerosis; AND
Note: See Appendix B for examples of disease-modifying agents used for multiple sclerosis.

b) At least 6 months will elapse between treatment courses; AND
Note: For example, if the patient has already received a course of therapy there will be a minimum of 6 months separating the first dose of the previous course and the first dose of the requested course of therapy.

c) Patient meets ONE of the following [(1) or (2)]:

(1) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability Status Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Items Multiple Sclerosis Walking

Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and or attenuation of brain volume loss; OR

(2) Patient experienced stabilization, slow progression, or improvement in at least one symptoms such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND

d) Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

Dosing. Approve up to 2,000 mg (total) administered as one or two intravenous infusions administered over 1 month.

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13. Neuromyelitis Optica Spectrum Disorder. Approve for 1 month if prescribed by or in consultation with a neurologist.

Dosing. Approve ONE of the following (A or B):

A) Up to 375 mg/m^2 administered intravenously for 4 doses separated by at least 7 days; OR

B) Up to two 1,000 mg doses administered as an intravenous infusion separated by at least 2 weeks.

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14. Primary Central Nervous System Lymphoma. ***[eviCore]*** Approve for 1 year if prescribed by or in consultation with an oncologist.

Dosing: Approve up to 375 mg/m^2 administered intravenously with doses separated by at least 7 days.

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15. Systemic Lupus Erythematosus (SLE) [Lupus]. Approve for the duration noted if the patient meets ONE of the following (A or B):

Note: This includes nephrotic syndrome in a patient with SLE.

A) Initial Therapy. Approve for 1 month (adequate duration to receive one course) if the patient meets BOTH of the following (i and ii):

i. Patient has tried at least ONE standard immunomodulating or immunosuppressant agent; AND
Note: Examples of standard immunomodulating or immunosuppressant agents include hydroxychloroquine, corticosteroids (e.g., prednisone, methylprednisolone), methotrexate, azathioprine, mycophenolate, and cyclophosphamide.

ii. The medication is prescribed by or in consultation with a rheumatologist, nephrologist, or neurologist.

B) Patient has Already Received a Course of a Rituximab Product for SLE. Approve for 1 month (adequate duration to receive one course) if 6 months or greater will elapse between treatment courses
Note: There will be a minimum of 6 months separating the first dose of the previous rituximab course and the first dose of the requested course of rituximab.

Dosing. Approve the requested dose.

16. **Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma.** *[eviCore]* Approve for 1 year if prescribed by or in consultation with an oncologist.

    Dosing. Approve up to 375 mg/m^2 administered intravenously with doses separated by at least 7 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of rituximab intravenous products is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**B-Cell Lymphoma:** High-grade B-cell lymphoma was added as an example of a B-Cell Lymphoma. To align with guidelines, dosing was updated to approve up to two doses per cycle. **Rheumatoid Arthritis:** Note was clarified to state that a previous trial of a biologic applies to one biologic other than the requested drug. A biosimilar of the requested biologic does not count. A requirement was added for a patient who has already received two or more courses of a rituximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Graft-Versus-Host Disease:** For initial therapy, the initial approval was changed to be for 1 month (previously was for 1 year). A requirement was added for a patient who has already received a course of a rituximab product to have at least one objective or subjective response to therapy. **Multiple Sclerosis:** For the required previous trial of at least one other disease-modifying agent for multiple sclerosis, it was clarified that inadequate efficacy or significant intolerance was according to the prescriber. Examples of disease-modifying agents used for multiple sclerosis were moved to an appendix (previously listed as examples in a note within the criteria). For a patient who has been receiving a rituximab product for 1 year or longer, response criteria were developed for reauthorization in which the patient either experienced a beneficial clinical response when assessed by at least one objective measure (with examples provided in a Note), or the patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation.	07/20/2022
Annual Revision	**Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis:** Dosing was updated to specify a total of four doses for initial therapy. For follow up treatment, a total of six doses was specified for patients ≥ 18 years of age and two doses for patients < 18 years of age. **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitors:** This condition of approval was added. **Multiple Sclerosis:** For initial therapy, trial of at least one other disease-modifying agent was changed to require a trial of at least two other disease-modifying agents. **Neuromyelitis Optica Spectrum Disorder:** A total of four weekly doses for a regimen of 375 mg/m^2 intravenous was specified.	08/16/2023

APPENDIX A

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzaa SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	RA
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; ^ Off-label use of Kineret in JIA supported in guidelines; DMARDs – Disease-modifying antirheumatic drug.

APPENDIX B

Medication	Mode of Administration
Aubagio® (teriflunomide tablets)	Oral
Avonex® (interferon beta-1a intramuscular injection)	Injection (self-administered)
Bafiertam® (monomethyl fumarate delayed-release capsules)	Oral
Betaseron® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Briumvi™ (ublituximab-xiij intravenous infusion)	Injection
Copaxone® (glatiramer acetate subcutaneous injection, generic)	Injection (self-administered)
Extavia® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Gilenya® (fingolimod capsules)	Oral
Glatopa® (glatiramer acetate subcutaneous injection)	Injection (self-administered)
Kesimpta® (ofatumumab subcutaneous injection)	Injection (self-administered)
Lemtrada® (alemtuzumab intravenous infusion)	Intravenous infusion
Mavenclad® (cladribine tablets)	Oral
Mayzent® (siponimod tablets)	Oral
Ocrevus® (ocrelizumab intravenous infusion)	Intravenous infusion
Plegridy® (peginterferon beta-1a subcutaneous or intramuscular injection)	Injection (self-administered)
Ponvory™ (ponesimod tablets)	Oral
Rebif® (interferon beta-1a subcutaneous injection)	Injection (self-administered)
Tascenso ODT™ (fingolimod orally disintegrating tablets)	Oral
Tecfidera® (dimethyl fumarate delayed-release capsules, generic)	Oral
Tysabri® (natalizumab intravenous infusion)	Intravenous infusion
Vumerity® (diroximel fumarate delayed-release capsules)	Oral
Zeposia® (ozanimod capsules)	Oral

CARECONTINUUM™

MEDICAL STEP MANAGEMENT POLICY

POLICY: Rituximab Products Medical Step Management Alternative Policy (Biosimilars Preferred)

- Riabni™ (rituximab-arrx intravenous infusion – Amgen)
- Rituxan® (rituximab intravenous infusion – Genentech)
- Rituxan Hycela™ (rituximab and hyaluronidase human subcutaneous injection – Biogen and Genentech/Roche)
- Ruxience™ (rituximab-pvvr intravenous infusion – Pfizer)
- Truxima® (rituximab-abbs intravenous infusion – Celltrion/Teva)

REVIEW DATE: 09/06/2023

OVERVIEW

Rituximab products are CD20-directed cytolytic antibodies.[1-5] The antigen CD20 is expressed on > 90% of B-cell non-Hodgkin's lymphomas. B-cells are thought to play a role in the pathogenesis of rheumatoid arthritis and associated chronic synovitis.

Riabni, Ruxience, and Truxima are approved as biosimilar to Rituxan intravenous, indicating no clinically meaningful differences in safety and effectiveness and the same mechanism of action, route of administration, dosage form, and strength as Rituxan intravenous. However, minor differences in clinically inactive components are allowed. At this time, only biosimilarity has been established, not interchangeability. Rituxan Hycela is a combination of rituximab and hyaluronidase human for subcutaneous administration. It contains the identical molecular antibody of rituximab available in Rituxan intravenous, but hyaluronidase has been added to facilitate systemic delivery.

POLICY STATEMENT

This Medical Step Management program has been developed to encourage the use of Preferred Products. For all medications (Preferred and Non-Preferred), the patient is required to meet the respective *Utilization Management Medical Policy* criteria. The program also directs the patient to the Preferred Product. Requests for Non-Preferred Products will be reviewed using the exception criteria (below). All approvals are provided for a duration as directed in the respective *Utilization Management Medical Policy* criteria.

*For Non-Preferred Products noted with **[eviCore]**, some indications and/or approval conditions are managed by eviCore healthcare for those clients who use eviCore for oncology and/or oncology-related reviews. Refer to the corresponding Utilization Management Medical Policy for affected indications. For these oncology and/or oncology-related conditions, a prior authorization review should be directed to eviCore at www.eviCore.com.*

Automation: None.

Preferred Product: Riabni, Ruxience, Truxima
Non-Preferred Products: Rituxan Intravenous, Rituxan Hycela

RECOMMENDED EXCEPTION CRITERIA

Non-Preferred Products	Exception Criteria
Rituxan Intravenous *[eviCore]*	**1.** Approve if the patient meets BOTH of the following (A and B): **A)** Patient meets the *Rituximab Intravenous Products Utilization Management Medical Policy* criteria; AND **B)** Patient meets ONE of the following (i or ii): **i.** Patient meets both of the following (a and b): **a)** Patient has tried one of Riabni, Ruxience, or Truxima; AND **b)** Patient cannot continue to use the Preferred medication due to a formulation difference in the inactive ingredient(s) [e.g., differences in stabilizing agent, buffering agent, and/or surfactant] which, according to the prescriber, would result in a significant allergy or serious adverse reaction; OR **ii.** Patient has already been started on or has previously received Rituxan Intravenous.
Rituxan Hycela	**1.** Approve if the patient meets BOTH of the following (A and B): **A)** Patient meets the *Oncology – Rituxan Hycela Utilization Management Medical Policy* criteria; AND **B)** Patient meets ONE of the following (i, ii, or iii): **i.** Patient has tried one of Riabni, Ruxience, or Truxima but, according to the prescriber, cannot continue to use this product; OR **ii.** Patient cannot use a Preferred medication due to an inability to obtain intravenous access; OR **iii.** Patient has already been started on or has previously received Rituxan Hycela.

REFERENCES

1. Rituxan® intravenous infusion [prescribing information]. South San Francisco, CA: Genentech; December 2021.
2. Ruxience™ intravenous infusion [prescribing information]. New York, NY: Pfizer; November 2021.
3. Truxima® intravenous infusion [prescribing information]. North Wales, PA: Teva/Celltrion; February 2022.
4. Rituxan Hycela™ subcutaneous injection [prescribing information]. South San Francisco, CA: Biogen and Genentech/Roche; June 2021.
5. Riabni™ intravenous infusion [prescribing information]. Thousand Oaks, CA: Amgen; June 2022.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/24/2022
Annual Revision	No criteria changes.	09/06/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Scenesse Utilization Management Medical Policy
- Scenesse® (afamelanotide subcutaneous implant – Clinuvel)

REVIEW DATE: 01/10/2024

OVERVIEW

Scenesse, a melanocortin 1 receptor agonist, is indicated for the treatment of **erythropoietic protoporphyria (EPP)**, to increase pain-free light exposure in adults with a history of phototoxic reactions.[1] Scenesse is a controlled-release dosage form that is implanted subcutaneously (SC). Scenesse should be administered by a healthcare professional. A single implant which contains 16 mg of afamelanotide is inserted SC above the anterior supra-iliac crest once every 2 months.

Disease Overview

Porphyrias are disorders caused by enzyme defects in heme biosynthesis.[2] There are at least eight different types of porphyrias, which are classified as cutaneous or acute depending on the specific enzyme that is deficient. EPP is a cutaneous porphyria characterized by extreme photosensitivity. It is estimated to occur in 2 to 5 in 1,000,000 individuals.[3]

EPP occurs due to excessive accumulation of protoporphyrin, a heme precursor. Classic EPP is autosomal recessive and occurs due to a defect in the enzyme ferrochelatase, the final enzymatic step in heme biosynthesis.[4] An X-linked subtype of EPP, often referred as X-linked protoporphyria (XLP), accounts for 2% to 10% of all EPP cases. This type develops due to a gain-of-function mutation in an upstream enzyme in heme biosynthesis, leading to excess protoporphyrin production.[3,4] The two subtypes share the same biochemical and clinical features, although females with XLP may be less severely affected. Diagnosis is confirmed by one or both of the following: 1) biochemically via markedly elevated free erythrocyte protoporphyrin, and/or 2) molecular genetic testing.[2,3]

In both EPP subtypes, protoporphyrin accumulation in superficial skin vessels leads to phototoxicity upon light exposure, resulting in the hallmark symptoms of burning, tingling, and itching, which often occur without visible damage.[2-4] Phototoxic pain is not responsive to analgesics, including narcotics; management is focused on prevention of phototoxic episodes.[3]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Scenesse. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Scenesse as well as the monitoring required for adverse events and long-term efficacy, approval requires Scenesse to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Scenesse is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Erythropoietic Protoporphyria (Including X-Linked Protoporphyria).** Approve for 1 year if the patient meets the following (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has a history of at least one porphyric phototoxic reaction; AND
   - **C)** The diagnosis is confirmed by at least one of the following (i or ii):
     - **i.** Free erythrocyte protoporphyrin level above the normal reference range for the reporting laboratory; OR
     - **ii.** Molecular genetic testing consistent with the diagnosis; AND
   - **D)** The agent is prescribed by or in consultation with a dermatologist, gastroenterologist, hepatologist, or physician specializing in the treatment of cutaneous porphyrias.

   Dosing. Approve a single Scenesse implant (containing 16 mg of afamelanotide) to be inserted subcutaneously no more frequently than once every 2 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Scenesse is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Scenesse® subcutaneous implant [prescribing information]. Menlo Park, CA: Clinuvel; October 2022.
2. Balwani M. Erythropoietic protoporphyria and X-linked protoporphyria. National Organization of Rare Disorders. Updated 2022. Available at: https://rarediseases.org/rare-diseases/erythropoietic-protoporphyria/. Accessed on December 28, 2023.
3. Balwani M, Bloomer J, Desnick R; Porphyrias Consortium of the NIH-Sponsored Rare Diseases Clinical Research Network. Erythropoietic protoporphyria, autosomal recessive. Updated September 7, 2017. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available at: https://www.ncbi.nlm.nih.gov/books/NBK100826/. Accessed on December 28, 2023.
4. Balwani M, Naik H, Anderson KE, et al. Clinical, biochemical, and genetic characterization of North American patients with erythropoietic protoporphyria and X-linked protoporphyria. *JAMA Dermatol.* 2017;153(8):789-796.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	No criteria changes.	01/11/2023
Annual Revision	No criteria changes.	01/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Sickle Cell Disease – Adakveo Utilization Management Medical Policy
- Adakveo® (crizanlizumab-tmca intravenous infusion– Novartis)

REVIEW DATE: 01/03/2024

OVERVIEW
Adakveo, a monoclonal antibody, is indicated to **reduce the frequency of vasoocclusive crises** due to **sickle cell disease** in patients ≥ 16 years of age.[1]

Clinical Efficacy
All of the patients included in the 52-week pivotal study (SUSTAIN) had a history of two to ten vasoocclusive crises in the previous 12 months.[2] Concomitant use of hydroxyurea was allowed during the study and approximately 60% of patients were on concomitant hydroxyurea therapy. At Week 52, compared with placebo, the annual rate of pain crises was significantly lower and the time to first and second sickle cell-related pain crises was significantly delayed in the Adakveo group. In addition, treatment with Adakveo decreased the annual rate of hospitalized days, compared with placebo.

Dosing Information
Adakveo is given by intravenous infusion over a period of 30 minutes at Week 0, Week 2, and every 4 weeks thereafter; the dose is 5 mg/kg.[1]

Guidelines
The American Society of Hematology guidelines for sickle cell disease: management of acute and chronic pain associated with sickle cell disease (2020) does not address the use of Adakveo.[3] The National Institutes of Health – National Heart, Lung, and Blood Institute issued the Evidence-Based Management of Sickle Cell Disease, Expert Panel Report in 2014.[4] These guidelines were published prior to the approval of Adakveo. Hydroxyurea has been shown to reduce the frequency of painful episodes, the incidence of acute coronary syndrome events, and the need for transfusions and hospitalizations. Hydroxyurea is recommended for use in most patients with sickle cell disease; however, it is not recommended for use in pregnant females or women who are breastfeeding. Females and males of reproductive potential are advised to use effective contraception during and after treatment with hydroxyurea.[4-6] Hydroxyurea can also cause myelosuppression and treatment should not be initiated in patients with depressed bone marrow function.[5,6]

POLICY STATEMENT
Prior Authorization is recommended for medical benefit coverage of Adakveo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Adakveo as well as the monitoring required for adverse events and long-term efficacy, approval requires Adakveo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Adakveo is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. Sickle Cell Disease. Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, and iv):

- **i.** Patient is ≥ 16 years of age; AND
- **ii.** Patient has had at least one sickle cell-related crisis in the previous 12-month period; AND
- **iii.** Patient meets ONE of the following (a, b, or c):
  - **a)** Patient is currently receiving a hydroxyurea product; OR
  - **b)** According to the prescriber, patient has tried a hydroxyurea product and has experienced inadequate efficacy or significant intolerance; OR
  - **c)** According to the prescriber, patient is not a candidate for hydroxyurea therapy; AND
    Note: Examples of patients who are not candidates for hydroxyurea therapy include patients who are pregnant or who are planning to become pregnant and patients with an immunosuppressive condition (such as cancer).
- **iv.** The medication is prescribed by or in consultation with a physician who specializes in sickle cell disease (e.g., a hematologist).

B) Patient is Currently Receiving Adakveo. Approve if the patient meets ALL of the following (i, ii, and iii):

- **i.** Patient is ≥ 16 years of age; AND
- **ii.** According to the prescriber, patient is receiving clinical benefit from Adakveo therapy; AND
  Note: Examples of clinical benefit include reduction in the number of vasoocclusive crises/sickle cell-related crises; delay in time to sickle cell-related crises; and reduction in the number of days in the hospital.
- **iii.** The medication is prescribed by or in consultation with a physician who specializes in sickle cell disease (e.g., a hematologist).

Dosing. Approve the following dosing regimens (A and B):

A) Up to 5 mg/kg given by intravenous infusion at Weeks 0 and 2; AND

B) Up to 5 mg/kg given by intravenous infusion for up to once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Adakveo is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Adakveo® intravenous infusion [prescribing information]. East Hanover, NJ: Novartis; September 2022.
2. Ataga KI, Kutlar J, Kanter K, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. *N Engl J Med*. 2017;376(5):429-439.
3. Brandow AM, Carroll CP, Creary S, et al. American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. *Blood Adv*. 2020;4:2656-2701.

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4. The National Institutes of Health – National Heart, Lung, and Blood Institute Evidence-Based Management of Sickle Cell Disease, Expert Panel Report 2014. Available at: https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf. Accessed on December 3, 2023.
5. Droxia® capsules [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; July 2021.
6. Siklos® tablets [prescribing information]. Bryn Mawr, PA: Medunik; November 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/07/2022
Annual Revision	No criteria changes.	01/03/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Site of Care Utilization Management Medical Policy

REVIEW DATE: 02/07/2024

OVERVIEW

For many disease states and medication therapies, infusion therapy in a lower-intensity setting, defined as a home infusion provider, at a provider's office, or an ambulatory infusion suite, is a safe and effective alternative to a higher intensity setting. For many patients, receiving infusion therapy in one of these lower-intensity settings is also preferred over therapy in a higher intensity setting such as a hospital or outpatient hospital setting.

POLICY STATEMENT

This policy provides clinical criteria for selection of patients for infusion therapy provided in a lower intensity setting and away from a higher intensity setting (i.e., hospital or hospital outpatient setting). Patients are assessed to ensure that a lower-intensity setting is clinically appropriate. Initial or loading doses of some drugs or biologics are administered in a hospital or outpatient hospital setting because additional monitoring is required for possible adverse reactions during initiation of therapy. This document provides clinical criteria for direction to a lower-intensity setting for drugs or biologics administered by a nurse.

Documentation: Documentation is required, as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

RECOMMENDED AUTHORIZATION CRITERIA

For agents listed in Table 1, infusion therapy will be directed to a lower-intensity setting, defined as a home infusion provider, at a provider's office, or an ambulatory infusion suite, unless ONE of the following are met (A or B):

A) Medications listed in Table 1 will be administered in a lower-intensity setting if none of the following apply (1, 2, 3, 4, or 5) [that is, if the patient meets any one of these situations, a lower-intensity setting is not appropriate]:

1. The patient's condition is clinically unstable such that immediate access to services in a hospital setting may be required **[documentation required]**: Approve for 3 months.
   Note: Examples of emergency access to services in a hospital include emergency resuscitation equipment and personnel, inpatient admission, or intensive care. Examples of clinical conditions may include fluid overload status or acute mental status changes.
2. The patient has physical or cognitive impairments such that immediate access to services in a hospital setting may be required: Approve for 1 year.
3. Patient is less than 18 years of age and a caregiver is not available to assist during administration of the drug or biologic: Approve for 1 year.
4. The patient has previously had a severe or potentially life-threatening adverse event with the currently prescribed drug, biologic, or a similar medication (e.g., anaphylaxis, seizure), such that immediate access to services in a hospital setting may be required **[documentation required]**: Approve for 1 year.

Note: Examples of a severe or potentially life-threatening adverse event include anaphylaxis and seizure.

5. According to the prescriber, the medication is not suitable for home infusion therapy AND there is not another lower-intensity setting (e.g., ambulatory infusion center or physician's office) within 50 miles of the patient's home that is able to administer the drug: Approve for 1 year.

B) Initial dose(s) or loading doses of some drugs/biologics may be administered in a higher-intensity setting (e.g., hospital, outpatient hospital infusion center) to allow for adequate transition time and prevent a delay in care. A limited number of doses for use in a higher intensity setting (i.e., hospital or outpatient hospital setting) will be authorized. See Table 1.
Note: After these dose(s) are given the therapy will be given in a lower-intensity setting, provided the patient does not have any of the circumstances listed in Criteria A above.

Table 1. Medications that can be Directed to a Lower-Intensity Setting.

Medication	Doses Prior to Use in a Lower-Intensity Setting	Notes
Alpha-1 Deficiency		
Alpha1-Proteinase Inhibitor (Human) intravenous infusion (Aralast® NP, Glassia®, Zemaira®)	--	Weight based dose administered once weekly. Warnings for hypersensitivity and anaphylactic reactions.
Amyloidosis		
Amvuttra™ (vutrisiran subcutaneous injection)	--	Administered by a healthcare professional once every 3 months.
Onpattro® (patisiran intravenous infusion)	Up to 2 doses	Administered by a healthcare professional once every 2 weeks. Warning for infusion-related reactions.
Tegsedi® (inotersen subcutaneous injection)	--	Boxed Warnings for thrombocytopenia and glomerulonephritis. Warnings for stroke, cervicocephalic arterial dissection, liver injury, and hypersensitivity reactions.
Asthma and Allergy		
Cinqair® (reslizumab intravenous infusion)	Up to 3 doses	Weight-based dose administered by a healthcare provider once every 4 weeks. Boxed Warning for anaphylaxis.
Fasenra® (benralizumab subcutaneous injection)	Up to 3 doses	Administered once every 4 weeks for 3 doses, then once every 8 weeks.
Nucala® (mepolizumab subcutaneous injection)	Up to 3 doses	Administered once every 4 weeks. Warning for hypersensitivity reactions.
Tezspire® (tezepelumab-ekko subcutaneous injection)	--	Administered once every 4 weeks. Warning for hypersensitivity reactions.
Xolair® (omalizumab subcutaneous injection)	Up to 4 doses	Administered once every 2 or 4 weeks. Boxed Warning for anaphylaxis.
Blood Cell Deficiency		
Aranesp® (darbepoetin alfa subcutaneous injection)	--	Treatment interval ranges from once weekly to once every 4 weeks. Boxed Warnings for increased risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence.
epoetin alfa injection (Epogen®, Procrit®, Retacrit®)	--	Treatment interval is once weekly or three times weekly. Boxed Warnings for increased risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence.
Mircera® (methoxy polyethylene glycol-epoetin beta intravenous infusion or subcutaneous injection)	--	Treatment interval is once weekly or once monthly.

Filgrastim Intravenous or Subcutaneous Products (Granix®, Neupogen®, Nivestym®, Releuko®, Zarxio®)	--	Administration varies. Warnings for fatal splenic rupture, acute respiratory distress syndrome, serious allergic reactions (including anaphylaxis), fatal sickle cell crises, glomerulonephritis, and thrombocytopenia.
Pegfilgrasim Subcutaneous Products (Neulasta®, Fulphila™, Fylnetra®, Nyvepria™, Stimufend®, Udenyca™, Ziextenzo™)	--	Administered once per chemotherapy cycle. Warnings for fatal splenic rupture, acute respiratory distress syndrome, serious allergic reactions (including anaphylaxis), fatal sickle cell crises, glomerulonephritis, and thrombocytopenia.
Leukine® (sargramostim intravenous infusion or subcutaneous injection)	--	Administration varies. Warning for hypersensitivity reaction, infusion-related reactions, effusions and capillary leak syndrome, and supraventricular arrhythmias.
Rolvedon™ (eflapegrastim-xnst subcutaneous injection)	--	Given once every 2 weeks.
Cancer		
Xgeva® (denosumab subcutaneous injection)	--	Maintenance dosing is once every 4 weeks. Some indications have initial dosing on Days 8 and 15 of the first month of therapy. Warnings for hypersensitivity reactions and severe symptomatic hypocalcemia.
Bone Modifiers		
Evenity® (romosozumab-aqqg subcutaneous injection)	--	Administered by a healthcare provider once every month for 12 months. Boxed Warning for risk of myocardial infarction, stroke, and cardiovascular death.
Prolia® (denosumab subcutaneous injection)	--	Given once every 6 months.
Zoledronic Acid (Reclast®, generic)	--	Administered once yearly or once every 2 years. Warning for renal impairment (monitor creatinine clearance before each dose).
Complement Inhibitors		
Soliris® (eculizumab intravenous infusion)	--	Given weekly for 4 doses followed by a 5th dose 1 week later, then once every 2 weeks thereafter. Boxed Warning for serious meningococcal infections. Warnings for infusion-related reactions. Available under a Risk Evaluation and Mitigation Strategy program.
Ultomiris® (ravulizumab-cwvz intravenous infusion)	--	Given as a loading dose followed by a maintenance dose 2 weeks later, then once every 8 weeks. Boxed Warning for serious meningococcal infections. Warnings for other infections and infusion-related reactions.
Endocrine Disorders		
Aveed® (testosterone undecanoate intramuscular injection)	Up to 2 doses	Given at Weeks 0 and 4, then once every 10 weeks thereafter. Boxed Warnings for serious pulmonary oil microembolism reactions and anaphylaxis. Warnings for venous thromboembolism and edema.
Crysvita® (burosumab-twza subcutaneous injection)	--	Weight-based dosing given every 2 to 4 weeks. Warnings for hypersensitivity, and hyperphosphatemia and risk of nephrocalcinosis.
Fensolvi® (leuprolide acetate subcutaneous injection)	1 dose	One injection given by a healthcare provider once every 6 months. Warnings for psychiatric events, convulsions, and pseudotumor cerebri.
Lupron Depot (leuprolide acetate for depot suspension)	--	One intramuscular injection given every month or every 3 months.
Triptodur™ (triptorelin extended-release injectable suspension)	1 dose	One intramuscular injection given every 6 months.
Sandostatin® LAR Depot (octreotide acetate intramuscular injection)	--	Administered by a healthcare provider once every 4 weeks. Warnings for cholelithiasis, glucose metabolism, thyroid function, and cardiac function.
Signifor® LAR (pasireotide intramuscular injection)	--	Administered by a healthcare provider once every 4 weeks. Warnings for hyperglycemia, diabetes, and ketoacidosis; bradycardia and QT prolongation; liver test elevations; cholelithiasis; and pituitary hormone deficiencies.
Somatuline® Depot (lanreotide deep subcutaneous injection)	--	Administered by a healthcare provider once every 4 weeks.

Lanreotide subcutaneous injection		Warnings for cholelithiasis, hyperglycemia and hypoglycemia, cardiovascular abnormalities, and thyroid function abnormalities.
Enzyme Deficiencies		
Aldurazyme (laronidase intravenous infusion)**	Minimum of 3 months, on a stable dose**	Weight-based dose administered weekly. Boxed Warning regarding anaphylaxis.
Cerezyme® (imiglucerase intravenous infusion)**	Minimum of 3 months, on a stable dose**	Weight-based dose administered up to three times per week.
Elaprase® (idursulfase intravenous infusion)**	Minimum of 3 months, on a stable dose**	Weight-based dose administered once weekly. Boxed Warning regarding anaphylaxis.
Elelyso® (taliglucerase alfa intravenous infusion)**	Minimum of 3 months, on a stable dose**	Weight-based dose administered once weekly. Warning for anaphylaxis, allergic reactions.
Elfabrio® (pegunigalsidase alfa intravenous infusion)	Minimum of 3 months, on a stable dose**	Weight-based dose administered once every 2 weeks. Boxed Warning for anaphylaxis and hypersensitivity reactions. Warning for infusion reactions and membranoproliferative glomerulonephritis.
Fabrazyme® (afalsidase beta intravenous infusion)**	Minimum of 3 months, on a stable dose**	Weight-based dose administered once every 2 weeks. Warning for anaphylaxis, hypersensitivity reactions, and infusion reactions.
Kanuma (sebelipase alfa intravenous infusion)**	Minimum of 3 months, on a stable dose**	Weight-based dose administered once a week or once every 2 weeks. Warning for anaphylaxis, severe hypersensitivity.
Lumizyme® (alglucosidase alfa intravenous infusion)**	Minimum of 3 months, on a stable dose**	Weight-based dose administered once every 2 weeks. Boxed Warnings regarding anaphylaxis, hypersensitivity and immune-mediated reactions, and cardiorespiratory failure.
Mepsevii® (vestronidase alfa-vjbk intravenous infusion)**	Minimum of 3 months, on a stable dose**	Weight-based dose administered once every 2 weeks. Boxed Warning regarding anaphylaxis.
Naglazyme® (galsulfase intravenous infusion)**	Minimum of 3 months, on a stable dose**	Weight-based dose administered once weekly. Warnings for anaphylaxis, hypersensitivity reactions, immune-mediated reactions, acute cardiorespiratory failure, acute respiratory complications, and infusion reactions.
Nexviazyme™ (avalglucosidase alfa-ngpt intravenous infusion)**	Minimum of 3 months, on a stable dose**	Weight-based dose administered once every 2 weeks. Boxed Warnings for severe hypersensitivity reactions, infusion-associated reactions, and acute cardiorespiratory failure.
Pombiliti™ (cipaglucosidase alfa intravenous infusion)	Minimum of 3 months, on a stable dose**	Weight-based dose administered once every other week. Boxed Warning regarding hypersensitivity reactions including anaphylaxis, infusion-associated reactions, and risk of acute cardiorespiratory failure.
Revcovi® (elapegademase-lvir intramuscular injection)	Up to 4 doses	Weight-based dose administered once weekly. Warning for injection site bleeding in those with thrombocytopenia.
Vimizim (elosulfase alfa intravenous infusion)**	Minimum of 3 months, on a stable dose**	Weight-based dose administered once every week. Boxed Warning regarding anaphylaxis.
VPRIV® (velaglucerase alfa intravenous infusion)**	Minimum of 3 months, on a stable dose**	Weight-based dose given every 2 weeks.
Xenpozyme™ (olipudase alfa-rpcp intravenous infusion)	Minimum of 3 months, on a stable dose**	Weight-based dose administered once every 2 weeks. Boxed Warning for severe hypersensitivity reactions, including anaphylaxis.
Hematology		
Altuviiio™ (antihemophilic factor [recombinant] Fc-VWF-XTEN fusion protein-ehtl intravenous injection)	--	Dosing is individualized. Contraindicated in patients who have previously experienced severe hypersensitivity reactions, including anaphylaxis, to Altuviiio.
Nplate® (romiplostim subcutaneous injection)	Must be on a stable maintenance dose prior to a	Weight-based maintenance dose administered once every week.

	lower-intensity setting.	
Corifact® (Factor XIII Concentrate [human] intravenous infusion)	Up to 3 doses	Adjust dose to maintain 5% to 20% trough level of factor XIII activity. Most patients do not require dose adjustment for prophylaxis (i.e., 40 IU/kg is effective for most patients). Warning for hypersensitivity reaction and thrombotic events.
Enjaymo™ (sutimlimab-jome intravenous infusion)	Up to 4 doses	Weight-based weekly dosing for 2 weeks, then once every 2 weeks. Warning for infusion-related reactions.
Ceprotin® (protein C concentrate [human] intravenous infusion)	--	Weight-based dose given every 28 days.
RiaSTAP® (fibrinogen concentrate [human] intravenous infusion)	--	Weight-based dose given every 28 days.
Tretten® (coagulation Factor XIII A-Subunit [recombinant] intravenous infusion)	--	Weight-based dose given every 28 days.
Vonvendi® (von Willebrand factor [recombinant] intravenous infusion)	--	Dosing is individualized.
Factor VIII Products Extended Half-Life Products: Adynovate, Eloctate, Esperoct, Jivi Standard Half-Life Products: Advate, Afstyla, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, Xyntha Plasma-Derived Standard Half-Life Products: Hemofil M, Alphanate, Humate-P, Koate, Wilate	--	Dosing is individualized.
Factor IX Products Extended Half-Life Products: Alprolix, Idelvion, Rebinyn Standard Half-Life Products: BeneFIX, Ixinity, Rixubis Plasma-Derived Standard Half-Life Products: AlphaNine SD, Mononine, Profilnine	--	Dosing is individualized.
NovoSeven® RT (coagulation Factor VIIa [recombinant] intravenous infusion)	--	Weight-based dose given every 28 days.
FEIBA® (anti-inhibitor coagulant complex intravenous infusion)	--	Weight-based dose given every 28 days.
Hemlibra® (emicizumab-kxwh subcutaneous injection)	--	Dosing is individualized.
Hereditary Angioedema		
Berinert, Cinryze, icatibant (Firazyr, generic), Haegarda, Kalbitor, Ruconest, Takhzyro	--	Dosing is individualized.
Gout		
Krystexxa® (pegloticase intravenous infusion)	Up to 2 doses	Administered once every two weeks. Boxed Warning for anaphylaxis and infusion reactions, glucose-6-phosphate dehydrogenase deficiency associated hemolysis, and methemoglobinemia. Warning for exacerbation of heart failure.
Hepatology		
Givlaari® (givosiran subcutaneous injection)	--	Weight-based dose administered by a healthcare professional once monthly.

		Warnings for anaphylactic reaction, hepatic toxicity, renal toxicity, and injection site reactions.
Human Immunodeficiency Virus		
Apretude® (cabotegravir intramuscular injection)	Up to 2 doses	Administered by a healthcare provider and given monthly for two consecutive months followed by maintenance dosing once every 2 months. Boxed Warning for drug resistance. Warnings for hypersensitivity reactions and hepatotoxicity.
Cabenuva® (cabotegravir extended-release intramuscular injection; rilpivirine extended-release intramuscular injection)	Up to 2 doses	Injected monthly or every 2 months. Must be administered by a healthcare provider by gluteal intramuscular injection.
Sunlenca® (lenacapavir subcutaneous injection)	1 dose	Maintenance dosing is every 6 months.
Trogarzo® (ibalizumab-uiyk intravenous infusion)	--	Administered by a healthcare provider as a loading dose followed by a maintenance dose every 2 weeks thereafter.
Immune Deficiency		
Immune Globulin – Intravenous (e.g., Asceniv, Bivigam, Flebogamma, Gammagard Liquid, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Octagam, Panzyga, Privigen Liquid)	--	Dose is adjusted to achieve the desired trough levels and clinical response. Boxed Warning due to an associated risk of renal dysfunction, acute renal failure, osmotic nephropathy, and mortality.
Immune Globulin – Subcutaneous (e.g., Cutaquig, Cuvitru***, Gammagard Liquid, Gammaked, Gamunex-C, Hizentra***, HyQvia***, Xembify)	--	Dose is adjusted to achieve the desired trough levels and clinical response. Boxed Warning for thrombosis.
Cytogam® (cytomegalovirus immune globulin [human] intravenous infusion)	--	Weight-based dose administered within 72 hours of transplant, then at Weeks 2, 4, 6, 8, 12, and 16 post-transplant.
Inflammatory Conditions		
Actemra® (tocilizumab intravenous infusion)	Up to 2 doses	Dose every 2 or 4 weeks. Boxed Warning for serious infection.
Cimzia® (certolizumab pegol subcutaneous injection)	--	First three doses given every 2 weeks, then given every 2 or 4 weeks thereafter. Boxed Warnings for serious infections and malignancy.
Cosentyx® (secukinumab intravenous infusion)	Up to 1 dose	Weight-based dose given once every 4 weeks. Warnings for infections, hypersensitivity reactions, inflammatory bowel disease, eczematous eruptions, risk of hypersensitivity in latex-sensitive individuals.
Entyvio® (vedolizumab intravenous infusion)	Up to 3 doses	First three doses given at 0, 2, and 6 Weeks then every 8 weeks thereafter. Warnings for infusion-related reactions and hypersensitivity reactions, infections, and progressive multifocal leukoencephalopathy.
Ilaris® (canakinumab subcutaneous injection)***	--	Nursing provided by the manufacturer. Weight-based dosing administered every 4 to 8 weeks. Warning for infection.
Ilumya® (tildrakizumab-asmn subcutaneous injection)	Up to 2 doses	Administered by a healthcare provider at Weeks 0 and 4, then every 12 weeks thereafter. Warning for hypersensitivity and infection.
Infliximab Intravenous Products (Avsola®, Inflectra®, Remicade®, Renflexis®, infliximab)	Up to 3 doses	Weight-based dose given, first doses at 0, 2, and 6 weeks, then every 6 to 8 weeks. Boxed Warning for serious infection and malignancy. If transitioning to accelerated (over 1 hour) /rapid (over 30 minute) infliximab infusions MUST have a minimum of 3 uneventful infusions in a controlled setting prior to a lower-intensity setting.
Orencia® (abatacept intravenous infusion)	Up to 3 doses	Weight-based dose given at Week 0, 2, and 4, then every 4 weeks thereafter. Warning for hypersensitivity and anaphylaxis and serious infections.

Simponi Aria® (golimumab intravenous infusion)	Up to 2 doses	Weight-based dosing given at Weeks 0 and 4, then every 8 weeks thereafter. Boxed Warnings for serious infections and malignancy.
Inflammatory/Oncology		
Rituximab Intravenous Products (Rituxan, Riabni, Ruxience, Truxima)	Up to 3 doses	Dose varies by indication. Boxed Warnings for fatal infusion-related reactions, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy.
Lupus		
Benlysta® (belimumab intravenous infusion)	Up to 3 doses	First three doses given every 2 weeks, then given every 4 weeks thereafter. Warnings for serious infection, progressive multifocal leukoencephalopathy, hypersensitivity (including anaphylaxis), and depression/suicidality.
Saphnelo® (anifrolumab-fnia intravenous infusion)	Up to 2 doses	Given once every 4 weeks. Warnings for serious infections, hypersensitivity reactions, including anaphylaxis, and malignancy.
Metabolic Disorders		
Evkeeza® (evinacumab-dgnb intravenous infusion)	Up to 2 doses	Given as a weight-based infusion ever 4 weeks. Warning for serious hypersensitivity reactions.
Leqvio® (inclisiran subcutaneous injection)	Up to 2 doses	Given as a subcutaneous injection by a healthcare provider at baseline and Month 3, then every 6 months thereafter.
Nulibry® (fosdenopterin intravenous infusion)	Up to 12 doses	Given as a weight-based dose once daily.
Oxlumo® (lumasiran subcutaneous injection)	Up to 2 doses	Given as a weight-based dose by a healthcare provider once every month.
Migraine		
Vyepti® (eptinezumab-jjmr intravenous infusion)	1 dose	Given as by a healthcare provider once every month. Warning for hypersensitivity reactions.
Miscellaneous Conditions		
Uplizna® (inebilizumab-cdon intravenous infusion)	Up to 2 doses	Administered at Week 0 and 2 followed by subsequent infusion 6 months after the initial infusion, then once every 6 months thereafter. Warnings for infusion reactions and infections.
Multiple Sclerosis		
Lemtrada® (alemtuzumab intravenous infusion)	Up to 5 doses	Given as a first course (with a dose given on 5 consecutive days) and a second course 12 months after the first course (with a dose given on 3 consecutive days) with repeat subsequent treatment courses administered as needed at least 12 months after the prior course. Boxed Warnings for autoimmunity, infusion reactions, stroke, and malignancies. Warnings for glomerular nephropathies, hemophagocytic lymphohistiocytosis, thrombotic thrombocytopenic purpura, acquired hemophilia A, infections, and progressive multifocal leukoencephalopathy.
Briumvi™ (ublituximab-xiiy intravenous infusion)	Up to 2 doses	First dose given and then a second dose 2 weeks later, and then one dose every 6 months.
Ocrevus® (ocrelizumab intravenous infusion)	Up to 2 doses	First dose given and then a second dose 2 weeks later, and then one dose every 6 months. Warnings for infusion reactions, infections, progressive multifocal leukoencephalopathy, and malignancies.
Tysabri® (natalizumab intravenous infusion)	Up to 3 doses	Administered once every 4 weeks. Boxed Warning for progressive multifocal leukoencephalopathy. Warnings for hepatotoxicity, hypersensitivity reactions (including anaphylaxis), and thrombocytopenia.
Neurological Conditions		
Radicava® (edaravone intravenous infusion)	Up to 14 doses	Given once daily for 14 days followed by a 14-day drug-free period; subsequent cycles daily use for 10 days out of a 14-day period followed by 14-day drug-free periods. Warnings for hypersensitivity reactions and sulfite allergy.
Rystiggo® (rozanolixizumab-noli subcutaneous infusion)	Up to 4 doses	Weight-based dose given by a healthcare provider once weekly. Aseptic meningitis and hypersensitivity reactions have been reported.
Vyvgart® (efgartigimod alfa-fcab intravenous infusion)	--	Given once weekly for 4 weeks. Subsequent cycles are based on clinical evaluation. Warnings for hypersensitivity reactions.

Vyvgart® Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection)	--	Given once weekly for 4 weeks. Subsequent cycles are based on clinical evaluation. Warnings for hypersensitivity reactions.
Ophthalmic Conditions		
Tepezza® (teprotumumab-trbw intravenous infusion)	--	Weight-based dosing administered once every 3 weeks. Warnings for infusion reactions, exacerbation of preexisting inflammatory bowel disease, and hyperglycemia.
Respiratory Syncytial Virus		
Synagis® (palivizumab intramuscular injection)	1 dose	Weight-based dose administered monthly. Warnings for anaphylaxis and anaphylactic shock.
Sickle Cell Disease		
Adakveo® (crizanlizumab-tmca intravenous infusion)	Up to 2 doses	Weight-based dose given at Week 0 and 2, then every 4 weeks thereafter. Warnings for infusion-related reactions.
Transplant		
Nulojix® (belatacept intravenous infusion)	Up to 6 doses	Maintenance starts at end of Week 16. Six doses would have been given prior to maintenance. Boxed Warnings for post-transplant lymphoproliferative disorder, other malignancies, and serious infections. Warning for progressive multifocal leukoencephalopathy.

** Minimum of 3 months, on a stable dose, with uneventful Enzyme Replacement Therapy (ERT) infusions in a controlled setting required prior to a lower-intensity setting; *** Administration training must be done via the manufacturer program, then can be supported at a lower-intensity site after training is complete.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	This policy was changed to direct to a lower-intensity setting, defined as a home infusion provider, a provider's office, or an ambulatory infusion suite (previously directed specifically to the home setting). The approval duration for a patient who is clinically unstable such that immediate access to services in a hospital setting may be required was changed to 3 months (previously was 1 year). An exception to allow therapy at a higher intensity setting (e.g., hospital or outpatient hospital setting) was added for a patient who, according to the prescriber, was not a candidate for home infusion therapy and there was not access to another lower-intensity setting within 50 miles of the patient's home. • The following drugs and number of override doses approved prior to a lower-intensity setting were added to the policy: Amvuttra (up to 2 doses), Onpattro (up to 2 doses), Cinqair (up to 3 doses), Fasenra (up to 3 doses), Nucala (up to 3 doses), Tezspire (up to 3 doses), Xolair (up to 4 doses), Evenity (up to 2 doses), Aveed (up to 2 doses) Fensolvi (up to 1 dose), Lupron Depot (1 dose), Triptodur (1 dose), Nexviazyme (minimum of 6 months of therapy), Revcovi (up to 4 doses), Xenpozyme (minimum of 6 months of therapy), Enjaymo (up to 4 doses), Krystexxa (up to 2 doses), Apretude (up to 2 doses), Cabenuva (up to 2 doses), Sunlenca (1 dose), Ilumya (up to 2 doses), Skyrizi intravenous (1 dose), rituximab products (up to 3 doses), Saphnelo (up to 2 doses), Evkeeza (up to 2 doses), Leqvio (up to 2 doses), Nulibry (up to 12 doses), Oxlumo (up to 2 doses), Vyepti (1 dose), Uplizna (up to 2 doses), Lemtrada (up to 5 doses), Briumvi (up to 2 doses), Tysabri (up to 3 doses), Radicava intravenous (up to 14 doses), Vyvgart (up to 2 doses), Synagis (1 dose), Adakveo (up to 2 doses). • The following drugs with no override doses prior to direction to a lower-intensity setting were added to the policy: Mircera, Releuko, Fylnetra, Nyvepria, Stimufend, Rolvedon, Bivigam, Flebogamma, Prolia, zolendronic acid (Reclast, generic), RiaSTAP. • The following drugs have override doses added prior to approval in a lower-intensity setting (previously was 0 doses): Actemra intravenous (up to 2 doses), Cimzia (up to 3 doses), Orencia intravenous (up to 3 doses), Simponi Aria (up to 3 doses), and Trogarzo (up to 2 doses). • For the following drugs, the number of doses approved prior to approval was changed to be a minimum of 6 months of therapy: Aldurazyme (previously was	07/05/2023

	up to 6 doses), Cerezyme (previously was up to 3 doses), Elaprase (previously was up to 6 doses), Elelyso (previously was up to 4 doses), Fabrazyme (previously was up to 4 doses), Kanuma (previously was up to 6 doses), Mepsevii (previously was up to 8 doses), Naglazyme (previously was up to 6 doses), Vimizim (previously was up to 6 doses), and VPRIV (previously was up to 3 doses). • The following drugs were removed from the policy and are no longer targeted for Site of Care: Forteo, Tymlos, Myalept, Signifor, Mozobil, DDAVP, Stimate, Actemra subcutaneous, Siliq, Simponi subcutaneous, Stelara subcutaneous, Taltz, Tremfya, Duopa, Apokyn, epoprostenol products, and treprostinil products.	
Selected Revision	The following changes were made: • The number of doses prior to use in a lower-intensity setting was changed to zero doses for the following medications: Amvuttra (was up to 2 doses), Tegsedi (was up to 4 doses), Tezspire (was up to 3 doses), Evenity (was up to 2 doses), Soliris (was up to 5 doses), Ultomiris (was up to 2 doses), Lupron Depot (was 1 dose), Trogarzo (was up to 2 doses), Cimzia (was up to 3 doses), Ilaris (was up to 3 doses), Vyvgart (was up to 2 doses), and Lanreotide SC injection (previously not addressed in the policy). • For Aransep, it was clarified that this policy only applies to subcutaneous administration. • Simponi Aria was changed to allow up to 2 doses prior to use in a lower-intensity setting (previously was up to 3 doses). • Skyrizi IV was removed from targeting for induction therapy. • The following medications were changed to allow a minimum of 3 months on a stable dose (previously was a minimum of 6 months of therapy): Aldurazyme, Cerezyme, Elaprase, Elelyso, Fabrazyme, Kanuma, Lumizyme, Mepsevii, Naglazyme, Nexviazyme, Vimizim, VPRIV, and Xenpozyme.	09/13/2023
Early Annual Revision	The exception for when the patient's medical status or therapy requires enhanced monitoring that cannot be provided in a lower-intensity setting was removed. The exception for when the patient has a history of cardiac or pulmonary conditions that may increase the risk of severe adverse reactions was removed. The exception for a patient who has physical or cognitive impairments was reworded to apply to those that may require immediate access to services in a hospital setting (previously worded as a lower-intensity setting would present an unnecessary health risk). The exception for a patient with a severe or potentially life-threatening adverse event was reworded to apply to those who may require immediate access to services in a hospital setting (previously worded as the adverse event cannot be managed using premedication in a lower-intensity setting). Documentation requirements were added for when the patient's condition is clinically unstable such that immediate access to services in a hospital setting may be required, and when the patient has previously had a severe or potentially life-threatening adverse event with the prescribed agent. The following medications were added to allow override doses at a lower-intensity setting: Rystiggo (up to 4 doses), Cosentyx intravenous (up to 1 dose), Altuviiio (no override doses), Vyvgart Hytrulo (no override doses), Elfabrio (a minimum of 3 months on a stable dose), Pombility (a minimum of 3 months on a stable dose).	02/07/2024

CARECONTINUUM

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Somatostatin Analogs – Lanreotide Products Utilization Management Medical Policy
- Lanreotide subcutaneous injection – Cipla
- Somatuline® Depot (lanreotide subcutaneous injection – Ipsen)

REVIEW DATE: 05/15/2024

OVERVIEW

The lanreotide products are somatostatin analogs indicated for the following uses:[1,2]

- **Acromegaly**, in patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy, is not an option. The goal of treatment in acromegaly is to reduce growth hormone and insulin-like growth factor-1 levels to normal.
- **Gastroenteropancreatic neuroendocrine tumors (GEP-NETs)**, in adult patients with unresectable, well or moderately differentiated, locally advanced or metastatic GEP-NETs to improve progression-free survival.

Additionally, Somatuline Depot is indicated for **carcinoid syndrome**, in adult patients.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for **neuroendocrine and adrenal tumors** (version 1.2023 – August 2, 2023) recommend Somatuline Depot for the management of carcinoid syndrome; tumors of the gastrointestinal tract, lung, thymus (carcinoid tumors), and pancreas (including glucagonomas, gastrinomas, VIPomas, insulinomas); pheochromocytomas; and paragangliomas.[3] Patients who have local unresectable disease and/or distant metastases and clinically significant tumor burden or progression should be started on therapy with a somatostatin analog to potentially control tumor growth.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of lanreotide products. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with lanreotide products as well as the monitoring required for adverse events and long-term efficacy, approval requires lanreotide products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

*Indications and/or approval conditions noted with **[EviCore]** are managed by EviCore healthcare for those clients who use EviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to EviCore at www.EviCore.com.*

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of lanreotide products is recommended in those who meet one of the following criteria:

I. Coverage of Somatuline Depot is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. Acromegaly. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

A) Patient meets ONE of the following (i, ii, or iii):

i. Patient has had an inadequate response to surgery and/or radiotherapy; OR

ii. Patient is NOT an appropriate candidate for surgery and/or radiotherapy; OR

iii. Patient is experiencing negative effects due to tumor size (e.g., optic nerve compression); AND

B) Patient has (or had) a pre-treatment (baseline) insulin-like growth factor-1 (IGF-1) level above the upper limit of normal based on age and gender for the reporting laboratory; AND

Note: Pre-treatment (baseline) refers to the IGF-1 level prior to the initiation of any somatostatin analog (e.g., Mycapssa [octreotide delayed-release capsules], an octreotide acetate injection product [e.g., Bynfezia Pen, Sandostatin {generics}, Sandostatin LAR Depot], Signifor LAR [pasireotide injection], Somatuline Depot [lanreotide injection], dopamine agonist [e.g., cabergoline, bromocriptine], or Somavert [pegvisomant injection]). Reference ranges for IGF-1 vary among laboratories.

C) The medication is prescribed by or in consultation with an endocrinologist.

Dosing. Approve up to 120 mg administered subcutaneously no more frequently than once every 4 weeks.

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2. Carcinoid Syndrome. *[EviCore]* Approve for 1 year if the medication is prescribed by or in consultation with an oncologist, endocrinologist, or gastroenterologist.

Dosing. Approve up to 120 mg administered subcutaneously no more frequently than once every 4 weeks.

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3. Neuroendocrine Tumor(s) [NETs] of the Gastrointestinal Tract, Lung, Thymus (Carcinoid Tumors), and Pancreas (including glucagonomas, gastrinomas, vasoactive intestinal peptides-secreting tumors [VIPomas], insulinomas). *[EviCore]* Approve for 1 year if the medication is prescribed by or in consultation with an oncologist, endocrinologist, or gastroenterologist.

Dosing. Approve up to 120 mg administered subcutaneously no more frequently than once every 4 weeks.

Other Uses with Supportive Evidence

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4. Pheochromocytoma and Paraganglioma. *[EviCore]* Approve for 1 year if the medication is prescribed by or in consultation with an endocrinologist, oncologist, or neurologist.

Dosing. Approve up to 120 mg administered subcutaneously no more frequently than once every 4 weeks.

II. Coverage of lanreotide subcutaneous injection is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Acromegaly. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **A)** Patient meets ONE of the following (i, ii, or iii):
  - **i.** Patient has had an inadequate response to surgery and/or radiotherapy; OR
  - **ii.** Patient is NOT an appropriate candidate for surgery and/or radiotherapy; OR
  - **iii.** Patient is experiencing negative effects due to tumor size (e.g., optic nerve compression); AND
- **B)** Patient has (or had) a pre-treatment (baseline) insulin-like growth factor-1 (IGF-1) level above the upper limit of normal (ULN) based on age and gender for the reporting laboratory; AND
  Note: Pre-treatment (baseline) refers to the IGF-1 level prior to the initiation of any somatostatin analog (e.g., Mycapssa [octreotide delayed-release capsules], an octreotide acetate injection product [e.g., Bynfezia Pen, Sandostatin {generics}, Sandostatin LAR Depot], Signifor LAR [pasireotide injection], Somatuline Depot [lanreotide injection], dopamine agonist [e.g., cabergoline, bromocriptine], or Somavert [pegvisomant injection]). Reference ranges for IGF-1 vary among laboratories.
- **C)** The medication is prescribed by or in consultation with an endocrinologist.

Dosing. Approve up to 120 mg administered subcutaneously no more frequently than once every 4 weeks.

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2. Neuroendocrine Tumor(s) [NETs] of the Gastrointestinal Tract, Lung, Thymus (Carcinoid Tumors), and Pancreas (including glucagonomas, gastrinomas, vasoactive intestinal peptides-secreting tumors [VIPomas], insulinomas). ***[EviCore]*** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist, endocrinologist, or gastroenterologist.

Dosing. Approve up to 120 mg administered subcutaneously no more frequently than once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of lanreotide products is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Somatuline® Depot injection [prescribing information]. Basking Ridge, NJ: Ipsen; February 2023.
2. Lanreotide subcutaneous injection [prescribing information]. Warren, NJ: Cipla; September 2023.
3. The NCCN Neuroendocrine and Adrenal Tumors Clinical Practice Guidelines in Oncology (version 1.2023 – August 2, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 10, 2024.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/16/2023
Annual Revision	No criteria changes.	05/15/2024

CARECONTINUUM

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Somatostatin Analogs – Lutathera Utilization Management Medical Policy
- Lutathera® (lutetium Lu 177 dotatate intravenous infusion – Advanced Accelerator Applications USA)

REVIEW DATE: 05/15/2024

OVERVIEW

Lutathera, a radiolabeled somatostatin analog, is indicated in adult and pediatric patients ≥ 12 years of age for the treatment of somatostatin receptor-positive **gastroenteropancreatic neuroendocrine tumors** (NETs), including foregut, midgut, and hindgut neuroendocrine tumors.[1] The recommended dose of Lutathera is 7.4 gigabecquerel (GBq) [200 millicuries {mCi}] administered intravenously over 30 to 40 minutes, once every 8 weeks for a total of four doses.

Guidelines

According to the National Comprehensive Cancer Network (NCCN) guidelines for **neuroendocrine and adrenal tumors** (version 1.2023 – August 2, 2023), Lutathera may be considered for bronchopulmonary NETs, and thymus NETs if somatostatin receptor-positive and disease progression on an octreotide acetate injection product (e.g., Bynfezia Pen™, Sandostatin® [generics], Sandostatin® LAR Depot) or Somatuline® Depot (lanreotide injection). Somatostatin receptor-positive tumors are detected by somatostatin receptor-positive imaging (e.g., Gallium-68 dotatate imaging [positron emission tomography {PET}/computed tomography {CT} or PET/magnetic resonance imaging {MRI}] or somatostatin receptor-positive scintigraphy). Lutathera is recommended for tumors that are locoregional advanced disease and/or distant metastases. For pheochromocytomas or paragangliomas the same recommendations are made with the exception of using Lutathera in locally unresectable disease without prior use of an octreotide acetate injection product or Somatuline Depot.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Lutathera. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lutathera as well as the monitoring required for adverse events and long-term efficacy, approval requires Lutathera to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lutathera is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Neuroendocrine Tumors (NETs) of the Gastrointestinal Tract, Lung, Thymus (Carcinoid Tumors), and Pancreas.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 12 years of age; AND
   - **B)** Patient has locally advanced or metastatic disease; AND
   - **C)** Patient has somatostatin receptor-positive tumor as detected by somatostatin receptor-based imaging; AND
     Note: Examples of somatostatin receptor-based imaging include Gallium-68 dotatate imaging (positron emission tomography [PET]/computed tomography or PET/magnetic resonance imaging) or somatostatin receptor scintigraphy.
   - **D)** Patient has progressed on an octreotide acetate injection product (e.g., Bynfezia Pen, Sandostatin [generic], Sandostatin LAR Depot) or Somatuline Depot (lanreotide injection); AND
   - **E)** Lutathera is prescribed by or in consultation with an oncologist, radiologist, or endocrinologist.

   Dosing. Approve up to 7.4 GBq [200 mCi] administered intravenously no more frequently than once every 8 weeks for a maximum of 4 doses.

Other Uses with Supportive Evidence

2. **Pheochromocytoma and Paraganglioma.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has locally unresectable disease or distant metastases; AND
   - **C)** Patient has somatostatin receptor-positive tumor as detected by somatostatin receptor-based imaging; AND
     Note: Examples of somatostatin receptor-based imaging include Gallium-68 dotatate imaging (positron emission tomography [PET]/computed tomography or PET/magnetic resonance imaging) or somatostatin receptor scintigraphy.
   - **D)** Lutathera is prescribed by or in consultation with an oncologist or radiologist.

   Dosing. Approve up to 7.4 GBq [200 mCi] administered intravenously no more frequently than once every 8 weeks for a maximum of 4 doses.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lutathera is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Lutathera® intravenous infusion [prescribing information]. Millburn, NJ: Advanced Accelerator Applications USA; April 2024.
2. The NCCN Neuroendocrine and Adrenal Tumors Clinical Practice Guidelines in Oncology (version 1.2023 – August 2, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 10, 2024.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/16/2023
Early Annual Revision	**Neuroendocrine Tumors (NETs) of the Gastrointestinal Tract, Lung, Thymus (Carcinoid Tumors), and Pancreas:** The age requirement was changed from ≥ 18 to ≥ 12 years of age. There were no other changes to the criteria.	05/15/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Somatostatin Analogs – Sandostatin LAR Depot Utilization Management Medical Policy
- Sandostatin® LAR Depot (octreotide acetate intramuscular injection – Novartis)

REVIEW DATE: 05/15/2024

OVERVIEW

Sandostatin LAR Depot, a somatostatin analog, is indicated for the following uses:[1]

- **Acromegaly**, in patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy, is not an option. The goal of treatment in acromegaly is to reduce growth hormone and insulin-like growth factor-1 levels to normal.
- **Carcinoid tumors**, in patients with severe diarrhea and flushing episodes associated with metastatic carcinoid tumors.
- **Vasoactive intestinal peptide tumors (VIPomas)**, in patients with profuse watery diarrhea associated with vasoactive intestinal peptide (VIP)-secreting tumors.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines support use of Sandostatin LAR Depot in multiple conditions.

- **Central Nervous System Cancers:** Guidelines (version 1.2023 – March 24, 2023) recommend Sandostatin LAR Depot for the treatment of meningiomas that recur despite surgery and/or radiation therapy, or are not amenable to treatment with surgery or radiation therapy.[2]
- **Neuroendocrine and Adrenal Tumors:** Guidelines (version 1.2023 – August 2, 2023) recommend Sandostatin LAR Depot for the management of carcinoid syndrome; tumors of the gastrointestinal tract, lung, thymus (carcinoid tumors), and pancreas (including glucagonomas, gastrinomas, VIPomas, insulinomas); pheochromocytomas; and paragangliomas.[3] Patients who have local unresectable disease and/or distant metastases and clinically significant tumor burden or progression should be started on therapy with a somatostatin analog to potentially control tumor growth. The North American Neuroendocrine Tumor Society (NANETS) consensus guidelines for the surveillance and medical management of midgut NETs (2017) also recommend Sandostatin LAR Depot as a first-line initial therapy in most patients with metastatic midgut NETs for control of carcinoid syndrome and inhibition of tumor growth.[4]
- **Thymomas and Thymic Carcinomas:** Guidelines (version 1.2024 – November 21, 2023) recommend Sandostatin LAR Depot as a therapy option with or without concomitant prednisone therapy.[5] In patients with thymoma who have positive octreotide scan or symptoms of carcinoid syndrome, octreotide therapy may be useful.

POLICY STATEMENT

Prior Authorization is recommended for medical coverage of Sandostatin LAR Depot. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sandostatin LAR Depot as well as the monitoring required for adverse events and long-term efficacy, approval requires Sandostatin

LAR Depot to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

*Indications and/or approval conditions noted with **[EviCore]** are managed by EviCore healthcare for those clients who use EviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to EviCore at www.EviCore.com.*

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sandostatin LAR Depot is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. **Acromegaly.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient meets ONE of the following (i, ii, or iii):
     - **i.** Patient has had an inadequate response to surgery and/or radiotherapy; OR
     - **ii.** Patient is NOT an appropriate candidate for surgery and/or radiotherapy; OR
     - **iii.** Patient is experiencing negative effects due to tumor size (e.g., optic nerve compression); AND
   - **B)** Patient has (or had) a pre-treatment (baseline) insulin-like growth factor-1 (IGF-1) level above the upper limit of normal based on age and gender for the reporting laboratory; AND
     Note: Pre-treatment (baseline) refers to the IGF-1 level prior to the initiation of any somatostatin analog (e.g., Mycapssa [octreotide delayed-release capsules], an octreotide acetate injection product [e.g., Bynfezia Pen, Sandostatin {generic}, Sandostatin LAR Depot], Signifor LAR [pasireotide injection], Somatuline Depot [lanreotide injection], dopamine agonist [e.g., cabergoline, bromocriptine], or Somavert [pegvisomant injection]). Reference ranges for IGF-1 vary among laboratories.
   - **C)** The medication is prescribed by or in consultation with an endocrinologist.

   Dosing. Approve up to 40 mg administered intramuscularly no more frequently than once every 4 weeks.

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2. **Neuroendocrine Tumor(s) [NETs] of the Gastrointestinal Tract, Lung, Thymus (Carcinoid Tumors), and Pancreas (including glucagonomas, gastrinomas, vasoactive intestinal peptides-secreting tumors [VIPomas], insulinomas).** ***[EviCore]*** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist, endocrinologist, or gastroenterologist.

   Dosing. Approve up to 30 mg administered intramuscularly no more frequently than once every 4 weeks.

Other Uses with Supportive Evidence

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3. **Meningioma.** ***[EviCore]*** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist, radiologist, or neurosurgeon.

Dosing. Approve up to 40 mg administered intramuscularly no more frequently than once every 4 weeks.

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4. **Pheochromocytoma and Paraganglioma.** *[EviCore]* Approve for 1 year if the medication is prescribed by or in consultation with an endocrinologist, oncologist, or neurologist.

   Dosing. Approve up to 40 mg administered intramuscularly no more frequently than once every 4 weeks.

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5. **Thymoma and Thymic Carcinoma.** *[EviCore]* Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

   Dosing. Approve up to 40 mg administered intramuscularly no more frequently than once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sandostatin LAR Depot is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Sandostatin® LAR Depot intramuscular injection [prescribing information]. East Hanover, NJ: Novartis; July 2023.
2. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 1.2023 – March 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 10, 2024.
3. The NCCN Neuroendocrine and Adrenal Tumors Clinical Practice Guidelines in Oncology (version 1.2023 – August 2, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 10, 2024.
4. Strosberg JR, Halfdanarson TR, Bellizi AR, et al. The North American Neuroendocrine Tumor Society consensus guidelines for surveillance and medical management of midgut neuroendocrine Tumors. *Pancreas*. 2017;46(6):707-714.
5. The NCCN Thymomas and Thymic Carcinomas Clinical Practice Guidelines in Oncology (version 1.2024 – November 21, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 10, 2024.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/16/2023
Annual Revision	No criteria changes.	05/15/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Somatostatin Analogs – Signifor LAR Utilization Management Medical Policy
- Signifor® LAR (pasireotide intramuscular injection – Recordati Rare Diseases)

REVIEW DATE: 04/19/2024

OVERVIEW

Signifor LAR, a somatostatin analog, is indicated for the following uses:[1]

- **Acromegaly**, in patients who have had an inadequate response to surgery and/or for whom surgery is not an option. *In vivo* studies show that Signifor LAR lowers growth hormone and insulin-like growth factor-1 levels in patients with acromegaly.
- **Cushing's disease**, in patients for whom pituitary surgery is not an option or has not been curative.

Disease Overview

Cushing's syndrome refers to the general state of excessive levels of cortisol (hypercortisolism) in the blood.[2,3] Hypercortisolism can occur for reasons that are either endogenous or exogenous in nature (e.g., Cushing's disease, cortisol-containing medications, adrenal gland tumor, certain cancers). Cushing's disease (hypercortisolism caused by pituitary adenomas) is the most common type of adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome. Treatment for Cushing's syndrome requires a multi-modal approach. The goals of treatment are normalization of cortisol excess, long-term disease control, avoidance of recurrence, and reversal of clinical features.[4]

Guidelines

The Endocrine Society published clinical practice guidelines for the treatment of Cushing's syndrome in (2015) and Cushing's disease (2021).[5,6] Recorlev is recognized in the 2021 guidelines for Cushing's disease as investigational; further details regarding this therapy are not discussed. Treatment goals for Cushing's syndrome are to normalize cortisol levels or its action at the receptors to eliminate signs and symptoms of Cushing's syndrome. Best practice adjunctive management include treating co-morbidities associated with hypercortisolism (psychiatric disorders, diabetes, hypertension, hypokalemia, infections, dyslipidemia, osteoporosis, and poor physical fitness). First-line treatment involves resection of the tumor, unless surgery is not possible or is unlikely to meaningfully reduce excess glucocorticoid. Specifically for Cushing's disease, transsphenoidal selective adenomectomy by a surgeon with extensive experience in pituitary surgery is recommended. In patients with ACTH-dependent Cushing's syndrome who underwent noncurative surgery or for whom surgery was not possible, the guidelines advocate several second-line therapies (e.g., repeat transsphenoidal surgery, radiotherapy, medical therapy, and bilateral adrenalectomy). For Cushing's disease, the guidelines recommend all medical therapies as second-line options after transsphenoidal surgery. These involve steroidogenesis inhibitors (ketoconazole, Metopirone® [metyrapone capsules], Lysodren® [mitotane tablets], etomidate) in patients either with or without radiotherapy/radiosurgery; pituitary-directed medical treatments (cabergoline, Signifor® [pasireotide subcutaneous injection]) in patients who are not surgical candidates or who have persistent disease; and Korlym® (mifepristone tablets) in patients with diabetes or glucose intolerance who are not surgical candidates or who have persistent disease after transsphenoidal surgery.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Signifor LAR. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Signifor LAR as well as the monitoring required for adverse events and long-term efficacy, approval requires Signifor LAR to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Signifor LAR is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. **Acromegaly.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient meets ONE of the following (i, ii, or iii):
     - **i.** Patient has had an inadequate response to surgery and/or radiotherapy; OR
     - **ii.** Patient is NOT an appropriate candidate for surgery and/or radiotherapy; OR
     - **iii.** Patient is experiencing negative effects due to tumor size (e.g., optic nerve compression); AND
   - **B)** Patient has (or had) a pre-treatment (baseline) insulin-like growth factor-1 (IGF-1) level above the upper limit of normal based on age and gender for the reporting laboratory; AND
     Note: Pre-treatment (baseline) refers to the IGF-1 level prior to the initiation of any somatostatin analog (e.g., Mycapssa [octreotide delayed-release capsules], an octreotide acetate injection product [e.g., Bynfezia Pen, Sandostatin {generic}, Sandostatin LAR Depot], Signifor LAR [pasireotide injection], Somatuline Depot [lanreotide injection], dopamine agonist [e.g., cabergoline, bromocriptine], or Somavert [pegvisomant injection]). Reference ranges for IGF-1 vary among laboratories.
   - **C)** The medication is prescribed by or in consultation with an endocrinologist.

   Dosing. Approve up to 60 mg administered intramuscularly no more frequently than every 28 days.

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2. **Cushing's Disease.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 4 months of initial therapy if the patient meets ALL of the following (i and ii):
     - **i.** According to the prescriber, patient is not a candidate for surgery, or surgery has not been curative; AND
       Note: For patients with Cushing's disease/syndrome awaiting surgery, see *Other Uses with Supportive Evidence.*
     - **ii.** Signifor LAR is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's disease.
   - **B)** Patient is Currently Receiving Signifor LAR/Signifor. Approve for 1 year of continuation therapy if the patient has responded to Signifor/Signifor LAR, as determined by the prescriber.

Note: An example of patient response is decrease in the mean urinary free cortisol level.

Dosing. Approve up to 40 mg administered intramuscularly no more frequently than once every 28 days.

Other Uses with Supportive Evidence

3. Endogenous Cushing's Syndrome. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following (i, ii, or iii)
  - **i.** According to the prescriber, the patient is not a candidate for surgery or surgery has not been curative; OR
  - **ii.** Patient is awaiting surgery for **endogenous Cushing's Syndrome**; OR
  - **iii.** Patient is awaiting therapeutic response after radiotherapy for **endogenous Cushing's Syndrome**; AND
- **C)** The medication is prescribed by or in consultation with an endocrinologist or a physician who specialized in the treatment of Cushing's syndrome.

Dosing. Approve up to 40 mg administered intramuscularly no more frequently than once every 28 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Signifor LAR is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Signifor® LAR subcutaneous injection [prescribing information]. Lebanon, NJ: Recordati Rare Diseases; August 2023.
2. Sharma ST, Nieman LK, Feelders RA. Cushing's syndrome: epidemiology and developments in disease management. *Clin Epidemiol*. 2015;7:281–293.
3. Tritos NA, Biller BM. Advances in medical therapies for Cushing's syndrome. *Discov Med*. 2012;13(69):171-179.
4. Biller BMK, Grossman AB, Stewart PM, et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: A consensus statement. *J Clin Endocrinol Metab*. 2008;93:2454-2462.
5. Nieman LK, Biller BM, Findling JW. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2015;100(8):2807-2831.
6. Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. *Lancet Diabetes Endocrinol*. 2021;9(12):847-875.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/16/2023
Early Annual Revision	**Endogenous Cushing's Syndrome:** This condition was added under other uses with supportive evidence. **Endogenous Cushing's Syndrome – Patient Awaiting Surgery:** This condition was removed from the policy (now addressed under Endogenous Cushing's Syndrome). **Endogenous Cushing's Syndrome – Patient Awaiting Therapeutic Response After Radiotherapy:** This condition was removed from the policy (now addressed under Endogenous Cushing's Syndrome).	04/19/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Spinal Muscular Atrophy – Gene Therapy – Zolgensma Utilization Management Medical Policy

- Zolgensma® (onasemnogene abeparvovec-xioi intravenous infusion – Novartis)

REVIEW DATE: 11/01/2023

OVERVIEW

Zolgensma, an adeno-associated virus vector-based gene therapy, is indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.[1]

Limitations of use are that the safety and effectiveness of repeat administration of Zolgensma have not been evaluated.[1] The use of Zolgensma in patients with advanced spinal muscular atrophy (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been assessed. Use of Zolgensma in premature neonates before reaching full-term gestational age is not recommended because concomitant treatment with corticosteroids may adversely affect neurological development. Zolgensma therapy should be delayed until full-term gestational age is achieved. The definition of full-term pregnancy commences at 39 weeks and 0 days gestation.[2]

Disease Overview

Spinal muscular atrophy is a genetic, autosomal recessive muscular disorder caused by deletion or loss of function mutation in the SMN1 gene.[3-6] The reduced levels of survival motor neuron (SMN) protein causes degeneration of lower motor neurons.[6] Although the condition is a multisystem disorder, it is clinically characterized by progressive muscle weakness and atrophy. Patients have difficulties with ambulation, head control, feeding, and respiration. Cognitive development is not impacted. In the US, spinal muscular atrophy affects approximately one in 11,000 infants and has an average carrier frequency of one in 54 individuals; as many as 10,000 to 20,000 children and adults in the US may be impacted.[6] Although the condition can be present in individuals of any age, it is more frequently diagnosed in infants and children, as it is more severe in this population.[3-6] The phenotypic expression of the disease is impacted by the presence of the survival motor neuron 2 (SMN2) gene copy number. SMN1 is responsible for producing most of the effective SMN protein, although some SMN protein can be made by the SMN2 gene. Therefore, patients with a deletion of the SMN1 gene may have the potential for making some SMN protein through the SMN2 gene copy, although in most cases the resulting protein made by this gene is truncated and is not as effective or functional. Data have shown that patients with a higher number of SMN2 gene copies generally have a more mild phenotypic disease expression. Gene deletion testing for spinal muscular atrophy can be performed at many diagnostic laboratories. Table 1 describes disease types. A different manner of categorization classifies the three most common types as follows: Type 1 patients are "non-sitters", Type 2 patients are "sitters", and Type 3 patients are "walkers".[4,6]

Table 1. Types of Spinal Muscular Atrophy.[3-6]

SMA Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Gene Copy Number
0	Prenatal	Severe hypotonia and weakness; respiratory failure at birth. There is no achievement of motor milestones.	A few weeks to < 6 months	0 to 1
1	< 6 months	Poor muscle tone, lack of movement, and respiratory assistance needed at birth. Patients are never able to sit.	< 2 years	1 to 2

Table 1 (continued). Types of Spinal Muscular Atrophy.[3-6]

SMA Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Gene Copy Number
2	Before 18 months	Patients are able to sit. However, patients are unable to walk or stand without assistance.	75% of patients are alive at 25 years of age	2 to 3
3	> 18 months	Walks independently but may lose this ability as the disease progresses.	Normal	3 to 4
4	Adulthood	Walk until adulthood.	Normal	≥ 4

SMA – Spinal muscular atrophy; SMN2 – Survival motor neuron 2.

Besides Zolgensma, other therapies are available. **Spinraza®** (nusinersen intrathecal injection), a SMN2-directed antisense oligonucleotide, is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients.[7] Spinraza is given by intrathecal injection. Although studies and experience continue, the primary pivotal data include infantile-onset (Type 1) and later-onset (Type 2 and Type 3) spinal muscular atrophy primarily in children. Data are also available with Spinraza in presymptomatic infants who were genetically diagnosed with spinal muscular atrophy. There is an accumulation of data with Spinraza in adults as well.

Evrysdi® (risdiplam oral solution), a SMN2 splicing modifier, is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients.[8] The primary pivotal data include infantile-onset (Type 1) and later-onset (Type 2 and Type 3) spinal muscular atrophy primarily in children and adults up to 25 years of age. Trials are ongoing in older adults, as well as in presymptomatic infants who were genetically diagnosed with spinal muscular atrophy.

Clinical Efficacy

The efficacy of Zolgensma was evaluated in patients less than 2 years of age with spinal muscular atrophy who had bi-allelic mutations in the SMN1 gene.[1,9-14] One trial was an open-label, single-arm study which is ongoing (STR1VE [n = 21])[11] and the other was an open-label, single-arm, ascending-dose clinical trial (START [n = 15] {12 patients received a therapeutic dose}).[1,9,10] Symptoms onset occurred before patients were 6 months of age. All patients had genetically confirmed bi-allelic SMN1 gene deletions and two SMN2 gene copies. In both trials, Zolgensma was given as a single-dose intravenous infusion. Efficacy was assessed on parameters such as survival and achievement of developmental motor milestones (e.g., sitting without support). The definition of survival was the time from birth to either death or permanent ventilation. Other efficacy parameters were evaluated (e.g., assessment of Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders [CHOP-INTEND] scores, evaluation of ventilator use). The ongoing clinical trial involved 21 patients with infantile-onset spinal muscular atrophy. The mean CHOP-INTEND score was 31.0 (range, 18 to 47). The mean patient age at the time of treatment was 3.9 months (range 0.5 to 5.9 months). As of the March 2019 cutoff date, 19 patients were alive without permanent ventilation. Compared with natural history data, Zolgensma is effective as more patients attained the ability to sit without support.[1] The completed clinical trial involved 15 patients with infantile-onset spinal muscular atrophy.[1,9] Three patients were in a low-dose cohort and 12 patients were in a high-dose cohort.[1] At the time of treatment, the mean age of patients in the low-dose cohort was 6.3 months (range 5.9 to 7.2 months) and 3.4 months (range 0.9 to 7.9 months) in the high-dose group. The dose in the low-dose cohort was approximately one-third of the dosage received by patients in the high-dose cohort. At 24 months following Zolgensma infusion, one patient in the low-dose cohort met the endpoint of permanent ventilation; all 12 patients in the high-dose cohort were alive without permanent ventilation. In the high-dose cohort, 9 of 12 patients (75%) were able to stand and walk without assistance.[1,9] At longer-term follow-up from the START trial, all 10 patients followed in the high-dose group were alive without permanent ventilation at the dataset on June 11, 2020. In STR1VE, at the March 2019 data cutoff, 19 patients were alive without permanent ventilation.[1] Up until November 2019, data revealed that 13 of 22

patients achieved the coprimary endpoint of functional independent sitting for 30 seconds or longer at the 18 months of age study visit.[11] Other data are also available.[12-15]

Guidelines

The Spinal Muscular Atrophy Newborn Screening Multidisciplinary Working Group is comprised of clinicians and geneticists with expertise in spinal muscular atrophy who developed a treatment algorithm in 2018 for infants who have positive results from a newborn screening test for spinal muscular atrophy.[16] Spinal muscular atrophy Types 1 and 2 comprise a large majority of cases and account for many patients who screen positively for spinal muscular atrophy with three or fewer SMN2 gene copies. Immediate treatment is recommended in patients with two or three SMN2 gene copies. Treatment recommendations for patients who screen positive for spinal muscular atrophy and have only one SMN2 gene copy are more complicated. It is likely that patients with only one SMN2 gene copy will likely be symptomatic at birth and the physician should determine if treatment is warranted.[16] In 2020, the Working Group updated recommendations that infants diagnosed with spinal muscular atrophy via newborn screening with four SMN2 gene copies should receive immediate treatment.[17] Also, patients with five (or more) SMN2 gene copies should be observed and screened for symptoms.

Dosing

The recommended dose of Zolgensma is 1.1×10^{14} vector genomes (vg) per kg of body weight.[1] Administer Zolgensma as an intravenous infusion over 60 minutes. Starting 1 day prior to Zolgensma infusion, give systemic corticosteroids equivalent to oral prednisolone 1 mg/kg of body weight for a total of 30 days. Examine liver function after this juncture and follow recommended guidelines.

Safety

Zolgensma has a Boxed Warning regarding acute serious liver injury and acute liver failure.[1] Elevated aminotransferases can occur with Zolgensma. Patients with preexisting liver impairment may be at higher risk. Prior to infusion, evaluate liver function in all patients by clinical examination and laboratory testing. One day before Zolgensma infusion, commence administration of systemic corticosteroids equivalent to oral prednisolone at 1 mg/kg of body weight per day for a total of 30 days. Prior to administration of Zolgensma, evaluate creatinine and complete blood counts. Perform baseline anti-AAV9 antibody testing prior to Zolgensma infusion. Patients in the Zolgensma trials were required to have baseline anti-AAV9 antibody titers of $\leq$ 1:50.

POLICY STATEMENT

Prior Authorization is recommended for benefit coverage of Zolgensma. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zolgensma as well as the specialized training required for administration of Zolgensma, approval requires Zolgensma to be prescribed by a physician who has consulted with or who specializes in the condition. All approvals are provided for one dose per lifetime. The approval duration is 1 month to allow for an adequate timeframe to prepare and administer one dose of therapy. For certain criteria, verification is required as noted by **[verification in claims history required]**. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation.

Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with eviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to chart notes, laboratory tests, claims records, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zolgensma is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Spinal Muscular Atrophy – Treatment.** Approve for a one-time per lifetime dose if the patient meets the following (A, B, C, D, E, F, G, H, I, J, K, L M, and N):
   - **A)** Patient is less than 2 years of age; AND
   - **B)** If the patient is a premature neonate, full term gestational age of 39 weeks and 0 days has been met; AND
     Note: Full-term gestational age can be defined as the postmenstrual age (gestational age plus chronological age) being equal to ≥ 39 weeks and 0 days.
   - **C)** Patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic pathogenic variants in the survival motor neuron 1 (SMN1) gene **[documentation required]**; AND
     Note: Pathogenic variants may include homozygous deletion, compound heterozygous mutation, or a variety of other rare mutations.
   - **D)** Patient meets one of the following (i or ii):
     - **i.** Patient has three or fewer survival motor neuron 2 (SMN2) gene copies **[documentation required]**; OR
     - **ii.** Patient meets both of the following (a and b):
       - **a)** Patient has four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND
       - **b)** The number of survival motor neuron 2 (SMN2) gene copies has been determined by a quantitative assay capable of distinguishing between four SMN2 gene copies and five or greater SMN2 gene copies; AND
   - **E)** According to the prescribing physician, patient has started or will receive systemic corticosteroids equivalent to oral prednisolone at a dose of 1 mg/kg per day commencing 1 day prior to Zolgensma infusion and for a total of 30 days; AND
   - **F)** Baseline anti-AAV9 antibody titers are ≤ 1:50 **[documentation required]**; AND
   - **G)** Patient has undergone a liver function assessment within the last 30 days and meets all of the following (i, ii, iii, and iv):
     - **i.** Alanine aminotransferase levels are ≤ 2 times the upper limit of normal **[documentation required]**; AND
     - **ii.** Aspartate aminotransferase levels are ≤ 2 times the upper limit of normal **[documentation required]**; AND
     - **iii.** Total bilirubin levels are ≤ 2 times the upper limit of normal **[documentation required]**; AND
       Note: Patient with elevated bilirubin levels due to neonatal jaundice are acceptable.
     - **iv.** Prothrombin time results are ≤ 2 times the upper limit of normal **[documentation required]**; AND
   - **H)** Patient has undergone a renal function assessment within the last 30 days and has a creatinine level < 1.0 mg/dL **[documentation required]**; AND

I) A complete blood count has been obtained within the last 30 days and the patient meets both of the following (i and ii):
  i. White blood cell count is ≤ 20,000 cells per mm^3 **[documentation required]**; AND
  ii. Hemoglobin levels are between 8 g/dL and 18 g/dL **[documentation required]**; AND

J) Patient has not received Zolgensma in the past **[verification in claims history required]**; AND
Note: Verify through claims history that the patient has not previously received Zolgensma. If no claim for Zolgensma is present, the prescribing physician confirms that the patient has not previously received Zolgensma.

K) For a patient currently receiving or who has received prior treatment with Spinraza (nusinersen intrathecal injection), the prescribing physician confirms that further therapy with Spinraza will be discontinued; AND

L) For a patient currently receiving or who has received prior treatment with Evrysdi (risdiplam oral solution), the prescribing physician confirms that further therapy with Evrysdi will be discontinued; AND

M) Medication is prescribed by a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; AND

N) If criteria A through M are met, approve one single intravenous infusion of Zolgensma at a dose of 1.1×10^{14} vector genomes per kg (vg/kg) based on the current patient weight in kg (within the past 14 days) **[documentation required]**. Zolgensma is provided as a customized kit to meet dosing requirements for each patient per their documented weight (in kilograms). Configuration of the dose kit is based on weight (per the cited NDC) as in Table 2 below.

Dosing. The recommended dose of Zolgensma for single-dose intravenous infusion is 1.1×10^{14} vector genomes (vg)/kg based on the current patient weight in kg (within the last 14 days). Zolgensma is provided as a customized kit to meet dosing requirements for each patient per their documented weight (in kilograms). Refer to the appropriate NDC number below for approval.

Table 2. Dose of Zolgensma Based on Availability.[1]

Patient Weight Range (kg)	Dose Volume (mL)*	Zolgensma Kit Configuration			NDC Number
		5.5 mL vial	8.3 mL vial	Total Vials per Kit	
2.6 to 3.0	16.5	0	2	2	71894-120-02
3.1 to 3.5	19.3	2	1	3	71894-121-03
3.6 to 4.0	22.0	1	2	3	71894-122-03
4.1 to 4.5	24.8	0	3	3	71894-123-03
4.6 to 5.0	27.5	2	2	4	71894-124-04
5.1. to 5.5	30.3	1	3	4	71894-125-04
5.6 to 6.0	33.0	0	4	4	71894-126-04
6.1 to 6.5	35.8	2	3	5	71894-127-05
6.6 to 7.0	38.5	1	4	5	71894-128-05
7.1 to 7.5	41.3	0	5	5	71894-129-05
7.6 to 8.0	44.0	2	4	6	71894-130-06
8.1 to 8.5	46.8	1	5	6	71894-131-06
8.6 to 9.0	49.5	0	6	6	71894-132-06
9.1 to 9.5	52.3	2	5	7	71894-133-07
9.6 to 10.0	55.0	1	6	7	71894-134-07
10.1 to 10.5	57.8	0	7	7	71894-135-07
10.6 to 11.0	60.5	2	6	8	71894-136-08
11.1 to 11.5	63.3	1	7	8	71894-137-08
11.6 to 12.0	66.0	0	8	8	71894-138-08
12.1 to 12.5	68.8	2	7	9	71894-139-09
12.6 to 13.0	71.5	1	8	9	71894-140-09
13.1 to 13.5	74.3	0	9	9	71894-141-09
13.6 to 14.0	77.0	2	8	10	71894-142-10
14.1 to 14.5	79.8	1	9	10	71894-143-10
14.6 to 15.0	82.5	0	10	10	71894-144-10
15.1 to 15.5	85.3	2	9	11	71894-145-11
15.6 to 16.0	88.0	1	10	11	71894-146-11
16.1 to 16.5	90.8	0	11	11	71894-147-11
16.6 to 17.0	93.5	2	10	12	71894-148-12
17.1 to 17.5	96.3	1	11	12	71894-149-12
17.6 to 18.0	99.0	0	12	12	71894-150-12
18.1 to 18.5	101.8	2	11	13	71894-151-13
18.6 to 19.0	104.5	1	12	13	71894-152-13
19.1 to 19.5	107.3	0	13	13	71894-153-13
19.6 to 20.0	110.0	2	12	14	71894-154-14
20.1 to 20.5	112.8	1	13	14	71894-155-14
20.6 to 21.0	115.5	0	14	14	71894-156-14

* Dose volume is calculated using the upper limit of the patient weight range for pediatric patients < 2 years of age between 2.6 kg and 21.0 kg.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zolgensma is not recommended in the following situations:

1. **Patient has Complete Paralysis of All Limbs.** This is cited as a limitation of use in the Zolgensma prescribing information.[1] Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Zolgensma.

2. **Patient has Permanent Ventilator Dependence.** This is cited as a limitation of use in the Zolgensma prescribing information.[1] Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Zolgensma.

3. **Administration to Individuals In Utero.** Zolgensma is not approved for in utero administration per the prescribing information.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	10/05/2022
Selected Revision	The terminology, "Gene Therapy" was added to the title of the policy. For operational reasons, it was added to the Policy Statement that the approval duration is 1 month to allow for an adequate timeframe to prepare and administer one dose of therapy. In addition, the following changes were made: **Spinal Muscular Atrophy – Treatment:** Previously, a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 gene reported as at least one of the following was required: homozygous deletion, homozygous mutation, or compound heterozygous mutation [documentation required]. This was revised to state that a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic pathogenic variants in the survival motor neuron 1 gene [documentation required] is required with a Note added stating that pathogenic variants may include homozygous deletion, compound heterozygous mutation, or a variety of other rare mutations. Regarding the requirement that the patient has started or will receive systemic corticosteroids, the wording "According to the prescribing physician" was added. A documentation requirement was added to the requirement that baseline anti-AAV9 antibody titers are ≤ 1:50. Previously, baseline liver function testing was required before Zolgensma administration, with a Note stating that examples of tests include aspartate aminotransferase, alanine aminotransferase, total bilirubin, and prothrombin time. The requirement was revised to state that the patient has undergone a liver function assessment within the last 30 days and meets all of the following criteria: alanine aminotransferase levels are ≤ 2 times the upper limit of normal [documentation required]; aspartate aminotransferase levels are ≤ 2 times the upper limit of normal [documentation required]; total bilirubin levels are ≤ 2 times the upper limit of normal [documentation required] {with a Note stating that elevated bilirubin levels due to neonatal jaundice are acceptable}; and prothrombin time results are ≤ 2 times the upper limit of normal [documentation required]. Previously, creatinine was required to be examined prior to administration of Zolgensma; this was revised to state that the patient was undergone a renal function assessment within the last 30 days and has a creatinine level < 1.0 mg/dL [documentation required]. Previously, a complete blood count was required to be examined prior to administration (including hemoglobin and platelet counts). This requirement was revised to state a complete blood count has been obtained within the last 30 days and the patient has a white blood cell count ≤ 20,000 cells per mm^3 [documentation required] and hemoglobin levels are between 8 g/dL and 18 g/dL [documentation required]. The requirement to examine troponin I levels prior to administration of Zolgensma was deleted. The criteria that state "prescriber" were changed to "prescribing physician". **Dosing:** The Dosing section was revised (refer to the policy) and 15 additional NDC numbers were added to reflect Zolgensma kit configurations available in weights ranging from 13.6 to 21.0 kg. **Conditions Not Recommended for Approval:** Administration to Individuals in Utero was added as a new situation in which use of Zolgensma is not approved.	3/22/2023
Annual Revision	For Spinal Muscular Atrophy, regarding the requirement which mandates that a premature neonate to reach full term gestational age of 39 weeks and 0 days, a Note was added that full-term gestational age can be defined as the postmenstrual age (gestational age plus chronological age) being equal to ≥ 39 weeks and 0 days.	11/01/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Spinal Muscular Atrophy – Spinraza Utilization Management Medical Policy
- Spinraza® (nusinersen intrathecal injection – Biogen)

REVIEW DATE: 11/01/2023

OVERVIEW

Spinraza, a survival motor neuron 2 (SMN2)-directed antisense oligonucleotide, is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients.[1]

Disease Overview

Spinal muscular atrophy is a genetic, autosomal recessive muscular disorder caused by deletion or loss of function mutation in the survival motor neuron 1 (SMN1) gene.[2-5] The reduced levels of survival motor neuron (SMN) protein causes degeneration of lower motor neurons.[5] Although the condition is a multisystem disorder, it is clinically characterized by progressive muscle weakness and atrophy. Patients have difficulties with ambulation, head control, feeding, and respiration. Cognitive development is not impacted. In the US, spinal muscular atrophy affects approximately one in 11,000 infants and has an average carrier frequency of one in 54 individuals; as many as 10,000 to 20,000 children and adults in the US may be impacted.[5] Although the condition can be present in individuals of any age, it is more frequently diagnosed in infants and children, as it is more severe in this population.[2-5] The phenotypic expression of the disease is impacted by the presence of the SMN2 gene copy number. SMN1 is responsible for producing most of the effective SMN protein, although some SMN protein can be made by the SMN2 gene. Therefore, patients with a deletion of the SMN1 gene may have the potential for making some SMN protein through the SMN2 gene copy, although in most cases the resulting protein made by this gene is truncated and is not as effective or functional. Data have shown that patients with a higher number of SMN2 copies generally have a more mild phenotypic disease expression. Gene deletion testing for spinal muscular atrophy can be performed at many diagnostic laboratories. Of note, various motor ability assessments are used in clinical practice to characterize functional impairment in spinal muscular atrophy.[2-5] A variety of functional motor scales are utilized to evaluate patients.[6] Table 1 describes disease types. A different manner of categorization classifies the three most common types as follows: Type 1 patients are "non-sitters", Type 2 patients are "sitters", and Type 3 patients are "walkers".[3,5]

Table 1. Types of Spinal Muscular Atrophy.[2-5]

SMA Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Copy Gene Number
0	Prenatal	Severe hypotonia and weakness; respiratory failure at birth. There is no achievement of motor milestones.	A few weeks to < 6 months	0 to 1
1	< 6 months	Poor muscle tone, lack of movement, and respiratory assistance needed at birth. Patients are never able to sit.	< 2 years	1 to 2
2	Before 18 months	Patients are able to sit. However, patients are unable to walk or stand without assistance.	75% of patients are alive at 25 years of age	2 to 3
3	> 18 months	Walks independently but may lose this ability as the disease progresses.	Normal	3 to 4
4	Adulthood	Walk until adulthood.	Normal	≥ 4

SMA – Spinal muscular atrophy; SMN2 – Survival motor neuron 2.

Besides Spinraza, other therapies are available. **Evrysdi®** (risdiplam oral solution), a SMN2 splicing modifier, is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients.[7] The primary pivotal data include infantile-onset (Type 1) and later-onset (Type 2 and Type 3) spinal muscular atrophy primarily in children and adults up to 25 years of age. Data are also available in presymptomatic infants who were genetically diagnosed with spinal muscular atrophy.

Zolgensma® (onasemnogene abeparvovec-xioi intravenous infusion), an adeno-associated virus vector-based gene therapy, is indicated for the treatment of pediatric patients < 2 years of age with spinal muscular atrophy with bi-allelic mutations in the SMN1 gene.[8] The agent works by providing a copy of the gene encoding the SMN protein, which increases its production. Zolgensma is administered as a single-dose intravenous infusion over 60 minutes. Pivotal studies mainly involve infants with two or three SMN2 gene copies with primarily Type 1 or Type 2 disease.

Clinical Efficacy

Spinraza was investigated in a pivotal trial called ENDEAR, which was a Phase III, multicenter, multinational, randomized, double-blind, sham-procedure controlled study involving 121 symptomatic infants diagnosed with infantile-onset spinal muscular atrophy (Type I).[1,9] Patients were randomized 2:1 to receive either Spinraza (n = 80) or sham injection (n = 41).[1] Eligible patients were ≤ 7 months of age at the time of the first dose and diagnosed with spinal muscular atrophy with a symptom onset prior to 6 months of age. Baseline demographics were balanced between the Spinraza and control groups with the exception of age at first treatment (median age of 175 and 206 days, respectively).[1] At baseline, all infants were symptomatic, hypotonic and weak, which are features consistent with a phenotype that is most likely to be categorized as spinal muscular atrophy Type 1.[9] Patients had two SMN2 gene copies. The median time of treatment was 261 days (range 6 to 442 days).[1] Those who received Spinraza compared with sham-control experienced improvement on achieving motor milestone responses. Outcomes assessing survival also revealed improvements for patients receiving Spinraza vs. sham control.

CHERISH was a multicenter, double-blind, sham-controlled, Phase III trial which involved children with symptomatic later-onset spinal muscular atrophy who were 2 to 12 years of age (n = 126) with likely Type 2 or 3 disease (symptom onset after 6 months of age).[1,10] Patients were randomized (2:1) to receive Spinraza or sham injection. Three SMN2 gene copies were reported among 88% of patients; approximately 8% of patients had two SMN2 gene copies. The median age at screening was 4 years and 3 years in the Spinraza and sham procedure control groups, respectively.[1,10] Patients who received Spinraza experienced more improvement in motor milestones compared with sham control.

NURTURE was an open-label uncontrolled trial involving patients with presymptomatic spinal muscular atrophy who ranged in age from 3 days to 42 days at the time of the first dose (n = 25).[1,11] Patients were required to have two or three SMN2 gene copies.[11] Some patients who were given Spinraza prior to the onset of symptoms related to spinal muscular atrophy survived without requiring permanent ventilation beyond what would be anticipated based on their SMN2 copy number. Also, some patients also met age-appropriate growth and development motor milestones (e.g., ability to sit unassisted, stand, or walk). Data are available from almost a median of 3-year follow-up.

The EMBRACE trial showed benefits of Spinraza in infants/children with infantile- or later-onset spinal muscular atrophy who were not eligible for the ENDEAR or CHERISH studies.[12] Other data with Spinraza are also available, including an accumulation of data in adults.[13-26] Follow-up is available for up to 4 years. Patients had a slowing of decline, achieved milestones, and experienced additional improvement in scales assessing motor function.

Dosing

Spinraza is given intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures.[1] The recommended dosage is 12 mg (5 mL) per administration. Initiate Spinraza treatment with four loading doses. The first three loading doses should be administered at 14-day intervals. The fourth loading dose should be given 30 days after the third dose. A maintenance dose should be given once every 4 months thereafter. There are additional recommendations in patients who have missed doses. The safety and effectiveness of Spinraza in pediatric patients from newborn to 17 years of age have been established.

Guidelines

The Spinal Muscular Atrophy Newborn Screening Multidisciplinary Working Group is comprised of clinicians and geneticists with expertise in spinal muscular atrophy who developed a treatment algorithm in 2018 for infants who have positive results from a newborn screening test for spinal muscular atrophy.[27] Spinal muscular atrophy Types 1 and 2 comprise a large majority of cases and account for many patients who screen positively for spinal muscular atrophy with three or fewer SMN2 gene copies. Immediate treatment is recommended in patients with two or three SMN2 gene copies. Treatment recommendations for patients who screen positive for spinal muscular atrophy and have only one SMN2 gene copy is more complicated.[27] In 2020, the Working Group updated recommendations that infants diagnosed with spinal muscular atrophy via newborn screening with four SMN2 gene copies should receive immediate treatment.[28] Also, patients with five (or more) SMN2 gene copies should be observed and screened for symptoms.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Spinraza. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Due to the specialized skills required for evaluation and diagnosis of patients treated with Spinraza as well as the monitoring required for adverse events and long-term efficacy, approval requires Spinraza to be prescribed by a physician who has consulted with or who specializes in the condition. For certain criteria, verification is required as noted by **[verification in claims history required]**. All reviews will be forwarded to the Medical Director for evaluation.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Spinal Muscular Atrophy – Spinraza Utilization Management Medical Policy* through the Coverage Review Department and who is requesting reauthorization, are NOT required to re-submit documentation for reauthorization except for the criterion requiring documentation of response or benefit to Spinraza therapy.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Spinraza is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. Spinal Muscular Atrophy – Treatment. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets all of the following (i, ii, iii, iv, v, and vi):

i. Baseline motor ability assessment that suggest spinal muscular atrophy (based on age, motor ability, and development) has been performed from one of the following exams (a, b, c, d, e, f, or g) **[documentation required]**:

a) Bayley Scales of Infant and Toddler Development; OR
b) Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND); OR
c) Hammersmith Functional Motor Scale Expanded (HFMSE); OR
d) Hammersmith Infant Neurological Exam Part 2 (HINE-2); OR
e) Motor Function Measure-32 Items (MFM-32); OR
f) Revised Upper Limb Module (RULM) test; OR
g) World Health Organization motor milestone scale; AND

ii. Patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic pathogenic variants in the survival motor neuron 1 (SMN1) gene **[documentation required]**; AND

Note: Pathogenic variants may include homozygous deletion, compound heterozygous mutation, or a variety of other rare mutations.

iii. Patient meets one of the following (a or b):

a) Patient has two or three survival motor neuron 2 (SMN2) gene copies **[documentation required]**; OR
b) Patient meets both of the following criteria [(1) and (2)]:
(1) Patient has four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND
(2) Patient has objective signs consistent with spinal muscular atrophy Types 1, 2, or 3 **[documentation required]**; AND

iv. For a patient currently receiving or who has received prior treatment with Evrysdi (risdiplam oral solution), the prescribing physician confirms that further therapy with Evrysdi will be discontinued; AND

v. Patient has not received Zolgensma (onasemnogene abeparvovec-xioi intravenous infusion) in the past **[verification in claims history required]**; AND

Note: Verify through claims history that the patient has not previously received Zolgensma. If no claim for Zolgensma is present, the prescribing physician confirms that the patient has not previously received Zolgensma.

vi. Medication is prescribed by a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; OR

B) Patient Currently Receiving Spinraza Therapy. Approve for one dose (one dose to be used once within the next 4 months as maintenance therapy) if the patient meets all of the following (i, ii, iii, iv, v, vi, and vii).

i. Patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic pathogenic variants in the survival motor neuron 1 (SMN1) gene **[documentation required]**; AND

Note: Pathogenic variants may include homozygous deletion, compound heterozygous mutation, or a variety of other rare mutations.

ii. Patient meets one of the following (a or b):
- **a)** Patient has two or three survival motor neuron 2 (SMN2) gene copies **[documentation required]**; OR
- **b)** Patient meets both of the following [(1) and (2)]:
  - **(1)** Patient has four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND
  - **(2)** Patient has objective signs consistent with spinal muscular atrophy Types 1, 2, or 3 **[documentation required]**; AND

iii. Four months has elapsed since the last dose; AND

iv. For a patient currently receiving or who has received prior treatment with Evrysdi (risdiplam oral solution), the prescribing physician confirms that further therapy with Evrysdi will be discontinued; AND

v. Patient has not received Zolgensma (onasemnogene abeparvovec-xioi suspension for intravenous infusion) in the past **[verification in claims history required]**; AND
Note: Verify through claims history that the patient has not previously received Zolgensma. If no claim for Zolgensma is present, the prescribing physician confirms that the patient has not previously received Zolgensma.

vi. Medication is prescribed by a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; AND

vii. Patient must meet one of the following (a or b):
- **a)** Patient must have had a positive clinical response (for example, improvement or stabilization) from pretreatment baseline status (i.e., within the past 4 months) with Spinraza from one of the following [(1), (2), (3), (4), (5), (6), or (7)] **[documentation required]**:
  - **(1)** Bayley Scales of Infant and Toddler Development; OR
  - **(2)** Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND); OR
  - **(3)** Hammersmith Functional Motor Scale Expanded (HFMSE); OR
  - **(4)** Hammersmith Infant Neurological Exam Part 2 (HINE-2); OR
  - **(5)** Motor Function Measure-32 Items (MFM-32); OR
  - **(6)** Revised Upper Limb Module (RULM) test; OR
  - **(7)** World Health Organization motor milestone scale; OR
- **b)** According to the prescribing physician, the patient has responded to Spinraza and continues to benefit from ongoing Spinraza therapy by the most recent (i.e., within the past 4 months) physician monitoring/assessment tools **[documentation required]**.
  Note: Examples include pulmonary function tests showing improvement, bulbar function test results suggest benefits, reduced need for respiratory support, decrease in the frequency of respiratory infections or complications, and/or prevention of permanent assisted ventilation.

Dosing. Approve the following dosing regimens:

A) Initially give 12 mg intrathecally as four loading doses of which the first three loading doses should be given at 14-day intervals and the fourth loading dose should be given 30 days after the third dose; AND/OR

B) The maintenance dose is 12 mg intrathecally once every 4 months; AND/OR

C) Missed maintenance doses must meet the following (i, ii, or iii):

i. At least 8 months but less than 16 months from the last dose: approve one 12 mg intrathecal dose to be given as soon as possible, followed by one additional dose 14 days later; OR

Note: Thereafter, the regular maintenance dose schedule should be followed.

ii. At least 16 months but less than 40 months from the last dose: approve the 12 mg intrathecal maintenance dose to be given as soon as possible, followed by two additional doses that must be given 14 days apart; OR
Note: Thereafter, the regular maintenance dose schedule should be followed.

iii. At least 40 months from the last dose. Dosing should be restarted as recommended in criterion A and B.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Spinraza is not recommended in the following situations:

1. **Patient has Complete Paralysis of All Limbs.** Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Spinraza.

2. **Patient has Permanent Ventilator Dependence.** Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Spinraza.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	10/05/2022
Selected Revision	**Spinal Muscular Atrophy – Treatment:** For both Initial Therapy and for a Patient Currently Receiving Spinraza Therapy, the reference to the Bayley Scales of Infant and Toddler Development had the descriptor of "Third Edition (BSID-III) [Item 22]" removed; this scale is still noted in criteria as an updated edition has been released. Previously, a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 gene reported as at least one of the following was required: homozygous deletion, homozygous mutation, or compound heterozygous mutation [documentation required]. This was revised to state that a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic pathogenic variants in the survival motor neuron 1 gene [documentation required] is required with a Note added stating that pathogenic variants may include homozygous deletion, compound heterozygous mutation, or a variety of other rare mutations. The phrase "according to the prescriber" was removed from the requirement that the patient has objective signs consistent with spinal muscular atrophy Types 1, 2, and 3 since documentation is required. The criteria that state "prescriber" were changed to "prescribing physician". The requirement of the following laboratory tests to be performed prior to administration of Spinraza were deleted: prothrombin time and/or activated partial thromboplastin time, platelet count, and quantitative spot urine protein testing. The phrase "verification in claims history required" replaced the previous wording of "verification required by prescriber". **Dosing:** Recommendations were added regarding missed maintenance doses. Refer to the policy.	03/22/2023
Annual Revision	No criteria changes.	11/01/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Synagis Utilization Management Medical Policy
- Synagis® (palivizumab intramuscular injection – Sobi)

REVIEW DATE: 08/16/2023

OVERVIEW

Synagis, a respiratory syncytial virus (RSV) F protein inhibitor monoclonal antibody, is indicated for the **prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease**.[1] Safety and efficacy were established in children with bronchopulmonary dysplasia, infants with a history of premature birth, and children with hemodynamically significant congenital heart disease.

The safety and efficacy of Synagis for the treatment of RSV have not been established.[1] The recommended dose is 15 mg/kg intramuscularly once monthly (every 30 days). The first dose of Synagis should be administered prior to commencement of the RSV season and the remaining doses should be administered monthly throughout the RSV season.

RSV Seasonality

The Centers for Disease Control and Prevention National Respiratory and Enteric Virus Surveillance System provides reports determining RSV seasonality, nationally and by region. The COVID-19 pandemic disrupted RSV seasonality from 2020 to 2022.[2] To describe US RSV seasonality during pre-pandemic and pandemic periods, polymerase chain reaction (PCR) test results reported to the National Respiratory and Enteric Virus Surveillance System during July 2017 through February 2023 were analyzed. Seasonal RSV epidemics were defined as the weeks during which ≥ 3% of PCR test results were positive for RSV. Nationally, pre-pandemic seasons (2017 to 2020) began in October, peaked in December, and ended in April. During 2020/2021, the typical winter RSV epidemic did not occur. The 2021/2022 season began in May, peaked in July, and ended in January. The 2022/2023 season started (June) and peaked (November) later than the 2021/2022 season, but earlier than pre-pandemic seasons. In both pre-pandemic and pandemic periods, epidemics began earlier in Florida and the southeast and later in regions further north and west. Although the timing of the 2022/2023 season suggests that seasonal patterns are returning toward those observed in pre-pandemic years, off-season RSV circulation may continue.

During the 2022/2023 surveillance year, onset occurred in June, the proportion of positive PCR results peaked in November, and the peak was higher (19%) than that during pre-pandemic seasons (range 13% to 16%). The epidemic lasted 32 weeks until the offset occurred in January.

Guidelines

The American Academy of Pediatrics (AAP) Policy Statement on the Updated Guidance for Synagis Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for RSV Infection was updated on August 1, 2014 and reaffirmed in 2023.[3,13] Additionally, the AAP Red Book was updated in 2021.[4] The AAP Red Book provides eligibility criteria for prophylaxis of high-risk infants and children in the following situations: preterm infants with chronic lung disease, infants with congenital heart disease (including those who undergo cardiac transplantation during the RSV season), preterm infants (before 29 weeks, 0 days' gestation) without chronic lung disease or congenital heart disease, children with anatomic pulmonary abnormalities or neuromuscular disorders, and immunocompromised children. Data are insufficient to justify a recommendation for routine use of prophylaxis in patients with Down syndrome or among those with cystic fibrosis, unless other indications are present.

The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) [August 25, 2023] recommend one dose of Beyfortus (nirsevimab-alip intramuscular injection) for all infants < 8 months of age born during or entering their first RSV season (50 mg for infants < 5 kg and 100 mg for infants ≥ 5 kg).[11] ACIP recommends one dose of Beyfortus (200 mg, administered as two 100-mg injections given at the same time at different injection sites) for infants and children 8 to 19 months of age who are at increased risk for severe RSV disease and entering their second RSV season.

The ACIP and AAP have published considerations for the 2023/2024 RSV season with regard to Synagis vs. Beyfortus in high-risk infants (August 15, 2023).[12] In general, the joint recommendations mirror the ACIP recommendations above. In addition, if Beyfortus is administered, Synagis should not be administered later that season. If Synagis was initially administered for the season, and < 5 doses were administered, the infant should receive one dose of Beyfortus. No further Synagis should be administered. If Synagis was administered in the first RSV season, and the child is eligible for RSV prophylaxis in the second RSV season, the child should receive Beyfortus in the second RSV season, if available. An additional recommendation regarding Beyfortus is that in healthy infants born at the end of their first RSV season, who did not receive Beyfortus and are < 8 months of age entering their second RSV season, a single dose of Beyfortus may be given.

2022-2023 RSV Seasonality and Recommendations

Although typical RSV seasonality in the US occurs primarily in the fall and winter months, there was a rapid decrease in RSV infections in the US beginning in March 2020 following non-pharmacologic interventions to prevent COVID-19.[6] RSV activity remained very low through the traditional 2020-2021 fall-winter season but began to increase in spring 2021 and cases rose to a level similar to a fall-winter season throughout the US over the summer and fall of 2021.[7] This was a deviation from usual RSV epidemiology.[6,7] Because of the change in RSV circulation, AAP strongly supported consideration for use of Synagis in eligible patients during the interseasonal spread of RSV.[6] According to a statement released by AAP on December 17, 2021, the 2021-2022 winter RSV season is considered a new season, rather than a continuation of the interseason spread in the spring and summer of 2021.

As of July 2022, RSV activity in the US remains variable by region but is increasing in some parts of the country.[7] Due to the shift in RSV seasonality noted in 2021 and the current regional rise in interseason RSV cases, the AAP continues to support the use of Synagis in eligible infants in any region experiencing rates of RSV activity at any time in 2022 similar to a typical fall-winter season. The standard administration of Synagis, 5 consecutive monthly doses, is recommended by the AAP to provide serum levels associated with protection for 6 months, the length of a typical RSV season. The AAP will continue to monitor the interseasonal trends and update this guidance as needed if the RSV season extends longer than 6 months.

The start of the RSV season has historically been defined as case positivity rate of 10% by antigen or PCR testing.[8] However, a 10% threshold for PCR tests has been found to be imprecise for characterizing the RSV season. Therefore, other thresholds have been used for PCR tests. A 3% threshold has been found to be a simple method to assess the onset and offset of the RSV season (defining the RSV season onset as the first of 2 consecutive weeks when the weekly percentage of positive tests for RSV is > 3% and season offset as the last week that the percentage of positive tests is >3%).[8,9] A 10% threshold appears reasonable for antigen testing.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Synagis. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because five monthly doses of Synagis at 15 mg/kg per dose will provide more than 6 months of serum Synagis concentrations for most infants, administration of more than five monthly doses is not recommended within the continental US. Children who qualify for five monthly doses of Synagis should receive the first dose at the time of onset of the RSV season. For qualifying infants born during the RSV season, fewer than five monthly doses will be needed to provide protection until the RSV season ends in their region (maximum of five monthly doses). For the purposes of this policy, RSV season onset is defined as the first 2 consecutive weeks when the percentage of positive tests for RSV is > 3% by PCR or > 10% by antigen testing. RSV season offset is defined as the last week that the percentage of positive tests for RSV is > 3% by PCR of > 10% by antigen testing.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Synagis is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Chronic Lung Disease**. Approve for a maximum of 5 months during the RSV season if the patient meets one of the following (A or B):
   - **A)** Patient is < 12 months of age at the start of the RSV season and meets the following (i and ii):
     - **i.** Patient was born at < 32 weeks, 0 days gestation; AND
     - **ii.** Patient required > 21% oxygen for at least 28 days after birth; OR
   - **B)** Patient is ≥ 12 months of age but < 24 months of age at the start of the RSV season and meets the following (i, ii, and iii):
     - **i.** Patient was born at < 32 weeks, 0 days gestation; AND
     - **ii.** Patient required > 21% oxygen for at least 28 days after birth; AND
     - **iii.** Patient has required medical therapy (i.e., supplemental oxygen, diuretic therapy, or chronic corticosteroid therapy) during the 6 months before the start of the second RSV season.

   Dosing. Approve a dose of 15 mg/kg given intramuscularly once monthly during the RSV season.

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2. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Congenital Heart Disease.** Approve for a maximum of 5 months during the RSV season if the patient meets the following (A, B, and C):
   - **A)** Patient is < 12 months of age at the start of the RSV season; AND
   - **B)** According to the prescriber, patient meets one of the following (i, ii, iii, or iv):
     - **i.** Patient is considered to have hemodynamically significant cyanotic congenital heart disease; OR
     - **ii.** Patient meets all of the following (a, b, and c):
       - **a)** Patient has acyanotic heart disease; AND
       - **b)** Patient is receiving medication to control heart failure; AND
       - **c)** Patient will require cardiac surgical procedures; OR
     - **iii.** Patient has moderate to severe pulmonary hypertension; OR
     - **iv.** Patient meets both of the following (a and b):
       - **a)** Patient has lesions that have been adequately corrected by surgery; AND
       - **b)** Patient continues to require medication for congestive heart failure; AND
   - **C)** Synagis is prescribed by or in consultation with a cardiologist or intensivist.

   Dosing. Approve a dose of 15 mg/kg given intramuscularly once monthly during the RSV season.

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3. **Respiratory Syncytial Virus (RSV), Prevention in a Patient Born Prematurely.** Approve for a maximum of 5 months during the RSV season if the patient meets the following (A and B):
   - **A)** Patient is < 12 months of age at the start of the RSV season; AND
   - **B)** Patient was born before 29 weeks, 0 days gestation (≤ 28 weeks, 6 days gestation).

   Dosing. Approve a dose of 15 mg/kg given intramuscularly once monthly during the RSV season.

Other Uses with Supportive Evidence

4. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Anatomic Pulmonary Abnormalities or a Neuromuscular Disorder.** Approve for a maximum of 5 months during the RSV season if the patient meets the following (A and B):
   A) Patient is < 12 months of age at the start of the RSV season; AND
   B) According to the prescriber, the patient's condition compromises the handling of respiratory secretions.

   Dosing. Approve a dose of 15 mg/kg given intramuscularly once monthly during the RSV season.

5. **Respiratory Syncytial Virus (RSV), Prevention in an Immunocompromised Patient.** Approve for a maximum of 5 months during the RSV season if the patient meets the following (A, B, and C):
   Note: Examples of immunocompromised patients include those receiving chemotherapy and those with hematopoietic stem cell transplant or solid organ transplant.
   A) Patient is < 24 months of age at the start of the RSV season; AND
   B) According to the prescriber, the patient is/will be profoundly immunocompromised during the RSV season; AND
   C) Synagis is prescribed by or in consultation with an immunologist or an infectious diseases specialist.

   Dosing. Approve a dose of 15 mg/kg given intramuscularly once monthly during the RSV season.

6. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Cardiac Transplant.** Approve for a maximum of 5 months during the RSV season if the patient meets the following (A, B, and C):
   Note: A patient with cardiac transplant may also be immunocompromised. In a patient who does not meet criteria for cardiac transplant below, please see criterion 5 above (Respiratory Syncytial Virus [RSV], Prevention in an Immunocompromised Patient).
   A) Patient is < 24 months of age at the start of the RSV season; AND
   B) Patient has undergone or will undergo cardiac transplantation during the current RSV season; AND
   C) Synagis is prescribed by or in consultation with a cardiologist, intensivist, or transplant physician.

   Dosing. Approve a dose of 15 mg/kg given intramuscularly once monthly during the RSV season.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Synagis is not recommended in the following situations:

1. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Cystic Fibrosis Who Does Not Meet Any of the Approval Criteria.** The AAP guidelines for RSV note that routine use of Synagis prophylaxis in patients with cystic fibrosis, including neonates diagnosed with cystic fibrosis by newborn screening, is not recommended unless other indications are present.[4] Available studies indicate the incidence of RSV hospitalization in children with cystic fibrosis is uncommon and unlikely to be different from children without cystic fibrosis.[3] A Cochrane Review identified one trial (presented in poster/abstract form) eligible for their review of Synagis prophylaxis in children with cystic fibrosis.[5] In this prospective, double-blind, placebo-controlled, multi-center study, 14.1% vs. 14.9% of Synagis and placebo-treated patients, respectively were hospitalized within the first 6 months, and only one

patient in each group was identified with RSV infection. There were no deaths in either group of patients during the first 6 months follow-up; this outcome was not reported at 12 months follow-up.

2. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Down Syndrome Who Does Not Meet Any of the Approval Criteria.** Data suggest that children with Down syndrome have a slightly higher hospitalization rate for RSV, but the absolute number of hospitalizations is small, and a number of children with Down syndrome are at increased risk because of other qualifying risk factors (e.g., congenital heart disease, abnormalities of the respiratory tract, muscle dystonia).[3]

3. **Respiratory Syncytial Virus (RSV), Treatment of Disease.** There are limited data investigating Synagis for the treatment of established RSV infections. Passive antibody administration is not effective in treatment of RSV disease and is not approved or recommended for this indication.[3,4] If any infant or young child receiving monthly Synagis prophylaxis experiences a breakthrough RSV hospitalization, monthly prophylaxis should be discontinued because of the extremely low likelihood of a second RSV hospitalization (< 0.5%).[4]

4. **Use in a Patient who has Received Beyfortus (nirsevimab-alip intramuscular injection) in the Same RSV Season.** Synagis should not be administered to infants who have already received Beyfortus for the same RSV season.[10,11,12] However, if Synagis was initially administered for the season, and < 5 doses were administered, the infant should receive one dose of Beyfortus.[12] No further Synagis should be administered. If Synagis was administered in the first RSV season, and the child is eligible for RSV prophylaxis in the second RSV season, the child should receive Beyfortus in the second RSV season, if available. Note: The RSV season is generally 6 months in duration.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Update	**02/03/2022:** No criteria changes. The policy statement was updated with coverage recommendations for the 2021-2022 winter respiratory syncytial virus (RSV) season, in alignment with American Academy of Pediatrics recommendations. Approval durations will be authorized to align with usual RSV seasonality for the region, regardless of any doses received prior to the usual season during 2021 interseasonal spread. Doses received during interseasonal spread (i.e., outside of typical RSV seasonality for the region) do not count toward the maximum approvable five monthly doses for the 2021-2022 winter season.	NA
Early Annual Revision	**Policy Statement:** The policy statement was updated to remove the coverage recommendations for the 2021-2022 winter respiratory syncytial virus (RSV) season (see Update 2/03/2022 above). A new statement was added to define the RSV season: RSV season onset is defined as the first 2 consecutive weeks when the percentage of positive tests for RSV is > 3% by polymerase chain reaction (PCR) or > 10% by antigen testing. RSV season offset is defined as the last week that the percentage of positive tests for RSV is > 3% by PCR of > 10% by antigen testing.	08/10/2022
Annual Revision	**Conditions Not Recommended for Approval:** Use in a patient who has received Beyfortus (nirsevimab-alip intramuscular injection) in the same RSV season was added as a condition not recommended for approval.	08/16/2023
Update	**09/05/2023:** No criteria changes. Published recommendations for Beyfortus from the Advisory Committee on Immunization Practices as well as the American Academy of Pediatrics were added to the overview and supportive text.	09/05/2023

CARECONTINUUM™

MEDICAL STEP MANAGEMENT POLICY

POLICY: Testosterone Injectable Products Medical Step Management Policy

- Depo®-Testosterone (testosterone cypionate intramuscular injection – Pfizer, generics)
- testosterone enanthate intramuscular injection – Hikma, generic only
- Aveed™ (testosterone undecanoate intramuscular injection – Endo)
- Testopel® (testosterone subcutaneous pellet – Endo)
- Xyosted™ (testosterone enanthate subcutaneous injection – Antares)

REVIEW DATE: 09/06/2023

OVERVIEW

Testosterone regimens can be administered orally, parenterally, or transdermally. All the injectable agents are indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.[1-5] The prescribing information define those patients and/or conditions for which testosterone replacement products are indicated:

- **Primary hypogonadism (congenital or acquired),** for testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchiectomy.
- **Hypogonadotropic hypogonadism (congenital or acquired),** for gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation.

The diagnosis of male hypogonadism is based on both signs/symptoms and low testosterone levels. By restoring normal levels of testosterone, the replacement regimens correct symptoms of hypogonadism, which can include malaise, loss of muscle strength, depressed mood, and decreased libido.[6]

Testopel and Delatestryl (testosterone enanthate) are also indicated for **delayed puberty.**[2,3] Delatestryl (testosterone enanthate) [per the product labeling] may also be used secondarily in **advanced inoperable metastatic mammary cancer** in women who are between 1 and 5 years postmenopausal.[2] The goal of therapy is ablation of ovaries. Per labeling, it also can be used in premenopausal women with breast cancer that have benefited from oophorectomy and are considered to have hormone-responsive tumors.

POLICY STATEMENT

This Medical Step Management program has been developed to encourage the use of the Preferred Products. For all medications (Preferred and Non-Preferred), the patient is required to meet the *Testosterone Injectable Products Utilization Management Medical Policy Advanced Clinical Evaluation* criteria. The program also directs the patient to try one Preferred Product prior to the approval of a Non-Preferred Product. Requests for Non-Preferred Products will also be reviewed using the exception criteria (below). All approvals are provided for the duration noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a male, regardless of the individual's gender identity or gender expression; females are defined as individuals with the biological traits of a female, regardless of the individual's gender identity or gender expression.

Documentation: Documentation is required for use of previous therapy as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory

reports prescription claims records, prescription receipts, and/or other information. For patient cases in which documentation is required, if this documentation has been previously received upon a prior coverage review, the documentation requirement is considered to be met.

Automation: None.

Preferred Products: Depo-Testosterone (testosterone cypionate intramuscular injection, generic), testosterone enanthate intramuscular injection
Non-Preferred Products: Aveed, Testopel, Xyosted

RECOMMENDED EXCEPTION CRITERIA

Non-Preferred Products	Exception Criteria
Testopel Aveed Xyosted	**1.** Approve for 1 year if the patient meets the following criteria (A and B): **A)** Patient meets the standard *Testosterone Injectable Products Utilization Management Medical Policy – Advanced Clinical Evaluation* criteria; AND **B)** Patient has tried one of Depo-Testosterone (testosterone cypionate intramuscular injection, generics) or testosterone enanthate intramuscular injection **[documentation required].**

REFERENCES

1. Depo®-Testosterone [prescribing information]. New York, NY: Pfizer; August 2018.
2. Testosterone enanthate injection [prescribing information]. Berkeley Heights, NJ: Hikma; January 2021.
3. Testopel® [prescribing information]. Malvern, PA: Endo; August 2018.
4. Aveed™ [prescribing information]. Malvern, PA: Endo; August 2021.
5. Xyosted [prescribing information]. Ewing, NJ: Antares a; November 2019.
6. Lee M. Erectile Dysfunction. Urologic Disorders. In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A pathophysiologic approach. 8th ed. New York: McGraw Hill Medical; 2008: 1437-1454.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Documentation:** The following statement was added to the Policy Statement: "For patient cases in which documentation is required, if this documentation has been previously received upon a prior coverage review, the documentation requirement is considered to be met".	10/19/2022
Early Annual Revision	Updated the policy required to be met from Testosterone Injectable Products Utilization Management Medical Policy to the Testosterone Injectable Products Utilization Management Medical Policy – Advanced Clinical Evaluation.	09/06/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT ADVANCED CLINICAL EVALUATION MEDICAL POLICY

POLICY: Testosterone Injectable Products Utilization Management Medical Policy – Advanced Clinical Evaluation

- Depo®-Testosterone (testosterone cypionate intramuscular injection – Pfizer, generic)
- testosterone enanthate intramuscular injection – Hikma, generic only
- Aveed™ (testosterone undecanoate intramuscular injection – Endo)
- Testopel® (testosterone subcutaneous pellet – Endo)
- Xyosted™ (testosterone enanthate subcutaneous injection – Antares)

REVIEW DATE: 09/06/2023

OVERVIEW

Testosterone regimens can be administered orally, parenterally, or transdermally. All the injectable agents are indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.[1-5] The prescribing information defines those patients and/or conditions for which testosterone replacement products are indicated:

- **Primary hypogonadism (congenital or acquired),** for testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchiectomy.
- **Hypogonadotropic hypogonadism (congenital or acquired),** for gonadotropin or luteinizing hormone-releasing hormone deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation.

The diagnosis of male hypogonadism is based on both signs/symptoms and low testosterone levels. By restoring normal levels of testosterone, the replacement regimens correct symptoms of hypogonadism, which can include malaise, loss of muscle strength, depressed mood, and decreased libido.[6]

Testopel and testosterone enanthate are also indicated for **delayed puberty.**[2,3] Testosterone enanthate (per the product labeling) may also be used secondarily in **advanced inoperable metastatic mammary cancer** in women who are between 1 and 5 years postmenopausal.[2] The goal of therapy is ablation of ovaries. Per labeling, it also can be used in premenopausal women with breast cancer that have benefited from oophorectomy and are considered to have hormone-responsive tumors.

Dosing Information

Testosterone injections are used in clinical practice as intramuscular or subcutaneous injections. For Depo-Testosterone and testosterone enanthate, as replacement therapy for male hypogonadism, the suggested dose is 50 to 400 mg every 2 to 4 weeks.[1,2] In general, total doses of above 400 mg per month are not required because of prolonged action of the preparation.[2] For delayed puberty, various dosage regimens have been used, but dosage is generally within the range of 50 to 200 mg every 2 to 4 weeks.[2] The suggested dosage for testosterone injection varies depending on the age, sex, and diagnosis of the individual patient; dosage is adjusted according to the patient's response and the appearance of adverse reactions.[1-3] The recommended dose of Aveed is 3 ml (750 mg) injected intramuscularly, followed by 3 ml (750 mg) injected after 4 weeks, then 3 ml (750 mg) injected every 10 weeks thereafter.[4] The suggested dose for Testopel (testosterone pellet) is 150 mg to 450 mg subcutaneously every 3 to 6 months; dosages for delayed puberty are generally in the lower range.[3] Xyosted is administered subcutaneously once weekly[5] and dosages above 100 mg per week have not been studied.

Guidelines

- **Hypogonadism:** Guidelines from the American Urological Association (2018) note that clinicians should use a total testosterone level below 300 ng/dL as a reasonable cut-off in support of the diagnosis of low testosterone.[7] The guidelines additionally note that a diagnosis of low testosterone should be made only after two total testosterone measurements are taken on separate occasions with both conducted in an early morning fashion. Clinical diagnosis should be made when patients have low testosterone levels combined with signs and symptoms. The Endocrine Society guidelines on testosterone therapy in men with hypogonadism (2018) recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency and unequivocally and consistently low serum total testosterone and/or free testosterone concentrations (when indicated).[8]
- **Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-To-Male Gender Reassignment (i.e., Endocrinologic Masculinization):** A clinical practice guideline published by the Endocrine Society (2017) recommends that, prior to initiation of hormonal therapy, the treating endocrinologist should confirm the diagnostic criteria of gender dysphoria/gender incongruence and the criteria for the endocrine phase of gender transition.[9] The clinician should also evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment. Guidelines mention that clinicians can use either parenteral or transdermal preparations to achieve appropriate testosterone values. Testosterone regimens for transgender males include testosterone enanthate or cypionate of 100 mg to 200 mg intramuscularly every 2 weeks or subcutaneously at 50% (of the intramuscular dosage) per week.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of injectable testosterone. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a male, regardless of the individual's gender identity or gender expression; females are defined as individuals with the biological traits of a female, regardless of the individual's gender identity or gender expression. Because of the specialized skills required for evaluation and diagnosis of patients treated with injectable testosterone as well as the monitoring required for adverse events and long-term efficacy, some approvals require injectable testosterone to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of injectable testosterone as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory reports, prescription claims records, prescription receipts, and/or other information. For patient cases in which documentation is required, if this documentation has been previously received upon a prior coverage review, the documentation requirement is considered to be met.

Automation: None.

*Indications and/or approval conditions noted with **[eviCore]** are managed by eviCore healthcare for those clients who use eviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to eviCore at www.eviCore.com.*

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of injectable testosterone are recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. **Hypogonadism (Primary or Secondary) in Males* [Testicular Hypofunction/Low Testosterone with Symptoms].** Approve for 1 year if the patient meets the following (A or B):
   Note: The pre-treatment timeframe refers to signs and symptoms of androgen deficiency and serum testosterone levels prior to the administration of any testosterone therapy.
   - **A)** Initial Therapy. Approve in a patient with hypogonadism as confirmed by the following (i, ii, and iii):
     - **i.** Patient has had persistent signs and symptoms of androgen deficiency (pre-treatment); AND
       Note: Signs and symptoms of androgen deficiency include depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, and loss of libido.
     - **ii.** Patient has had two pre-treatment serum testosterone (total or bioavailable) measurements **[documentation required]**, each taken in the morning, on two separate days; AND
     - **iii.** The two serum testosterone levels are both low, as defined by the normal laboratory reference values **[documentation required]**.
   - **B)** Patients Currently Receiving Testosterone Therapy. Approve if the patient meets the following (i and ii):
     - **i.** Patient has had persistent signs and symptoms of androgen deficiency (pre-treatment); AND
       Note: Signs and symptoms of androgen deficiency include depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, and loss of libido.
     - **ii.** Patient has had at least one pre-treatment serum testosterone (total or bioavailable) level **[documentation required]**, which was low, as defined by the normal laboratory reference values **[documentation required]**.

   *Refer to the Policy Statement

   Dosing. Approve the following dosing regimens (A, B, C, D, or E):
   - **A)** Depo-Testosterone (testosterone cypionate intramuscular injection, generics): Up to 400 mg administered subcutaneously or intramuscularly every 1 to 4 weeks, not to exceed 400 mg every 2 weeks; OR
   - **B)** Testosterone enanthate intramuscular injection: Up to 400 mg administered subcutaneously or intramuscularly every 1 to 4 weeks, not to exceed 400 mg every 2 weeks; OR
   - **C)** Aveed: 750 mg administered intramuscularly, followed by 750 mg injected after 4 weeks, then 750 mg injected every 10 weeks thereafter; OR
   - **D)** Testopel: Up to 150 mg to 450 mg subcutaneously up to every 3 to 6 months; OR
   - **E)** Xyosted: Up to 100 mg subcutaneously once weekly.

2. **Delayed Puberty or Induction of Puberty in Males* 14 years of Age or Older.** Approve Depo-Testosterone (testosterone cypionate intramuscular injection, generics), testosterone enanthate intramuscular injection, or Testopel for 6 months

   *Refer to the Policy Statement

   Dosing. Approve the following dosing regimens (A, B, or C):
   A) Depo-Testosterone (testosterone cypionate intramuscular injection, generics): Up to 400 mg administered subcutaneously or intramuscularly every 1 to 4 weeks, not to exceed 400 mg every 2 weeks; OR
   B) Testosterone enanthate intramuscular injection: Up to 400 mg administered subcutaneously or intramuscularly every 1 to 4 weeks, not to exceed 400 mg every 2 weeks; OR
   C) Testopel: Up to 150 mg to 450 mg subcutaneously up to every 3 to 6 months.

3. **Breast Cancer in Females* *[eviCore]*.** Approve testosterone enanthate intramuscular injection for 6 months if prescribed by for in consultation with an oncologist.

   *Refer to the Policy Statement

   Dosing. Approve up to 400 mg administered subcutaneous or intramuscularly every 2 to 4 weeks.

Other Uses with Supportive Evidence

4. **Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-to-Male (FTM) Gender Reassignment (i.e., Endocrinologic Masculinization).** Approve for 1 year if prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.
   Note: For a patient who has undergone gender reassignment, use this FTM criterion for hypogonadism indication.

   Dosing. Approve the following dosing regimens (A, B, C, D, or E):
   A) Depo-Testosterone (testosterone cypionate intramuscular injection, generics): Up to 400 mg administered subcutaneously or intramuscularly every 1 to 4 weeks, not to exceed 400 mg every 2 weeks; OR
   B) Testosterone enanthate intramuscular injection: Up to 400 mg administered subcutaneously or intramuscularly every 1 to 4 weeks, not to exceed 400 mg every 2 weeks; OR
   C) Aveed: 750 mg administered intramuscularly, followed by 750 mg injected after 4 weeks, then 750 mg injected every 10 weeks thereafter; OR
   D) Testopel: Up to 150 mg to 450 mg subcutaneously up to every 3 to 6 months; OR
   E) Xyosted: Up to 100 mg subcutaneously once weekly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of injectable testosterone is not recommended in the following situations:

1. **To Enhance Athletic Performance.** Injectable testosterone products are not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Depo®-Testosterone [prescribing information]. New York, NY: Pfizer; August 2018.
2. Testosterone enanthate injection [prescribing information]. Berkeley Heights, NJ: Hikma; January 2021.
3. Testopel® [prescribing information]. Malvern, PA: Endo; August 2018.
4. Aveed™ [prescribing information]. Malvern, PA: Endo; August 2021.
5. Xyosted [prescribing information]. Ewing, NJ: Antares; November 2019
6. Lee M. Erectile Dysfunction. Urologic Disorders. In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A pathophysiologic approach. 8th ed. New York: McGraw Hill Medical; 2008: 1437-1454.
7. Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and Management of Testosterone Deficiency. American Urological Association. 2018. Available at: Testosterone Deficiency Guideline - American Urological Association (auanet.org). Accessed on September 1, 2023.
8. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103(5):1715-1744.
9. Hembree WC, Cohen-Kettenis P, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2017; 102(11):3869-3903.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/06/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Testosterone Injectable Products Utilization Management Medical Policy

- Depo®-Testosterone (testosterone cypionate intramuscular injection – Pfizer, generics)
- testosterone enanthate intramuscular injection – Hikma, generic only
- Aveed™ (testosterone undecanoate intramuscular injection – Endo)
- Testopel® (testosterone subcutaneous pellet – Endo)
- Xyosted™ (testosterone enanthate subcutaneous injection – Antares)

REVIEW DATE: 9/13/2023

OVERVIEW

Testosterone regimens can be administered orally, parenterally, or transdermally. All the injectable agents are indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.[1-5] The prescribing information defines those patients and/or conditions for which testosterone replacement products are indicated:

- **Primary hypogonadism (congenital or acquired),** for testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchiectomy.
- **Hypogonadotropic hypogonadism (congenital or acquired),** for gonadotropin or luteinizing hormone-releasing hormone deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation.

The diagnosis of male hypogonadism is based on both signs/symptoms and low testosterone levels. By restoring normal levels of testosterone, the replacement regimens correct symptoms of hypogonadism, which can include malaise, loss of muscle strength, depressed mood, and decreased libido.[6]

Testopel and testosterone enanthate are also indicated for **delayed puberty.**[2,3] Testosterone enanthate (per the product labeling) may also be used secondarily in **advanced inoperable metastatic mammary cancer** in women who are between 1 and 5 years postmenopausal.[2] The goal of therapy is ablation of ovaries. Per labeling, it also can be used in premenopausal women with breast cancer that have benefited from oophorectomy and are considered to have hormone-responsive tumors.

Dosing Information

Testosterone injections are used in clinical practice as intramuscular or subcutaneous injections. For Depo-Testosterone and testosterone enanthate, as replacement therapy for male hypogonadism, the suggested dose is 50 to 400 mg every 2 to 4 weeks.[1,2] In general, total doses of above 400 mg per month are not required because of prolonged action of the preparation.[2] For delayed puberty, various dosage regimens have been used, but dosage is generally within the range of 50 to 200 mg every 2 to 4 weeks.[2] The suggested dosage for testosterone injection varies depending on the age, sex, and diagnosis of the individual patient; dosage is adjusted according to the patient's response and the appearance of adverse reactions.[1-3] The recommended dose of Aveed is 3 ml (750 mg) injected intramuscularly, followed by 3 ml (750 mg) injected after 4 weeks, then 3 ml (750 mg) injected every 10 weeks thereafter.[4] The suggested dose for Testopel (testosterone pellet) is 150 mg to 450 mg subcutaneously every 3 to 6 months; dosages for delayed puberty are generally in the lower range.[3] Xyosted is administered subcutaneously once weekly[5] and dosages above 100 mg per week have not been studied.

Guidelines

- **Hypogonadism:** Guidelines from the American Urological Association (2018) note that clinicians should use a total testosterone level below 300 ng/dL as a reasonable cut-off in support of the diagnosis of low testosterone.[7] The guidelines additionally note that a diagnosis of low testosterone should be made only after two total testosterone measurements are taken on separate occasions with both conducted in an early morning fashion. Clinical diagnosis should be made when patients have low testosterone levels combined with signs and symptoms. The Endocrine Society guidelines on testosterone therapy in men with hypogonadism (2018) recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency and unequivocally and consistently low serum total testosterone and/or free testosterone concentrations (when indicated).[8]
- **Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-To-Male Gender Reassignment (i.e., Endocrinologic Masculinization):** A clinical practice guideline published by the Endocrine Society (2017) recommends that, prior to initiation of hormonal therapy, the treating endocrinologist should confirm the diagnostic criteria of gender dysphoria/gender incongruence and the criteria for the endocrine phase of gender transition.[9] The clinician should also evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment. Guidelines mention that clinicians can use either parenteral or transdermal preparations to achieve appropriate testosterone values. Testosterone regimens for transgender males include testosterone enanthate or cypionate of 100 mg to 200 mg intramuscularly every 2 weeks or subcutaneously at 50% (of the intramuscular dosage) per week.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of injectable testosterone. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a male, regardless of the individual's gender identity or gender expression; females are defined as individuals with the biological traits of a female, regardless of the individual's gender identity or gender expression. Because of the specialized skills required for evaluation and diagnosis of patients treated with injectable testosterone as well as the monitoring required for adverse events and long-term efficacy, some approvals require injectable testosterone to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

*Indications and/or approval conditions noted with **[eviCore]** are managed by eviCore healthcare for those clients who use eviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to eviCore at www.eviCore.com.*

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of injectable testosterone are recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Hypogonadism (Primary or Secondary) in Males* [Testicular Hypofunction/Low Testosterone with Symptoms].** Approve for 1 year if the patient meets the following (A or B):
   Note: The pre-treatment timeframe refers to signs and symptoms of androgen deficiency and serum testosterone levels prior to the administration of any testosterone therapy.
   - **A)** Initial Therapy. Approve in a patient with hypogonadism as confirmed by the following (i, ii, and iii):
     - **i.** Patient has had persistent signs and symptoms of androgen deficiency (pre-treatment); AND
       Note: Signs and symptoms of androgen deficiency include depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, and loss of libido.
     - **ii.** Patient has had two pre-treatment serum testosterone (total or bioavailable) measurements, each taken in the morning, on two separate days; AND
     - **iii.** The two serum testosterone levels are both low, as defined by the normal laboratory reference values.
   - **B)** Patients Currently Receiving Testosterone Therapy. Approve if the patient meets the following (i and ii):
     - **i.** Patient has had persistent signs and symptoms of androgen deficiency (pre-treatment); AND
       Note: Signs and symptoms of androgen deficiency include depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, and loss of libido.
     - **ii.** Patient has had at least one pre-treatment serum testosterone (total or bioavailable) level, which was low, as defined by the normal laboratory reference values.

   *Refer to the Policy Statement

   Dosing. Approve the following dosing regimens (A, B, C, D, or E):
   - **A)** Depo-Testosterone (testosterone cypionate intramuscular injection, generics): Up to 400 mg administered subcutaneously or intramuscularly every 1 to 4 weeks, not to exceed 400 mg every 2 weeks; OR
   - **B)** Testosterone enanthate intramuscular injection: Up to 400 mg administered subcutaneously or intramuscularly every 1 to 4 weeks, not to exceed 400 mg every 2 weeks; OR
   - **C)** Aveed: 750 mg administered intramuscularly, followed by 750 mg injected after 4 weeks, then 750 mg injected every 10 weeks thereafter; OR
   - **D)** Testopel: Up to 150 mg to 450 mg subcutaneously up to every 3 to 6 months; OR
   - **E)** Xyosted: Up to 100 mg subcutaneously once weekly.

2. **Delayed Puberty or Induction of Puberty in Males* 14 years of Age or Older.** Approve Depo-Testosterone (testosterone cypionate intramuscular injection, generics), testosterone enanthate intramuscular injection), or Testopel for 6 months.

   *Refer to the Policy Statement

   Dosing. Approve the following dosing regimens (A, B, or C):
   - **A)** Depo-Testosterone (testosterone cypionate intramuscular injection, generics): Up to 400 mg administered subcutaneously or intramuscularly every 1 to 4 weeks, not to exceed 400 mg every 2 weeks; OR
   - **B)** Testosterone enanthate intramuscular injection: Up to 400 mg administered subcutaneously or intramuscularly every 1 to 4 weeks, not to exceed 400 mg every 2 weeks; OR

C) Testopel: Up to 150 mg to 450 mg subcutaneously up to every 3 to 6 months.

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3. Breast Cancer in Females* ***[eviCore]*****.** Approve testosterone enanthate intramuscular injection for 6 months if prescribed by for in consultation with an oncologist.

*Refer to the Policy Statement

Dosing. Approve up to 400 mg administered subcutaneously or intramuscularly every 2 to 4 weeks.

Other Uses with Supportive Evidence

4. Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-to-Male (FTM) Gender Reassignment (i.e., Endocrinologic Masculinization). Approve for 1 year if prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.
Note: For a patient who has undergone gender reassignment, use this FTM criterion for hypogonadism indication.

Dosing. Approve the following dosing regimens (A, B, C, D, or E):
A) Depo-Testosterone (testosterone cypionate intramuscular injection, generics): Up to 400 mg administered subcutaneously or intramuscularly every 1 to 4 weeks, not to exceed 400 mg every 2 weeks; OR
B) Testosterone enanthate intramuscular injection: Up to 400 mg administered subcutaneously or intramuscularly every 1 to 4 weeks, not to exceed 400 mg every 2 weeks; OR
C) Aveed: 750 mg administered intramuscularly, followed by 750 mg injected after 4 weeks, then 750 mg injected every 10 weeks thereafter; OR
D) Testopel: Up to 150 mg to 450 mg subcutaneously up to every 3 to 6 months; OR
E) Xyosted: Up to 100 mg subcutaneously once weekly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of injectable testosterone is not recommended in the following situations:

1. To Enhance Athletic Performance. Injectable testosterone products are not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Depo®-Testosterone [prescribing information]. New York, NY: Pfizer; August 2018.
2. Testosterone enanthate injection [prescribing information]. Berkeley Heights, NJ: Hikma; January 2021.
3. Testopel® [prescribing information]. Malvern, PA: Endo; August 2018.
4. Aveed™ [prescribing information]. Malvern, PA: Endo; August 2021.
5. Xyosted [prescribing information]. Ewing, NJ: Antares; November 2019.
6. Lee M. Erectile Dysfunction. Urologic Disorders. In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A pathophysiologic approach. 8th ed. New York: McGraw Hill Medical; 2008: 1437-1454.

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7. Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and Management of Testosterone Deficiency. American Urological Association. 2018. Available at: Testosterone Deficiency Guideline - American Urological Association (auanet.org). Accessed on September 1, 2023.
8. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103(5):1715-1744.
9. Hembree WC, Cohen-Kettenis P, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2017; 102(11):3869-3903.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Hypogonadism:** "Patient continuing therapy" was updated to "Patient currently receiving testosterone therapy". **Documentation:** The following statement was added to the Policy Statement: "For patient cases in which documentation is required, if this documentation has been previously received upon a prior coverage review, the documentation requirement is considered to be met".	10/19/2022
Early Annual Revision	**Documentation:** Removal of documentation from the policy.	09/13/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Thrombocytopenia – Nplate Utilization Management Medical Policy
- Nplate® (romiplostim subcutaneous injection – Amgen)

REVIEW DATE: 04/24/2024

OVERVIEW

Nplate, a thrombopoietin receptor agonist, is indicated for the treatment of:[1]

- **Hematopoietic syndrome of acute radiation syndrome**, to increase survival in adults and pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation.
- **Immune thrombocytopenia (ITP), in adults** who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
- **Immune thrombocytopenia (ITP), in pediatric patients ≥ 1 year of age** with ITP for at least 6 months who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Nplate should only be utilized in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.[1] Nplate should not be used in an attempt to normalize platelet counts.

Guidelines

Nplate is mentioned in various clinical guidlines.

- **Chemotherapy Induced Thrombocytopenia:** The National Comprehensive Cancer Network (NCCN) guidelines for hematopoietic growth factors (version 3.2024 – January 30, 2024) recommend consideration of Nplate for the management of suspected chemotherapy induced thrombocytopenia (category 2A) in addition to other modalities (e.g., platelet transfusion, chemotherapy dose reduction, or change in treatment regimen).[14]
- **Immune Thrombocytopenia:** The American Society of Hematology has updated guidelines for ITP (2019). For adults with ITP for at least 3 months who are corticosteroid-dependent or unresponsive to a corticosteroid, a thrombopoietin receptor agonist (Nplate or Promacta® [eltrombopag tablets and oral suspension]) or a splenectomy are recommended.[2] In children with newly diagnosed ITP who have non-life-threatening mucosal bleeding, corticosteroids are recommended. For children who have non-life-threatening mucosal bleeding and do not respond to first-line treatment, thrombopoietin receptor agonists are recommended.
- **Myelodysplastic Syndrome (MDS):** NCCN recommendations regarding MDS (version 1.2024 – February 12, 2024) state to consider treatment with a thrombopoietin receptor agonist in patients with lower-risk MDS who have severe or life-threatening thrombocytopenia.[3] Data are available that describe the use of Nplate in patients with MDS.[4-13] The data with Nplate are discussed noting an increased rate of platelet response and decreased overall bleeding events among patients with low to intermediate risk MDS.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Nplate. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing

documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Regarding the approval duration of one dose, the approval is for 30 days, which is an adequate duration for the patient to receive one dose. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nplate as well as the monitoring required for adverse events and long-term efficacy, approval for some indications requires Nplate to be prescribed by or in consultation with a physician who specializes in the condition being treated.

*Indications and/or approval conditions noted with **[eviCore]** are managed by eviCore healthcare for those clients who use eviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to eviCore at www.eviCore.com.*

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nplate is recommended in those who meet ONE of the following criteria:

FDA-Approved Indications

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1. Hematopoietic Syndrome of Acute Radiation Syndrome. *[eviCore]* Approve for one dose if the patient has been acutely exposed to myelosuppressive doses of radiation.

Dosing. Approve up to 10 mcg/kg administered subcutaneously given once.

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2. Immune Thrombocytopenia. Approve if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):

- **i.** Patient meets ONE of the following (a or b):
  - **a)** Patient has a platelet count < 30 x 10^9/L (< 30,000/mcL); OR
  - **b)** Patient meets BOTH of the following [(1) and (2)]:
    - **(1)** Patient has a platelet count < 50 x 10^9/L (< 50,000/mcL); AND
    - **(2)** According to the prescriber the patient is at an increased risk of bleeding; AND
- **ii.** Patient meets ONE of the following (a or b):
  - **a)** Patient has tried at least one other therapy; OR
    Note: Examples of therapies are systemic corticosteroids, intravenous immunoglobulin, anti-D immunoglobulin, Promacta (eltrombopag tablets and oral suspension), Tavalisse (fostamatinib tablets), Doptelet (avatrombopag tablets) and ritixumab.
  - **b)** Patient has undergone splenectomy; AND
- **iii.** Medication is prescribed by or in consultation with a hematologist; OR

B) Patient is Currently Receiving Nplate. Approve for 1 year if the patient meets BOTH of the following (i and ii):

- **i.** According to the prescriber the patient demonstrates a beneficial clinical response; AND
  Note: A beneficial response can include increased platelet counts, maintenance of platelet counts, and/or a decreased frequency of bleeding episodes.
- **ii.** Patient remains at risk for bleeding complications.

Dosing. Approve up to 10 mcg/kg subcutaneously no more frequently than once weekly.

Other Uses with Supportive Evidence

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3. Thrombocytopenia, Chemotherapy Induced. ***[eviCore]*** Approve if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL the following (i, ii, iii, and iv):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has a platelet count < 100 x 10^9/L (< 100,000/mcL); AND
- **iii.** Patient meets ONE of the following (a or b):
  - **a)** Patient has thrombocytopenia at least 3 weeks after the most recent dose of chemotherapy; OR
  - **b)** Patient has experienced a delay in chemotherapy administration related to thrombocytopenia; AND
- **iv.** Medication is prescribed by or in consultation with a hematologist or an oncologist; OR

B) Patient is Currently Receiving Nplate. Approve for 6 months if the patient meets the ALL of following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient continues to receive treatment with chemotherapy; AND
- **iii.** Patient demonstrates a beneficial clinical response according to the prescriber.
  Note: A beneficial response can include increased platelet counts, maintenance of platelet counts, and/or decreased frequency of bleeding episodes.

Dosing. Approve up to 10 mcg/kg subcutaneously no more frequently than once weekly.

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4. Thrombocytopenia in Myelodysplastic Syndrome. ***[eviCore]*** Approve if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL the following (i, ii, and iii):
- **i.** Patient has low- to intermediate-risk myelodysplastic syndrome; AND
- **ii.** Patient meets ONE of the following (a or b):
  - **a)** Patient has a platelet count < 30 x 10^9/L (< 30,000/mcL); OR
  - **b)** Patient meets BOTH of the following [(1) and (2)]:
    - **(1)** Patient has a platelet count < 50 x 10^9/L (< 50,000/mcL); AND
    - **(2)** According to the prescriber the patient is at an increased risk for bleeding; AND
- **iii.** Medication is prescribed by or in consultation with a hematologist or an oncologist; OR

B. Patient is Currently Receiving Nplate. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** According to the prescriber the patient demonstrates a beneficial clinical response; AND
  Note: An example of a response is increased platelet counts, maintenance of platelet counts, and/or decreased frequency of bleeding episodes.
- **ii.** Patient remains at risk for bleeding complications.

Dosing. Approve up to 1,500 mcg subcutaneously no more frequently than twice weekly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nplate is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Nplate® subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; February 2022.
2. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv*. 2019;3(23):3829-3866.
3. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (Version 1.2024 – February 12, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 18, 2024.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Immune Thrombocytopenia:** The wording of "Continuation of Therapy" was changed to "Patient is Currently Receiving Nplate." **Thrombocytopenia in Myelodysplastic Syndrome:** The wording of "Continuation of Therapy" was changed to "Patient is Currently Receiving Nplate."	03/23/2022
Annual Revision	No criteria changes.	04/12/2023
Annual Revision	**Hematopoietic Syndrome of Acute Radiation Syndrome:** It was added that this indication will be routed to Evicore. **Thrombocytopenia, Chemotherapy Induced:** It was added that this indication will be routed to Evicore. **Thrombocytopenia in Myelodysplastic Syndrome:** It was added that this indication will be routed to Evicore.	04/24/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Transplantation – Nulojix Utilization Management Medical Policy
- Nulojix® (belatacept intravenous infusion – Bristol-Myers Squibb)

REVIEW DATE: 08/16/2023

OVERVIEW

Nulojix, a selective T-cell costimulation blocker, is indicated for **prophylaxis of organ rejection** in patients ≥ 18 years of age receiving a kidney transplant.[1] Nulojix is to be used in conjunction with basiliximab, mycophenolate mofetil, and corticosteroids.

The prescribed dose must be evenly divisible by 12.5 mg.[1] Use of higher than recommended doses or more frequent administration is not recommended due to the increased risk of post-transplant lymphoproliferative disorder predominately of the central nervous system (CNS), progressive multifocal leukoencephalopathy, and serious CNS infections. The dose is based on actual body weight of the patient at the time of transplantation and should not be modified during the course of treatment unless the patient's weight changes by > 10%.

Guidelines

Nulojix is not included in the guidelines. In 2009, the Kidney Disease Improving Global Outcomes (KDIGO) published extensive clinical practice guidelines for the care of kidney transplant recipients.[2] For maintenance therapy, it is recommended to employ a combination of immunosuppressive medications including a calcineurin inhibitor and an anti-proliferative agent, with or without corticosteroids. Compared to cyclosporine, tacrolimus reduces the risk of acute rejection and improves graft survival within the first year of transplantation. Tacrolimus is the first-line calcineurin inhibitor and it is suggested that tacrolimus (or cyclosporine) be initiated before or at the time of transplantation, rather than delayed until the onset of graft function. Mycophenolate should be used first-line as an anti-proliferative agent. Patients who are at low immunological risk and who receive induction therapy should have corticosteroid therapy discontinued during the first week post-transplantation. If a mammalian Target of Rapamycin (mTOR) inhibitor (Zortress® [everolimus], Rapamune® [sirolimus]) is used, it should not be commenced until graft function is established and surgical wounds are healed. In the case of no reported acute rejection, the lowest doses of maintenance immunosuppressive medications should be maintained 2 to 4 months post-transplant. Calcineurin inhibitors should be continued. Of note, many of the medications require the monitoring of levels (e.g., calcineurin inhibitor, mycophenolate mofetil, mTOR inhibitors).

Safety

Nulojix labeling contains a boxed warning for post-transplant lymphoproliferative disorder; other malignancies and serious infections; and use in liver transplant recipients.[1] Patients receiving Nulojix are at increased risk of developing post-transplant lymphoproliferative disorder, particularly those without immunity to the Epstein-Barr virus (EBV). Nulojix should only be used in individuals who are EBV seropositive; do not use in individuals who are EBV seronegative or with unknown EBV status. Individuals receiving Nulojix are at increased risk of developing infections or malignancies due to immunosuppression. Nulojix should not be used in liver transplant recipients due to an increased risk of graft loss and death.

Liver Transplantation

Nulojix has a boxed warning stating that use in liver transplant recipients is not recommended due to an increase risk of graft loss and death.[1]

In a partially-blinded, active-controlled, parallel group, Phase II trial (N = 260), patients receiving the first liver transplant were randomized 1:1:1:1:1 to basiliximab + Nulojix high-dose + mycophenolate mofetil; or Nulojix high-dose + mycophenolate mofetil; Nulojix low-dose + mycophenolate mofetil; tacrolimus + mycophenolate mofetil; or tacrolimus alone.[3] The primary endpoint was the composite of acute rejection, graft loss, and death at 6 months. Secondary endpoints included the incidence, severity, treatment, and outcome of acute rejection at 12 months; graft loss and death at 12 months; and change in renal function over time. At 6 months, the frequency of the composite endpoint was higher in the Nulojix groups (42% to 48%) compared to the tacrolimus groups (15% to 38%), driven mostly by a higher rate of acute rejection with Nulojix. An external Data Monitoring Committee stopped further enrollment in the Nulojix low-dose arm due to an increase in graft loss and death compared to the other arms of the study; however patients already on Nulojix low-dose were allowed to continue at the discretion of the investigator. At 12 months, there was a higher rate of acute rejection and death in the Nulojix groups compared to tacrolimus + mycophenolate mofetil. The long-term extension phase was terminated early when the Data Monitoring Committee determined there was continued graft loss and death in the Nulojix high-dose group.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Nulojix. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nulojix as well as the monitoring required for adverse events and long-term efficacy, approval requires Nulojix to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nulojix is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **Kidney Transplantation – Prophylaxis of Organ Rejection.** Approve for 1 year if the patient meets the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient is Epstein-Barr virus (EBV) seropositive; AND
   - **C)** Nulojix is prescribed by or in consultation with a transplant specialist physician or a physician associated with a transplant center.

   Dosing. Approve the following dosing regimen (A and B):
   - **A)** Each individual dose must not exceed 10 mg/kg administered by intravenous infusion; AND
   - **B)** Nulojix is administered no more than four times in the first 4 weeks (day of transplant, Day 5, end of Week 2, and end of Week 4), and then no more frequently than once every 4 weeks.

Other Uses with Supportive Evidence

2. Solid Organ Transplantation Other Than Kidney – Prophylaxis of Solid Organ Rejection in a Patient Currently Receiving Nulojix. Approve for 1 year if the patient meets the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient is Epstein-Barr virus (EBV) seropositive; AND
- **C)** Nulojix is prescribed by or in consultation with a transplant specialist physician or a physician associated with a transplant center.

Dosing. Approve the following dosing regimen (A and B):
- **A)** Each individual dose must not exceed 10 mg/kg administered by intravenous infusion; AND
- **B)** Nulojix is administered no more than four times in the first 4 weeks (day of transplant, Day 5, end of Week 2, and end of Week 4), and then no more frequently than once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nulojix is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Nulojix® intravenous infusion [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; July 2021.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. *Am J Transplant*. 2009;9(Suppl 3):S1 – S157.
3. Klintmalm GB, Feng S, Lake JR, et al. Belatacept-Based Immunosuppression in *De Novo* Liver Transplant Recipients: 1-Year Experience From a Phase II Randomized Study. *Am J Transplant*. 2014;14:1817-1827.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	07/20/2022
Annual Revision	No criteria changes.	08/16/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Transplantation – Omisirge Utilization Management Medical Policy
- Omisirge® (omidubicel-onlv intravenous infusion – Gamida)

REVIEW DATE: 08/09/2023

OVERVIEW

Omisirge, a nicotinamide modified allogeneic hematopoietic progenitor cell therapy derived from cord blood, is indicated for use in patients with hematologic malignancies who are planning to undergo umbilical cord blood transplantation following myeloablative conditioning to reduce the time to neutrophil recovery and the incidence of infection in adults and pediatric patients ≥ 12 years of age.[1]

Disease Overview

Stem cell transplantation is used to treat various hematologic malignancies and involves placing healthy stem cells into the patient to restore the normal production and function of blood cells.[2-6] Umbilical cord blood is one source of healthy stems cells used for allogeneic transplantation; others can be obtained from peripheral blood or bone marrow. After birth, the blood present in the umbilical cord and placenta contains valuable hematopoietic stems cells that are typically discarded as medical waste. However, through donation, umbilical cord blood cells can be stored and used later for patients with conditions such as hematologic malignancies. Around 70% of patients do not have an optimal matched family donor; therefore, cells can be obtained from an unrelated donor. Patients who are non-White generally have more difficulties finding a suitable donor.

Dosing Information

Omisirge is given as a single intravenous dose.[1] Omisirge is provided in two bags containing the two cryopreserved cell fractions (i.e., cultured fraction and non-cultured fraction). After it is made from the umbilical cord blood donor source, which takes about 21 days, Omisirge is shipped to the transplant center for a specific patient.

Safety

Omisirge has a Boxed Warning regarding infusion reactions, graft versus host disease, engraftment syndrome, and graft failure.[1]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Omisirge. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for one dose. The approval duration is 6 months to allow for an adequate timeframe to prepare and administer one dose of therapy.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Omisirge is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Umbilical Cord Blood Transplantation.** Approve for one dose if the patient meets the following (A, B, and C):
   - **A)** Patient is ≥ 12 years of age; AND
   - **B)** Patient has a hematologic malignancy; AND
     Note: Examples of hematologic malignancies are acute myelogenous leukemia, acute lymphoblastic leukemia, and chronic myeloid leukemia.
   - **C)** Omisirge is prescribed by or in consultation with a hematologist, oncologist, transplant specialist physician, or a physician associated with a transplant center.

   Dosing. Approve a single dose of Omisirge given by intravenous infusion.
   Note: Omisirge is provided in two separate bags containing the two cryopreserved cell fractions (i.e., cultured fraction and non-cultured fraction).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Omisirge is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Omisirge® intravenous infusion [prescribing information]. Boston, MA: Gamida; April 2023.
1. Food and Drug Administration News Release. FDA approves cell therapy for patients with blood cancers to reduce risk of infection following stem cell transplantation. April 17, 2023. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-cell-therapy-patients-blood-cancers-reduce-risk-infection-following-stem-cell. Accessed on July 19, 2023.
2. The NCCN Hematopoietic Cell Transplantation (HCT) Guidelines in Oncology (version 1.2023 – March 31, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 19, 2023.
3. Bazinet A, Popradi G. A general practitioner's guide to hematopoietic stem-cell transplantation. *Curr Oncol*. 2019;26(3):187-191.
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6. Dehn J, Spellman S, Hurley CK, et al. Selection of unrelated donors and cord blood units for hematopoietic cell transplantation: guidelines from the NMDP/CIBMTR. *Blood*. 2019;134(12):924-934.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/09/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Uplizna Utilization Management Medical Policy
- Uplizna® (inebilizumab-cdon intravenous infusion – Horizon Therapeutics)

REVIEW DATE: 04/10/2024

OVERVIEW

Uplizna, a CD19-directed cytolytic antibody, is indicated for the treatment of **neuromyelitis optica spectrum disorder** (NMOSD) in adults who are anti-aquaporin-4 antibody-positive.[1] The recommended dose is 300 mg administered as an intravenous (IV) infusion under the close supervision of an experienced healthcare professional. The initial infusion is followed 2 weeks later by a second 300 mg IV infusion. Subsequent doses are administered once every 6 months (starting 6 months after the first infusion).

Disease Overview

NMOSD is a rare, relapsing, autoimmune central nervous system inflammatory disorder that can lead to significant morbidity and mortality.[2,3] The predominant symptoms are inflammation of the optic nerve (optic neuritis) and inflammation of the spinal cord (myelitis). Optic neuritis may lead to pain inside the eye and can progress to blindness. Myelitis tends to affect some, and often all, motor, sensory, and autonomic functions (bladder and bowel). Affected patients may experience pain in the spine or limbs, mild to severe paralysis of the lower limbs, and loss of bowel and bladder control.

The Neuromyelitis Optica Study Group (NEMOS) published revised recommendations for the treatment of NMOSD in 2024.[4] The standard of care for the treatment of NMOSD attacks (for both AQP4-IgG-positive and double-negative cases) are high-dose glucocorticoids and/or apheresis therapy. Long term immunotherapy is recommended for patients with AQP4-IgG-positive NMOSD. NEMOS notes the first-choice therapies for the treatment of AQP4-IgG-positive NMOSD are Uplizna, Enspryng® (satralizumab-mwge subcutaneous injection), Soliris® (eculizumab intravenous infusion), Ultomiris® (ravulizumab-cwyz intravenous infusion), and rituximab. The order of preference for these therapies is unclear and further comparative trials and real-world data are needed. The choice of treatment is dependent on several factors, including disease activity and severity, mode and onset of action, possibility to combine it with immunosuppressive drugs, effect on autoimmune and other comorbidities, gender (family planning issues), frequency and route of administration, side effect profile as well as patient and physician preference. In general, if a patient fails a first-choice treatment, another first-choice treatment should be tried; other options include use of a second-choice treatment (azathioprine, mycophenolate mofetil, low-dose oral glucocorticoids) or the addition of a second-choice treatment to the regimen.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Uplizna. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Uplizna as well as the monitoring required for adverse events and long-term efficacy, approval requires Uplizna to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Uplizna is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. **Neuromyelitis Optica Spectrum Disorder**. Approve if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Diagnosis of neuromyelitis optica spectrum disorder was confirmed by blood serum test for anti-aquaporin-4 antibody positive disease; AND
     - **iii.** The medication is being prescribed by or in consultation with a neurologist.
   - **B)** Patient is Currently Receiving Uplizna. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Diagnosis of neuromyelitis optica spectrum disorder was confirmed by blood serum test for anti-aquaporin-4 antibody positive disease; AND
     - **iii.** According to the prescriber, patient has had clinical benefit from the use of Uplizna; AND
       Note: Examples of clinical benefit include reduction in relapse rate, reduction in symptoms (e.g., pain, fatigue, motor function), and a slowing progression in symptoms.
     - **iv.** The medication is being prescribed by or in consultation with a neurologist.

   Dosing. Approve ONE of the following dosing regimens (A or B):
   - **A)** 300 mg by intravenous infusion once every 2 weeks for two doses; OR
   - **B)** 300 mg by intravenous infusion once every 6 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Uplizna is not recommended in the following situations:

1. **Concomitant Use With a Rituximab Product, Enspryng (satralizumab-mwge subcutaneous injection), or Soliris (eculizumab intravenous infusion).** There is no evidence to support additive efficacy of combining Uplizna with rituximab, Enspryng, or Soliris.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Uplizna® intravenous infusion [prescribing information]. Deerfield, IL: Horizon Therapeutics; July 2021.
2. National Organization for Rare Disorders. Neuromyelitis Optica Spectrum Disorder. Last updated July 27, 2022. Available at: https://rarediseases.org/rare-diseases/neuromyelitis-optica/. Accessed on April 5, 2024.
3. Chan KH, Lee CY. Treatment of neuromyelitis optica spectrum disorders. *Int J Mol Sci*. 2021;22(16):8638.
4. Kűmpfel T, Giglhuber K, Aktas O, et al. Update on the diagnosis and treatment of neuromyelitis optica spectrum disorders (NMOSD) – revised recommendations of the Neuromyelitis Optica Study Group (NEMOS). Part II: Attack therapy and long-term management. *J Neurol*. 2024;271:141-176.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	07/12/2023
Selected Revision	**Neuromyelitis Optica Spectrum Disorder – Initial Therapy:** Removed criterion that required prior use of two systemic therapies and criterion that patient has had a history of at least one relapse in the last 12 months or two relapses in the last 2 years. Uplizna is listed as a first-line treatment option in the Neuromyelitis Optica Study Group (NEMOS) recommendations for the treatment of Neuromyelitis Optica Spectrum Disorder (2024).	03/27/2024
Early Annual Revision	**Conditions Not Recommended for Approval:** Ultomiris (ravulizumab-cwyz intravenous infusion) received FDA approval for treatment of NMOSD and was added to the criterion "Concomitant Use with a Rituximab Product, Enspryng (satralizumab-mwge subcutaneous injection), or Soliris (eculizumab intravenous infusion)".	04/10/2024

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Xiaflex Utilization Management Medical Policy
- Xiaflex® (collagenase clostridium histolyticum intralesional injection – Endo)

REVIEW DATE: 09/06/2023

OVERVIEW

Xiaflex, a combination of bacterial collagenases, is indicated for the following uses:[1]
- **Dupuytren's contracture** with a palpable cord in adults.
- **Peyronie's disease** in adult men with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.

Disease Overview

Dupuytren's contracture is a disorder of the palmar and digital fascia of the hand.[2] Abnormal deposition of collagen initially causes nodules in the palm of the hand, which may thicken and lead to formation of cords. As the disease progresses, the cords gradually contract, leading to flexion deformities of the fingers. Joint contractures are typically painless but are associated with significant functional impairment. In clinical studies of Dupuytren's contracture, patients were eligible to participate if they had a finger contraction of 20 degrees to 100 degrees in a metacarpophalangeal joint or 20 degrees to 80 degrees in a proximal interphalangeal joint.[1]

Peyronie's disease is an acquired penile abnormality caused by fibrosis of the tunica albuginea, which may lead to pain, deformity, erectile dysfunction, and/or distress.[3] Peyronie's disease has a variable course; for most patients, pain will resolve over time without intervention but curvature deformities are less likely to resolve without treatment. Intralesional therapy with Xiaflex may be used to treat curvature associated with Peyronie's disease and is supported by American Urological Association guidelines (2015).

Dosing Considerations

For treatment of Dupuytren's contracture, the dose of Xiaflex is 0.58 mg per injection into a palpable cord with a contracture of an metacarpophalangeal or proximal interphalangeal joint.[1] Two palpable cords affecting two joints or one palpable cord affecting two joints in the same finger may be injected per treatment visit. Injections may be administered up to three times per cord at approximately 4-week intervals.

For treatment of Peyronie's disease, one treatment course consists of four cycles.[1] Each cycle consists of two Xiaflex injection procedures (1 to 3 days apart). Up to four cycles of Xiaflex may be administered, given at approximately 6-week intervals. The safety of more than one treatment course (8 total injections) is unknown. If the curvature deformity is less than 15 degrees after the first, second, or third treatment cycle, or if further treatment is not clinically indicated, then subsequent treatment cycles should not be administered.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Xiaflex. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e.,

Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Xiaflex, approval requires it to be administered by a healthcare provider with expertise in the condition being treated.

Medical benefit coverage is not recommended for Xiaflex for cosmetic uses.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xiaflex is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. Dupuytren's Contracture. Approve Xiaflex for 3 months if the patient meets all of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) At baseline (prior to initial injection of Xiaflex), the patient had contracture of a metacarpophalangeal or proximal interphalangeal joint of at least 20 degrees; AND

C) As part of the current treatment course, the patient will be treated with up to three injections (maximum) per affected cord; AND

D) Xiaflex is administered by a healthcare provider experienced in injection procedures of the hand and in the treatment of Dupuytren's contracture.

Dosing. Approve if the dose meets all of the following (A, B, and C):

A) The dose is 0.58 mg per injection into an affected cord; AND

B) A maximum of two cords (up to 1.16 mg) are injected per treatment visit; AND
Note: If there are other affected cords in the same hand, treatment may be administered to those on a different day.

C) For each affected cord, subsequent doses are administered no sooner than 4 weeks following the previous Xiaflex injection.

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2. Peyronie's Disease. Approve Xiaflex for 6 months if the patient meets all of the following (A, B, C, and D):

A) Patient is ≥18 years of age; AND

B) Patient meets one of the following (i or ii):

i. At baseline (prior to use of Xiaflex), the patient has a penile curvature deformity of at least 30 degrees; OR

ii. In a patient who has received prior treatment with Xiaflex, the patient has a penile curvature deformity of at least 15 degrees; AND

C) Patient has not previously been treated with a complete course (8 injections) of Xiaflex for Peyronie's disease; AND

D) Xiaflex is being administered by a healthcare provider experienced in the treatment of male urological diseases.

Dosing. Approve if the dose meets all of the following (A and B):

A) Up to a total of eight 0.58 mg injections; AND

Note: This is enough Xiaflex to treat with four dosing cycles, each consisting of two 0.58 mg injections given 1 to 3 days apart.
Note: For a patient who has already received one or more injections of Xiaflex, approve the duration requested up to the amount needed to complete one course of therapy (e.g., a patient who has received 3 injections may be approved for 5 additional injections to complete one course of therapy).

B) Cycles are separated by at least 6 weeks from the previous Xiaflex cycle.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xiaflex is not recommended in the following situations:

1. **Cosmetic Uses (e.g., cellulite of buttocks).** Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical medical benefit.

2. **Retreatment for Peyronie's Disease.** For Peyronie's disease, the safety of more than one treatment course (8 injections) is not known.[1]

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Xiaflex® intralesional injection [prescribing information]. Malvern, PA: Endo Pharmaceuticals; August 2022.
2. Brazzelli M, Cruickshank M, Tassie E, et al. Collagenase clostridium histolyticum for the treatment of Dupuytren's contracture: systematic review and economic evaluation. Southampton (UK): NIHR Journals Library; 2015 Oct. Available at: https://www.ncbi.nlm.nih.gov/books/NBK326596/. Accessed on August 31, 2023.
3. Nehra A, Alterowitz R, Culkin D, et al. Peyronie's disease: AUA guideline. *J Urol.* 2015;194(3):745-753.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	No criteria changes.	01/11/2023
Early Annual Revision	**Dupuytren's Contracture**: The verbiage for the requirement "Patient will not be treated with more than a total of three injections (maximum) per affected cord" was updated to: "As part of the current treatment course, the patient will be treated with up to three injections (maximum) per affected cord." **Conditions Not Recommended for Approval**: The condition of **Retreatment** was changed to **Retreatment for Peyronie's Disease**. For this condition, the statement was removed that "For Dupuytren's contracture, injections and finger extension procedures may be administered up to three times per cord. However, this does not limit treatment of additional cords."	09/06/2023