Mass General Brigham
Health Plan

2025 Part B Medical Drugs Medical Necessity Guidelines

Effective: July 1, 2025
Updated: July 1, 2025

Mass General Brigham Advantage Secure (HMO-POS)
Mass General Brigham Advantage (PPO)
Mass General Brigham Advantage Premier (PPO)
Mass General Brigham Advantage Signature (PPO)
Mass General Brigham Advantage Group (PPO)

Reference number(s)
2423-A

Standard Medicare Part B Management Actemra and biosimilars

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Actemra	tocilizumab
Tofidence	tocilizumab-bavi
Tyenne	tocilizumab-aazg

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met, and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1-3]

- Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs.
- Adult patients with giant cell arteritis.
- Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.
- Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.
- Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS).
- Hospitalized adult patients with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

The following indication(s) is/are FDA-approved but the drug approved to treat the indication is usually self-administered and thus not covered by this policy.

- Adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) for slowing the rate of decline in pulmonary function.

Compendial Uses[4,5]

- Rheumatoid arthritis with no previous treatment failure
- Unicentric Castleman disease
- Multicentric Castleman disease
- Immunotherapy-related inflammatory arthritis
- Acute graft versus host disease
- Cytokine release syndrome (other than severe or life-threatening CAR T-cell induced CRS)
- Thyroid eye disease
- Polymyalgia rheumatica

Note: The criteria outlined in this policy is only applicable to coverage in the outpatient setting. Hospitalized members receiving treatment of COVID-19 will be managed according to the member's inpatient benefit.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Rheumatoid arthritis[1-4]

Authorization of 12 months may be granted for treatment of rheumatoid arthritis.

Juvenile idiopathic arthritis[1-3]

Authorization of 12 months may be granted for treatment of polyarticular or systemic juvenile idiopathic arthritis.

Giant cell arteritis[1-3]

Authorization of 12 months may be granted for treatment of giant cell arteritis.

Unicentric Castleman disease[5]

Authorization of 12 months may be granted for treatment of unicentric Castleman disease.

Multicentric Castleman disease[5]

Authorization of 12 months may be granted for treatment of multicentric Castleman disease.

Cytokine release syndrome[1,5]

- Authorization of 1 month may be granted for treatment of chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome (CRS).
- Authorization of 1 month may be granted for treatment of cytokine release syndrome in members with refractory CRS related to blinatumomab therapy.

Immunotherapy-related inflammatory arthritis[5]

Authorization of 12 months may be granted for treatment of immunotherapy-related inflammatory arthritis.

Acute graft versus host disease[5]

Authorization of 12 months may be granted for treatment of acute graft versus host disease.

Thyroid Eye Disease[4]

Authorization of 12 months may be granted for treatment of active Graves' orbitopathy.

Polymyalgia rheumatica (PMR)[5]

Authorization of 12 months may be granted for treatment of polymyalgia rheumatica (PMR).

Continuation of Therapy

Cytokine release syndrome and acute graft versus host disease

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

All other indications

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication listed in the coverage criteria section.
- The member is receiving benefit from therapy.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Actemra and its biosimilars.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs

    - Clinical Pharmacology
- NCCN Guideline: Hematopoietic cell transplantation
- NCCN Guideline: Management of immunotherapy-related toxicities
- NCCN Guideline: B-cell lymphomas
- The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Actemra are covered in addition to the following:

- Rheumatoid arthritis with no previous treatment failure
- Unicentric Castleman disease
- Multicentric Castleman disease
- Immunotherapy-related inflammatory arthritis
- Acute graft versus host disease
- Cytokine release syndrome (other than severe or life-threatening CAR T-cell induced CRS)
- Thyroid eye disease
- Polymyalgia rheumatica

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using tocilizumab to treat rheumatoid arthritis with no previous treatment failure can be found in the FUNCTION trial (Burmester et al). In the randomized FUNCTION trial in methotrexate-naive patients with early rheumatoid arthritis (N=1162), a significantly greater proportion of patients receiving tocilizumab 8 mg/kg with methotrexate compared with methotrexate alone achieved remission evaluated with a Disease Activity Score using 28 joints and erythrocyte sedimentation rate (DAS28-ESR) of less than 2.6 at week 24 (45% vs 15%). Tocilizumab 8 mg/kg plus methotrexate was also associated with a significant sustained DAS28-ESR response rate at week 52 compared with methotrexate alone (49% vs 20%), as well as an American College of Rheumatology (ACR) criteria improvement of 20% (ACR20), 50% (ACR50), and 70% (ACR70), and significantly greater inhibition of joint damage. Tocilizumab 8 mg/kg alone was significantly better than methotrexate alone for DAS28-ESR remission at weeks 24 and 52, but there was no significant difference between the 2 treatments for any of the ACR responses. After 2 years in the FUNCTION trial, DAS28-ESR remission was reported in 47.6% of patients in the tocilizumab 8 mg/kg plus methotrexate group and 43.5% in the tocilizumab 8 mg/kg monotherapy group compared with 16% in the methotrexate monotherapy group. More patients in the tocilizumab 8 mg/kg plus methotrexate group and the tocilizumab 8 mg/kg monotherapy group compared with the methotrexate monotherapy group achieved ACR20 (65.2% and 61.6% vs 25.4%), ACR50 (57.6% and 53.1% vs 22%), and ACR70 (46.6% and 39.4% vs 17.4%); the mean change from baseline to 2 years in vander Heijde-modified total Sharp score (vdH mTSS) was 0.19 and 0.62 versus 1.88.

Support for using tocilizumab to treat unicentric and multicentric Castleman disease can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using tocilizumab to treat immunotherapy-related inflammatory arthritis can be found in the National Comprehensive Cancer Network's guideline for management of immunotherapy-related toxicities. The NCCN Guideline indicates tocilizumab should be considered as additional disease modifying antirheumatic therapy for the management

of moderate or severe immunotherapy-related inflammatory arthritis if no improvement was noted after holding immunotherapy and treating with oral corticosteroids or if the provider was unable to taper corticosteroids.

Support for using tocilizumab to treat acute graft versus host disease can be found in the National Comprehensive Cancer Network's guideline for hematopoietic cell transplantation. The NCCN Guideline for hematopoietic cell transplantation supports the use of tocilizumab for acute graft-versus-host disease as additional therapy in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options.

Support for using tocilizumab to treat cytokine release syndrome can be found in the National Comprehensive Cancer Network's guideline for the management of immunotherapy-related toxicities. The NCCN Guideline supports the adding of tocilizumab for the management of the following immunotherapy-related conditions:

- Prolonged (more than three days) G1 cytokine release syndrome (CRS) in patients with significant symptoms, comorbidities, and/or in elderly patients
- CRS symptoms that persist for more than 24 hours in patients who have been treated with axicabtagene ciloleucel or brexucabtagene autoleucel
- G1 CRS that develops less than 72 hours after infusion in patients who have been treated with lisocabtagene maraleucel
- G2-G4 CRS
- G1-G4 neurotoxicity as additional single-dose therapy if concurrent CRS

Support for using tocilizumab to treat cytokine release syndrome can be found in the National Comprehensive Cancer Network's guideline for acute lymphoblastic leukemia. The NCCN Guideline for acute lymphoblastic leukemia indicates tocilizumab can be considered as supportive care for patients with severe cytokine release syndrome related to blinatumomab therapy.

Support for using tocilizumab to treat thyroid eye disease can be found in the 2021 European Group on Grave's orbitopathy (EUGOGO) clinical practice guidelines. Tocilizumab can be used as second-line treatment for patients with moderate to severe and active Graves' orbitopathy (GO) unresponsive to first-line therapy. In patients with glucocorticoid-resistant disease, tocilizumab should be considered as treatment may rapidly resolve inflammatory signs. Methylprednisolone IV in combination with oral mycophenolate sodium (or mofetil) is first-line treatment.

Support for using tocilizumab to treat polymyalgia rheumatica can be found in the National Comprehensive Cancer Network's guideline for guideline for management of immunotherapy-related toxicities. The NCCN Guideline indicates tocilizumab should be considered as additional disease modifying antirheumatic therapy for the management of polymyalgia rheumatica if unable to taper prednisone or no improvement in symptoms.

References

1. Actemra [package insert]. South San Francisco, CA: Genetech, Inc.; December 2022.
2. Tofidence [package insert]. Cambridge, MA: Biogen MA Inc.; September 2023.
3. Tyenne [package insert]. Lake Zurich, IL: Fresenius Kabi USA LLC; March 2024.
4. Micromedex Solutions [database online]. Ann Arbor, MI: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed January 22, 2024.
5. National Comprehensive Cancer Network. The NCCN Drugs & Biologics Compendium. https://www.nccn.org. Accessed January 22, 2024.
6. Burmester GR, Rigby WF, van Vollenhoven RF, et al: Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial. Ann Rheum Dis 2016; 75(6):1081-1091.

7. Burmester GR, Rigby WF, van Vollenhoven RF, et al: Tocilizumab combination therapy or monotherapy or methotrexate monotherapy in methotrexate-naive patients with early rheumatoid arthritis: 2-year clinical and radiographic results from the randomised, placebo-controlled FUNCTION trial. Ann Rheum Dis 2017; 76(7):1279-1284.
8. Bartalena L, Kahaly GJ, Baldeschi L, et al: The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. Eur J Endocrinol 2021; 185(4):G43-G67.

Reference number(s)
4797-A

Standard Medicare Part B Management
Acthar Gel - Purified Cortrophin Gel

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name	Dosage Form
Acthar Gel	repository corticotropin	injection
Purified Cortrophin Gel	repository corticotropin	injection

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Acthar Gel[1]

- Infantile Spasms: as monotherapy for the treatment of infantile spasms in infants and children under 2 years of age
- Multiple Sclerosis: treatment of acute exacerbations of multiple sclerosis in adults
- Rheumatic Disorders: as 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
- Collagen Diseases: during an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis)
- Dermatologic Diseases: severe erythema multiforme, Stevens-Johnson syndrome
- Allergic States: serum sickness
- Ophthalmic Diseases: 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, anterior segment inflammation
- Respiratory Diseases: symptomatic sarcoidosis

- Edematous State: to induce a diuresis or a remission of proteinuria in nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus

Purified Cortrophin Gel[21]

- Rheumatic Disorders: as 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; acute gouty arthritis.
- Collagen Diseases: during an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis).
- Dermatologic Diseases: severe erythema multiforme (Stevens-Johnson syndrome), severe psoriasis
- Allergic States: atopic dermatitis, serum sickness
- Ophthalmic Diseases: 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, anterior segment inflammation
- Respiratory Diseases: symptomatic sarcoidosis
- Edematous States: 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 exacerbation of multiple sclerosis

Compendial Uses

- Diagnostic testing of adrenocortical function
- Acquired epileptic aphasia
- Gout

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- For multiple sclerosis, nephrotic syndrome, rheumatic disorders, collagen diseases, dermatologic diseases, ophthalmic diseases, symptomatic sarcoidosis, and allergic states: chart notes detailing the outcome of the most recent trial with glucocorticoids, including dosage and duration of treatment.
- For gout: chart notes detailing the outcome of the most recent trial with a first-line treatment option (e.g., colchicine, nonsteroidal anti-inflammatory drug [NSAIDs], or glucocorticoids), including dosage and duration of treatment.

Exclusions

- Coverage of Purified Cortrophin Gel for the treatment of infantile spasms will be excluded.[22]

- Coverage of Acthar Gel for acute gouty arthritis, severe psoriasis, allergic conjunctivitis, and atopic dermatitis will be excluded.[1]
- Use of Acthar Gel in combination with Purified Cortrophin Gel will be excluded.

Coverage Criteria

Infantile Spasms (Acthar Gel only)[1,2.4-8]

Authorization of 6 months may be granted for treatment of infantile spasms in members who are less than 2 years of age.

Multiple Sclerosis[1,9-13,21]

Authorization of 3 weeks may be granted for treatment of acute exacerbations of multiple sclerosis when the member has had an inadequate response to a trial of parenteral or oral glucocorticoids.

Nephrotic Syndrome[1,14-18,21]

Authorization of 3 months may be granted for treatment of nephrotic syndrome when repository corticotropin is requested for induction of diuresis or for remission of proteinuria in a member who has had an inadequate response to a trial of parenteral or oral glucocorticoids.

Rheumatic Disorders[1,2,19,21]

Authorization of 3 months may be granted to members who are prescribed repository corticotropin as adjunctive treatment for rheumatic disorders (e.g., psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, acute gouty arthritis) when the member has had an inadequate response to a trial of parenteral or oral glucocorticoids.

Collagen Diseases[1,20,21]

Authorization of 3 months may be granted for treatment of collagen diseases (e.g., systemic lupus erythematosus, systemic dermatomyositis, polymyositis) when the member has had an inadequate response to a trial of parenteral or oral glucocorticoids.

Dermatologic Diseases[1,21]

Authorization of 3 months may be granted for treatment of dermatologic disorders (e.g., severe erythema multiforme, Stevens-Johnson syndrome, severe psoriasis) when the member has had an inadequate response to a trial of parenteral or oral glucocorticoids.

Ophthalmic Diseases[1,21,21]

Authorization of 3 months may be granted for treatment of ophthalmic diseases (e.g., allergic conjunctivitis, keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation) when the member has had an inadequate response to a trial of parenteral, oral, or topical ophthalmic glucocorticoids.

Symptomatic Sarcoidosis[1,21]

Authorization of 3 months may be granted for treatment of symptomatic sarcoidosis when the member has had an inadequate response to a trial of parenteral or oral glucocorticoids.

Allergic States[1,21]

Authorization of 1 month may be granted for treatment of allergic states (e.g., atopic dermatitis, serum sickness) when the member has had an inadequate response to a trial of parenteral or oral glucocorticoids.

Diagnostic Testing of Adrenocortical Function[3]

Authorization of 1 dose may be granted to members who are prescribed repository corticotropin for diagnostic testing of adrenocortical function when the member cannot be tested with Cosyntropin.

Acquired Epileptic Aphasia[2]

Authorization of 3 months may be granted for treatment of acquired epileptic aphasia.

Gout[2]

Authorization of 1 month may be granted for treatment of acute gout attack when the member has had an inadequate response with a first-line treatment option (e.g., colchicine, NSAIDs, or glucocorticoids).

Continuation of Therapy

Infantile Spasms (Acthar Gel only)[1]

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 6 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Acthar Gel
- The member is receiving benefit from therapy.

All Other Indications[1,21]

All members (including new members) requesting authorization for continuation of therapy must meet all requirements in the coverage criteria.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Acthar Gel and Purified Cortrophin Gel.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Infantile spasms: A U.S. consensus report.
- Evidence-based guideline update: Medical treatment of infantile spasms: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society
- Treatment of infantile spasms- a Cochrane Database Systematic Review
- Corticosteroids or ACTH for acute exacerbations in multiple sclerosis- a Cochrane Database Systematic Review
- EFNS guidelines on treatment of multiple sclerosis relapses: report of an EFNS task force on treatment of multiple sclerosis
- American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis
- KDIGO clinical practice guideline for glomerulonephritis

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Acthar Gel and Purified Cortrophin Gel are covered in addition to the following:

- Diagnostic testing of adrenocortical function
- Acquired epileptic aphasia
- Gout

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Acthar Gel or purified Cortrophin Gel to treat multiple sclerosis after an inadequate response to a trial of parenteral or oral glucocorticoids can be found in several published studies.

Thompson and colleagues compared the efficacy of high-dose intravenous methylprednisolone with intramuscular ACTH in the treatment of acute relapse in multiple sclerosis in a double-blind, randomized, controlled study involving 61 patients. There was a marked improvement in both groups in the course of the study, but no difference between them

in either the rate of recovery or the final outcome. High-dose IV methylprednisolone is a safe alternative to ACTH in the management of acute relapse in multiple sclerosis.

Additionally, Berkovich and Agius indicate that while high-dose methylprednisolone is recommended to induce a faster recovery from a clinical exacerbation, ACTH is an alternative for patients who do not respond to or tolerate corticosteroids.

Frohman et al published an article discussing the treatment of MS exacerbations. They state ACTH is an alternative approach to intravenous methylprednisolone. ACTH was noted to be more expensive than steroids, have more side effects, and gives less consistent results. ACTH can be used when a patient is unresponsive to corticosteroids or in cases in which ACTH's positive effects on bone via stimulation of dehydroepiandrosterone and mineralocorticoids may be desirable.

Support for using Acthar Gel or purified Cortrophin Gel to treat nephrotic syndrome after an in adequate response to a trial of parenteral or oral glucocorticoids can be found in a prospective trial by Bomback and colleagues. Fifteen subjects with resistant glomerular diseases were treated with ACTH gel (80 units subcutaneously twice weekly) for 6 months. Resistant membranous nephropathy (MN), minimal change disease (MCD), and focal segmental glomerulosclerosis (FSGS) were defined as failure to achieve sustained remission of proteinuria off immunosuppressive therapy with at least 2 treatment regimens (one of which was a corticosteroid); resistant IgA nephropathy was defined as >1 g/g urine protein:creatinine ratio despite maximally tolerated RAAS blockade. Remission was defined as stable or improved renal function with ≥50% reduction in proteinuria to <0.5 g/g (complete remission) or 0.5-3.5 g/g (partial remission). The study included 5 subjects with resistant idiopathic MN, 5 subjects with resistant MCD (n = 2)/FSGS (n = 3), and 5 subjects with resistant IgA nephropathy. Two resistant MN subjects achieved partial remission on ACTH therapy, although 3 achieved immunologic remission of disease (PLA(2)R antibody disappeared by 4 months of therapy). One subject with resistant FSGS achieved complete remission on ACTH; one subject with resistant MCD achieved partial remission but relapsed within 4 weeks of stopping ACTH. Two subjects with resistant IgA nephropathy demonstrated >50% reductions in proteinuria while on ACTH, with proteinuria consistently <1 g/g by 6 months. Three of 15 subjects reported significant steroid-like adverse effects with ACTH, including weight gain and hyperglycemia, prompting early termination of therapy without any clinical response.

Support for using Acthar Gel or purified Cortrophin Gel to treat rheumatic disorders after an inadequate response to a trial of parenteral or oral glucocorticoids can be found in the package insert and several guidelines. In the 2012 American College of Rheumatology Guidelines for Management of Gout, ACTH should be used in patients unable to take oral corticosteroids as an alternative to intra-articular, intravenous, or intramuscular corticosteroids.

Support for using Acthar Gel or purified Cortrophin Gel to treat collagen diseases after an inadequate response to a trial of parenteral or oral glucocorticoids can be found in a published retrospective case series by Levine. Five patients were described, all of whom received oral or parenteral corticosteroids prior to using ACTH. The patients tolerated ACTH for up to three months with no significant side effects and no need to taper therapy. The author concludes that ACTH should be considered as an option for refractory dermatomyositis and polymyositis.

Patel and colleagues (2016) stated that idiopathic inflammatory myopathies are a group of systemic autoimmune diseases that involve inflammation of skeletal muscle. The 2 most common forms are dermatomyositis and polymyositis, the former of which entails a skin component. There are few approved therapeutics available for treatment of this group of diseases and the first-line therapy is usually corticosteroid treatment. Considering that a large proportion of patients do not respond to or cannot tolerate corticosteroids, additional treatments are needed. There are second-line therapies available, but many patients are also refractory to those options. H.P. Acthar Gel (repository corticotropin injection [RCI]) is a melanocortin peptide that can induce steroid-dependent effects and steroid-independent effects. These

researchers presented a series of cases that involved the use of RCI in the management of dermatomyositis and polymyositis; RCI treatments resulted in improvement in 3 of 4 patients, despite failure with previous therapies. The use of RCI did not exacerbate any co-morbidity and no significant changes in blood pressure, weight, or glycemic control were observed. The authors concluded that these findings were encouraging and suggested that RCTs applying RCI to dermatomyositis and polymyositis are needed.

In an open-label, clinical trial, Aggarwal and colleagues (2018) evaluated the safety, efficacy, tolerability and steroid-sparing effect of RCI in refractory adult polymyositis (PM) and dermatomyositis (DM). Adults with refractory PM and DM were enrolled by 2 centers. Inclusion criteria included refractory disease defined as failing glucocorticoid and/or greater than or equal to 1 immunosuppressive agent, as well as active disease defined as significant muscle weakness and greater than 2 additional abnormal core set measures (CSMs) or a cutaneous 10 cm visual analog scale (VAS) score of greater than or equal to 3 cm and at least 3 other abnormal CSMs. All patients received RCI of 80 units subcutaneously twice-weekly for 24 weeks. The primary end-point was the International Myositis Assessment and Clinical Studies definition of improvement. Secondary end-points included safety, tolerability, steroid-sparing as well as the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism myositis response criteria (EULAR); 10 of the 11 enrolled subjects (6 DM, 4 PM) completed the study; 7 of 10 met the primary end-point of efficacy at a median of 8 weeks. There was a significant decrease in prednisone dose from baseline to conclusion (18.5 (15.7) versus 2.3 (3.2); $p < 0.01$). Most individual CSMs improved at week 24 compared with the baseline, with the muscle strength improving by greater than 10% and the physician global by greater than 40%; RCI was considered safe and tolerable. No patient developed significant weight gain or an increase of hemoglobin A1c or Cushingoid features. The authors concluded that treatment with RCI was effective in 70% of patients, safe and tolerable, and led to a steroid dose reduction in patients with adult myositis refractory to glucocorticoid and traditional immunosuppressive drugs. This was an open-label study with small sample size (n = 10); these preliminary findings need to be validated in well-designed studies.

Support for using Acthar Gel or purified Cortrophin Gel to treat dermatologic diseases after an inadequate response to a trial of parenteral or oral glucocorticoids can be found in a case series. Brown (2016) stated that although numerous therapeutic options are available for patients with psoriatic arthritis (PsA), a need for effective and tolerable treatments remains for patients with refractory disease who have failed previous therapies and continue to experience tender and/or swollen joints, pain, and disease activity. Repository corticotropin injection is believed to produce steroidogenic, steroid-independent, anti-inflammatory, and immunomodulatory effects in patients with rheumatic disorders, such as PsA. Limited literature exists on the use of RCI in patients with refractory PsA. In a case-series study, this investigator provided information on the clinical features of patients with refractory PsA and their response to RCI. A total of 9 patients treated with RCI for refractory PsA were retrospectively identified and included in the case series. All 9 patients experienced at least transient improvements in their active skin and joint disease. In some patients, it was necessary to titrate the RCI to an appropriate dose; RCI was used in some patients to bridge with another PsA therapy, such as apremilast or certolizumab; RCI was well-tolerated, but discontinued in 3 patients due to pre-existing conditions (hypertension and hyperglycemia). The author concluded that RCI may be a safe and effective option for patients with refractory PsA who failed therapy with multiple previous treatments. These preliminary findings need to be validated by well-designed studies.

Support for using Acthar Gel or purified Cortrophin Gel to treat ophthalmic disease after a trial of parenteral, oral or topical ophthalmic glucocorticoids can be found in a phase four, multicenter, open-label study. Wirta et al (2022) stated that non-infectious keratitis is a painful corneal inflammation treated with topical cyclosporine and other immunosuppressants. Additional therapeutic options are needed for keratitis that does not improve with standard therapies. In an open-label, multi-center, phase-IV clinical trial, these researchers examined the safety and effectiveness of RCI for the treatment of refractory severe non-infectious keratitis. Patients were 18 years of age or older with persistent severe keratitis despite treatment with topical immunosuppressants. Patients received 80 U of RCI

subcutaneously twice-weekly for 12 weeks followed by a 4-week taper. Assessments included all domains of the Impact of Dry Eye on Everyday Life (IDEEL) Questionnaire, Ocular Discomfort and 4-Symptom Questionnaire, and VAS. Corneal fluorescein and conjunctival lissamine green staining, Conjunctival Redness Scale, Schirmer's test, VA, slit lamp examination, and IOP were also examined. Safety was evaluated via treatment-related AEs. Analyses were carried out using the modified intent-to-treat (mITT) population (patients who received 1 dose or more of RCI and contributed any post-baseline effectiveness data). In the mITT population (n = 35), 50.0% (95% confidence interval [CI]: 33.2% to 66.8%) of patients experienced clinically important improvements in the symptom bother domain of the IDEEL Questionnaire at week 12 of RCI therapy. All domains of the IDEEL and the Ocular Discomfort and 4-Symptom Questionnaire showed improvements at week 12 of RCI treatment. The most pronounced improvements in the VAS at week 12 were for eye dryness and eye discomfort. Corneal staining, conjunctival staining, conjunctival redness, and tear production showed early improvements that were sustained through week 12. No new safety signals for RCI were identified. The authors concluded that RCI was safe and effective for refractory severe non-infectious keratitis that has not improved with other approved therapies.

These researchers stated that the findings of this study added to the body of literature for a condition that is still being examined extensively. They noted that drawbacks of this study included a relatively small sample size (n = 35), a short treatment period of 12 weeks, and a lack of a placebo comparator. However, because the patients were not permitted to receive standard therapies such as cyclosporine, lifitegrast, and corticosteroids during the study period, the observed improvements in the symptoms of keratitis were likely the result of RCI treatment. Moreover, these investigators stated that although the open-label study design was appropriate for this target population of patients with severe refractory keratitis, the safety and effectiveness of this treatment warrant further investigation in a randomized, placebo-controlled trial.

Additionally, Anesi and colleagues (2023) examined if subcutaneous RCI (Acthar gel) could be an effective potential therapeutic agent for non-infectious retinal vasculitis. Patients with active retinal vasculitis were followed with serial ultra-wide-field fluorescein angiograms and treated with 80 units of subcutaneous repository corticotropin injection twice-weekly. Primary outcome of greater than or equal to 50 % improvement in response level (RL) for retinal vasculitis and percent improvement in retinal vasculitis severity scoring (RVSS) by more than one quartile (greater than or equal to 25 %) at week 12 was met in 15 and 16 of the 30 total eyes, respectively, including 1 eye with severe retinal vasculitis in each group. Complete resolution of retinal vasculitis was observed in 7 eyes with a mean time of 17.1 weeks. Intra-ocular pressure (IOP) elevation requiring therapy and cataract progression were noted in 2 and 3 eyes, respectively; 1 patient stopped medication due to side effects (injection site reaction). The authors concluded that repository corticotropin injection was well-tolerated overall; it may be an effective therapeutic agent in the treatment of non-infectious retinal vasculitis. Moreover, these researchers stated that these findings should be validated with further well-designed studies with larger sample sizes.

The authors stated that this study had several drawbacks, which include its open-label status, a limited study period of only 24 weeks, the lack of a control population, varied etiology and severity of disease, concomitant use of other immunomodulatory medications, as well as the use of subjects either on or off these other forms of therapy. Participants of this study represented a variable group of disease processes that had retinal vasculitis, as might be expected in a condition or population being studied where the number of patients is few. Criticism could be made to this point of the validity of any conclusions brought forth in this study, however, with the etiology of these processes being at least agreeably non-infectious in nature, these investigators expected that these data contain merit in the way of an observed response of a non-infectious inflammatory process to a single given therapy. Lastly, although this trial was carried out with funding provided by “Mallinckrodt Pharmaceuticals, Bedminster, NJ”, the authors were solely responsible for protocol development, initiation of patient recruitment, administration of study protocol, as well as manuscript production.

Support for using Acthar Gel or purified Cortrophin Gel to treat symptomatic sarcoidosis after an inadequate trial or parenteral or oral glucocorticoids can be found in a study by Chopra and colleagues (2019). The authors stated that RCI (repository corticotropin injection) has regulatory approval for many indications, including symptomatic sarcoidosis. This large case-series study of patients with advanced symptomatic sarcoidosis treated with RCI described patient characteristics, utilization patterns, concomitant therapies, and physicians' assessments of treatment response. This trial included patients greater than or equal to 18 years of age and with symptomatic sarcoidosis who were treated with RCI in the previous 36 months and had completed a course of RCI or received RCI for greater than or equal to 6 months at the time of data collection. The study included 302 patients (mean age of 51 years; 52%, women) with a mean 4.8 years since initial diagnosis of sarcoidosis. Most patients (76%) had extra-pulmonary involvement, primarily in the skin (28%), joints (25%), heart (22%), and eyes (22%); 34% had multiple (greater than or equal to 2) organ involvement. The mean duration of RCI treatment was 32.5 weeks, with 61.6% of patients continuing RCI therapy for greater than or equal to 6 months. The RCI utilization pattern indicated an individualized approach to therapy, with a higher starting dose associated with a shorter duration of therapy compared with a lower starting dose. The percentage of patients who used corticosteroids decreased from 61.3% during the 3 months before initiation of RCI to 12.9% 3 months following RCI therapy; the mean daily dose of corticosteroid decreased from 18.2 mg to 9.9 mg. The proportion of patients given less than 10 mg/day of prednisone increased from 21% before RCI use to 47% 3 months after RCI use. According to physicians' assessments of change in patients' health status following RCI therapy, overall status improved in 95 % of patients, overall symptoms in 73%, lung function in 38%, and inflammation in 33%. The authors concluded that these findings suggested that RCI is a viable therapeutic option for patients with advanced symptomatic sarcoidosis and provided insights on patient characteristics and practice patterns to help clinicians determine appropriate use.

The authors stated that this study was limited by its reliance on data retrospectively collected via a survey of respondents who had access to patient medical records, which might have had errors and omissions. These investigators tried to minimize the impact of potential missing data by focusing on patients’ clinical aspects and physicians’ assessments, the types of information that are usually readily available in medical records or best known to the respondents who submitted data for this study. The study did not quantify patients’ outcomes such as diagnostic measurements and safety end-points. Furthermore, because of its inherent retrospective design, there may be a risk of bias, resulting in over-estimation of the effectiveness of RCI based on physicians’ assessments. Because this was an exploratory and hypothesis-generating study, these researchers did not make any comparisons between RCI and a control group or other treatments, which may also result in bias. It is important to note the following: RCI is indicated for symptomatic sarcoidosis; RCI is included in treatment guidelines from the Foundation for Sarcoidosis Research; and a randomized, phase-IV, double-blind, placebo-controlled clinical trial is ongoing to examine the safety and efficacy of Acthar gel in patients with pulmonary sarcoidosis. Another limitation was the use of the physicians’ assessments of improvement in a patient’s health status as a key descriptive end-point to evaluate RCI therapy. This subjective end-point relied on each individual physician’s interpretation of each patient’s medical record and the physician’s standards for assessing improvement. These researchers did not collect data on test results or other objective measures that physicians might have used to make their determinations. The retrospective and non-comparative study design did not allow the authors to discern whether patients were responding to known concomitant treatments or to therapies not known to the physician or not recorded in the medical records. The use of physicians’ assessment may have under-estimated the use of biologics in these patients; however, this could not be fully ascertained from the present study.

Support for using parenteral or oral glucocorticoids be found in several guidelines and the package insert. The American Academy of Allergy, Asthma and Immunology and the Joint Council of Allergy, Asthma and Immunology state systemic corticosteroids orally or intravenous may be necessary in severe cases of serum sickness. For atopic dermatitis, the American Academy of Dermatology and European guidelines for the treatment of atopic dermatitis (2018) both agree using corticosteroids is acceptable for acute flares but long-term oral corticosteroids are not recommended.

Support for using Acthar Gel or purified Cortrophin Gel for diagnostic testing of adrenocortical function can be found in the American Hospital Formulary Service-Drug Information (AHFS-DI) reference. Acthar Gel and purified Cortrophin Gel can be used as an aid in the diagnosis of adrenocortical insufficiency. The 30-minute cosyntropin test provides a good method of screening for primary adrenocortical insufficiency (Addison's disease) and is preferable to corticotropin for rapid screening since it is less likely to cause allergic reactions. When a greater stimulus to the adrenal cortex is desired, corticotropin or cosyntropin may be administered by IV infusion. If subnormal increases in plasma cortisol concentrations occur following administration of corticotropin or cosyntropin, additional tests providing prolonged stimulation of the adrenal cortex are required before impaired adrenocortical function can be diagnosed precisely and differentiation between primary and secondary adrenocortical insufficiency can be established.

Support for using Acthar Gel or purified Cortrophin Gel to treat acquired epileptic aphasia can be found in a case study reported by Lerman, Lerman-Sagie, and Kivity. Corticotropin 80 units/day was given for 3 months; after 3 weeks of treatment electroencephalographic results improved and after 6 months speech returned. When after 2 years the aphasia recurred corticotropin was immediately reinstituted; within a few weeks speech and electroencephalogram returned to normal. Landau-Kleffner syndrome is a rare syndrome of childhood characterized by an acquired aphasia associated with abnormal electroencephalogram, with about two-thirds of cases also exhibiting seizure activity.

Support for using Acthar Gel or purified Cortrophin Gel to treat gout can be found the gout guidelines from the American College of Rheumatology. Colchicine, NSAIDs, or glucocorticoids (oral, intraarticular, or IM) are recommended as first-line treatment for gout flares over adrenocorticotropic hormone (ACTH). For patients who cannot take medications by mouth, glucocorticoids (IM, IV, or intraarticular) are recommended over ACTH, although subcutaneous synthetic ACTH is a suggested alternative.

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Reference number(s)
3416-A

Standard Medicare Part B Management Adakveo

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Adakveo	crizanlizumab-tmca

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indication

Adakveo is indicated to reduce the frequency of vaso-occlusive crises (VOCs) in adults and pediatric patients aged 16 years and older with sickle cell disease.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Sickle cell disease, to reduce the frequency of vaso-occlusive crises

Authorization of 12 months may be granted for use in reducing the frequency of vaso-occlusive crises (VOCs) in members 16 years of age or older with sickle cell disease when both of the following criteria are met:

- The member has experienced at least one vaso-occlusive crisis within the previous 12 months.
- The member meets either of the following:

- Member has sickle hemoglobin C (HbSC), sickle β^+-thalassemia (HbSβ^+), or other genotypic variants of sickle cell disease (e.g., HbS-O Arab, HbS-Lepore).
- Member has homozygous hemoglobin S (HbSS) or sickle β^0-thalassemia (HbSβ^0) genotype AND meets any of the following:
    - Has experienced, at any time in the past, an inadequate response or intolerance to a trial of hydroxyurea
    - Has a contraindication to hydroxyurea
    - Will be using Adakveo with concurrent hydroxyurea therapy

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Adakveo.
- Adakveo is being used to treat an indication listed in the coverage criteria section.
- The member is receiving benefit from therapy. Benefit is defined as reduction in the frequency of vaso-occlusive crises, or maintenance of such reduction, since initiating therapy with Adakveo.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Adakveo.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Evidence-based management of Sickle Cell Disease (NHLBI)
- Guidelines for the use of hydroxycarbamide in children and adults (2018 British Society for Haematology)
- Hydroxyurea (hydroxycarbamide) for sickle cell disease (Cochrane Review)

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Adakveo are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for requiring a trial and inadequate response, intolerance, or contraindication to hydroxyurea can be found in the National Heart, Lung, and Blood Institute (NHLBI) recommendations, the 2018 British Society of Haematology Guidelines, and a Cochrane Review.

The 2014 expert panel report from the NHLBI recommends treatment with hydroxyurea in adults with sickle cell anemia (SCA) who have had three or more moderate to severe sickle cell pain crises in the last 12 months, pain that interferes with daily activities and quality of life, history of severe and/or recurrent acute chest syndrome (ACS), severe symptomatic chronic anemia, and in infants nine months of age and older, children, and adolescents regardless of severity, to reduce complications. The report notes that SCA refers to HbSS or HbSβ^0 thalassemia, while sickle cell disease (SCD) refers to all genotypes including SCA in addition to compound heterozygous disorders such as HbSC and HbSβ^+ thalassemia. For individuals with HbSC and HBSβ^+ thalassemia who have recurrent pain, the report recommends consideration of hydroxyurea in consultation with a sickle cell expert.

The 2018 British Society for Haematology guidelines for the use of hydroxyurea in SCD recommend the following for patients with HbSS or HbSβ^0 thalassemia:

- In infants who are nine to 42 months of age, hydroxyurea should be offered regardless of clinical severity to reduce sickle cell complications.
- In children older than 42 months of age, adolescents and adults, hydroxyurea should be offered in view of the impact on reduction of mortality.
- Adults and children should be treated with hydroxyurea if they have had three or more moderate to severe pain crisis in a 12-month period, have sickle cell pain that interferes with daily activities and quality of life, and have a history of severe and/or recurrent ACS.

For children and adults with genotypes other than HbSS or HbSβ^0 thalassemia, the guideline recommends consideration of hydroxyurea in those who have recurrent episodes of acute pain, ACS, or hospitalization.

A Cochrane Review by Rankine-Mullings and Nevitt included nine randomized controlled trials (RCT) that evaluated the use of hydroxyurea in SCD. The RCTs enrolled a total of 1,104 adults and children with SCD (HbSS, HbSC or HbSβ^0 thalassemia genotypes). The authors found there is evidence that hydroxyurea may be effective in decreasing the frequency of pain episodes and other acute complications in adults and children with HbSS or HbSβ^0 thalassemia genotypes, and in preventing life-threatening neurological events in those at risk of primary stroke. The authors noted that evidence of the effects of hydroxyurea on individuals with the HbSC genotype is limited.

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Reference number(s)
4777-A

Standard Medicare Part B Management Aduhelm

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Aduhelm	aducanumab-avwa

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Aduhelm is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease. Treatment with Aduhelm 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. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with Aduhelm. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- Initial requests:
  - Medical records (e.g., chart notes) documenting the following:
    - Diagnosis of mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease.

    - Presence of amyloid pathology documented by either of the following:
        - Baseline positron emission tomography (PET) scan
        - Lumbar puncture results
    - Current enrollment in a randomized controlled trial conducted under an investigational new drug (IND) application or National Institutes of Health (NIH)-supported trial.
- Continuation requests:
    - Continued enrollment in a randomized controlled trial conducted under an investigational new drug (IND) application or National Institutes of Health (NIH)-supported trial.

Coverage Criteria

Alzheimer's Disease

Authorization of 6 months may be granted for treatment of Alzheimer's disease (AD) when all of the following criteria are met:

- Member must have mild cognitive impairment due to AD or mild AD dementia.
- Member must meet one of the following criteria:
    - Have a positron emission tomography (PET) scan confirming the presence of amyloid pathology.
    - Have results from a lumbar puncture confirming at least one of the following detected in cerebrospinal fluid (CSF) as determined by the lab assay:
        - Presence of elevated phosphorylated tau (P-tau) protein and/or total tau (T-tau) protein, and reduced beta amyloid-42 (AB42)
        - Low AB42/AB40 ratio
        - Elevated P-Tau/AB42 ratio
        - Elevated T-Tau/AB42 ratio
- Member must currently be enrolled in a randomized controlled trial conducted under an investigational new drug (IND) application or National Institutes of Health (NIH)-supported trial.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 6 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Aduhelm.
- Aduhelm is being used to treat an indication listed in the coverage criteria.
- The member continues to be enrolled in a randomized controlled trial conducted under an investigational new drug (IND) application or National Institutes of Health (NIH)-supported trial.

Reference number(s)
4777-A

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Aduhelm.
- The available compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- National Coverage Determination (NCD) for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Aduhelm are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Using Aduhelm to treat mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease (AD) dementia is covered according to the conditions outlined in National Coverage Determination Manual section 200.3- Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease. Monoclonal antibodies directed against amyloid that are approved by the FDA for the treatment of AD based upon evidence of efficacy from a direct measure of clinical benefit may be covered in CMS-approved prospective comparative studies. Study data for CMS-approved prospective comparative studies may be collected in a registry.

Support for using a lumbar puncture to confirm amyloid pathology in cerebrospinal fluid can be found in an article published by Schindler et al. Decreases in cerebrospinal fluid (CSF) Aβ42 levels and increases in CSF total Tau (tTau) and phosphorylated Tau-181 (pTau) may be the earliest markers of AD brain pathology. The ratio of Aβ42 with another AD biomarker (e.g. tTau/Aβ42, pTau/Aβ42, or Aβ42/Aβ40) may provide the best correlation with amyloid PET measures.

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Reference number(s)
6251-A

Standard Medicare Part B Management
Adzynma

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Adzynma	ADAMTS13, recombinant-krhn

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indication

Adzynma is indicated for prophylactic or on demand enzyme replacement therapy (ERT) in adult and pediatric patients with congenital thrombotic thrombocytopenic purpura (cTTP).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- Initial requests: ADAMTS13 enzyme assay and ADAMTS13 genetic testing results supporting the diagnosis.
- Continuation of therapy requests: Medical records (e.g., chart notes, lab reports) documenting a response to therapy (e.g., reduction or maintenance of number of thrombotic thrombocytopenic purpura [TTP] events, increase in platelet count, decrease in lactate dehydrogenase [LDH] level).

Reference number(s)
6251-A

Coverage Criteria

Congenital Thrombotic Thrombocytopenic Purpura (cTTP)

Authorization of 6 months may be granted for the treatment of congenital thrombotic thrombocytopenic purpura (cTTP) when both of the following criteria are met:

- The diagnosis of cTTP has been confirmed by genetic testing with biallelic mutations in the ADAMTS13 gene.
- Member has an ADAMTS13 activity level of less than 10% at the time of diagnosis.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication listed in the coverage criteria section.
- The member is receiving benefit from therapy (e.g., reduction or maintenance of number of thrombotic thrombocytopenic purpura [TTP] events, increase in platelet count, decrease in lactate dehydrogenase [LDH] level).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Adzynma.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Adzynma are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using an enzyme assay and genetic testing to confirm the diagnosis of cTTP prior to initiating treatment with Adzynma can be found in the clinical trials cited in the prescribing information. To be included in the trial, the patient must have had a documented diagnosis of severe hereditary ADAMTS13 deficiency, defined as: A) Confirmed by molecular genetic testing, documented in participant history or at screening, and B) ADAMTS13 activity < 10 % as measured by the fluorescent resonance energy transfer- von Willebrand factor73 (FRETS-VWF73) assay, documented in participant history or at screening (participants currently receiving standard of care prophylactic therapy may exceed 10% ADAMTS13 activity at screening). Additionally, an article from The New England Journal of Medicine, cited in the prescribing information, indicates that hereditary TTP is caused by biallelic mutations in the gene ADAMTS13 that lead to a severe ADAMTS13 deficiency (ADAMTS13 activity <10% of that in normal plasma).

References

1. Adzynma [package insert]. Lexington, MA: Takeda Pharmaceuticals U.S.A., Inc.; November 2023.
2. Asmis LM, Serra A, Krafft A, et al. Recombinant ADAMTS13 for Hereditary Thrombotic Thrombocytopenic Purpura. N Engl J Med 2022; 387: 2356-2361.
3. Scully M, Antun A, Ctalan SR, et al. Recombinant ADAMTS13 in Congenital Thrombotic Thrombocytopenic Purpura. N Engl J Med 2024; 390(17):1584-1596. doi:10.1056/NEJMoa2314793.

Reference number(s)
4564-A

Standard Medicare Part B Management Amondys 45

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Amondys 45	casimersen

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Amondys 45 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.

This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with Amondys 45. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- Initial requests: laboratory confirmation of Duchenne muscular dystrophy (DMD) diagnosis with a DMD gene mutation that is amenable to exon 45 skipping (refer to examples in Appendix).
- Continuation of therapy requests: documentation (e.g., chart notes) of response to therapy.

Coverage Criteria

Duchenne muscular dystrophy

Authorization of 6 months may be granted for treatment of DMD when all of the following criteria are met:

- Genetic testing was conducted to confirm the diagnosis of DMD and to identify the specific type of DMD gene mutation.
- The DMD gene mutation is amenable to exon 45 skipping (refer to examples in Appendix).
- Treatment with Amondys 45 is initiated before the age of 14.
- The member is able to achieve an average distance of at least 300 meters while walking independently over 6 minutes.
- Dose will not exceed 30 mg/kg once weekly.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Amondys 45.
- Amondys 45 is being used to treat an indication in the coverage criteria section.
- The member has demonstrated a response to therapy as evidenced by remaining ambulatory (e.g., able to walk with or without assistance, not wheelchair dependent).
- The member will not exceed a dose of 30 mg/kg once weekly.

Appendix

Examples of DMD gene mutations (exon deletions) amenable to exon 45 skipping (not an all-inclusive list):

- Deletion of exon 44
- Deletion of exon 46-47
- Deletion of exon 46-48
- Deletion of exon 46-49
- Deletion of exon 46-51
- Deletion of exon 46-53
- Deletion of exon 46-55

Reference number(s)
4564-A

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Amondys 45.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Amondys 45 are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for requiring a minimum six minute walk time of greater than 300 meters can be found in the inclusion criteria for the ESSENCE trial.

References

1. Amondys 45 [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc; March 2023.
2. ClinicalTrials.gov. Study of SRP-4045 and SRP-4053 in DMD patients (ESSENCE). Available at: https://clinicaltrials.gov/ct2/show/NCT02500381. Accessed March 1, 2021.
3. Fletcher, S., et. al. Dystrophin Isoform Induction In Vivo by Antisense-mediated Alternative Splicing. The American Society of Gene & Cell Therapy. 2010;18(6):1218-1223.
4. Polavarapu K, Preethish-Kumar V, Sekar D, et al. Mutation pattern in 606 Duchenne muscular dystrophy children with a comparison between familial and non-familial forms: a study in an Indian large single-center cohort. J Neurol. 2019;266(9):2177-2185.

Reference number(s)
5499-A

Standard Medicare Part B Management Amvuttra

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Amvuttra	Vutrisiran

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Amvuttra is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- Initial requests:
  - Testing or analysis confirming a mutation in the TTR gene.
  - Medical record documentation confirming the member demonstrates signs and symptoms of polyneuropathy.
- Continuation requests: Chart notes or medical record documentation supporting clinical benefit of therapy compared to baseline.

Coverage Criteria

Polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis[1-3]

Authorization of 12 months may be granted for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (also called transthyretin-type familial amyloid polyneuropathy [ATTR-FAP]) when all of the following criteria are met:

- The diagnosis is confirmed by detection of a mutation in the TTR gene.
- Member exhibits clinical manifestations of ATTR-FAP (e.g., amyloid deposition in biopsy specimens, TTR protein variants in serum, progressive peripheral sensory-motor polyneuropathy).
- Member is not a liver transplant recipient.
- The requested medication will not be used in combination with any other medication approved for the treatment of hereditary transthyretin-mediated amyloidosis (e.g., Onpattro, Tegsedi, Vyndamax, Vyndaqel, Wainua).

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving treatment with the requested medication.
- The requested medication is being used to treat an indication enumerated in the coverage criteria section.
- There is a clinical benefit from therapy with the requested medication compared to baseline (e.g., improvement of neuropathy severity and rate of disease progression as demonstrated by the modified Neuropathy Impairment Scale+7 (mNIS+7) composite score, the Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score, polyneuropathy disability (PND) score, FAP disease stage, manual grip strength).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Amvuttra
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Guideline of transthyretin-related hereditary amyloidosis for clinicians.
- Hereditary Transthyretin Amyloidosis. In: GeneReviews.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Amvuttra are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using the above initial criteria can be found in a guideline from Ando and colleagues and a Gene Reviews chapter discussing hereditary transthyretin amyloidosis. The diagnosis of ATTR should be suspected in patients with progressive sensorimotor and/or autonomic neuropathy. The diagnosis of hereditary ATTR is established when characteristic clinical features are present, a biopsy shows amyloid deposits that bind to anti-TTR antibodies, and there is identification of mutations of the TTR gene.

The treatment for peripheral and autonomic neuropathy is orthotopic liver transplantation, TTR tetramer stabilizers, and gene-silencing therapies (such as Amvuttra). Liver transplantation provides a wild type gene expressing normal TTR in the liver. Successful liver transplantation results in the disappearance of the variant TTR protein and thus halts the progression of peripheral and/or autonomic neuropathy.

Pharmacologic treatment approaches for hereditary TTR amyloidosis (ATTR) include ribonucleic acid (RNA)-targeted therapies (e.g., Amvuttra, Onpattro, Tegsedi, Wainua) that interfere with hepatic TTR synthesis, and transthyretin tetramer stabilizers (e.g., Vyndaqel, Vyndamax) that reduce formation of TTR amyloid through stabilization of the tetramer configuration and subsequently prevent the release of amyloidogenic monomers. These therapies work to decrease TTR production. Currently, there is no literature supporting the combination use of any therapies approved for ATTR.

References

1. Amvuttra [package insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; February 2023.
2. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013; 8:31.
3. Sekijima Y. Hereditary Transthyretin Amyloidosis. 2001 Nov 5 [Updated 2021 June 17]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1194/. Accessed March 4, 2024.

Reference number(s)
6477-A

Standard Medicare Part B Management
Anktiva

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Anktiva	nogapendekin alfa inbakicept-pmln

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Anktiva is indicated with Bacillus Calmette-Guérin (BCG) for the treatment of adult patients with BCG-unresponsive nonmuscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Bladder Cancer[1]

Authorization of 6 months may be granted for treatment of bladder cancer when all of the following criteria are met:

- The member has non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors
- The disease is Bacillus Calmette-Guerin (BCG)-unresponsive
- The requested medication will be used in combination with Bacillus Calmette-Guerin (BCG)

- The member will receive maintenance doses at months 4, 7, 10, 13 and 19 after induction therapy.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months [for a total of 24 maintenance doses (37 months of treatment)] may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat an indication listed in the coverage criteria section
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease recurrence or progression while on the current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Anktiva.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Anktiva [package insert]. Bothell, WA: AGC Biologics; April 2024.

Reference number(s)
2477-A

Standard Medicare Part B Management Avastin and bevacizumab biosimilars - Oncology

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Avastin	bevacizumab
Alymsys	bevacizumab-maly
Avzivi	bevacizumab-tnjn
Mvasi	bevacizumab-awwb
Vegzelma	bevacizumab-adcd
Zirabev	bevacizumab-bvzr

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1-6]

Metastatic Colorectal Cancer (mCRC)

- Avastin/Alymsys/Avzivi/Mvasi/Vegzelma/Zirabev, in combination with intravenous fluorouracil-based chemotherapy, is indicated for the first- or second-line treatment of patients with metastatic colorectal cancer.
- Avastin/Alymsys/Avzivi/Mvasi/Vegzelma/Zirabev in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment of patients with metastatic colorectal cancer who have progressed on a first-line bevacizumab-containing regimen.

First-Line Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Avastin/Alymsys/Avzivi/Mvasi/Vegzelma/Zirabev, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer.

Recurrent Glioblastoma (GBM)

Avastin/Alymsys/Avzivi/Mvasi/Vegzelma/Zirabev is indicated for the treatment of recurrent glioblastoma in adults.

Metastatic Renal Cell Carcinoma (mRCC)

Avastin/Alymsys/Avzivi/Mvasi/Vegzelma/Zirabev, in combination with interferon alfa, is indicated for the treatment of metastatic renal cell carcinoma.

Persistent, Recurrent, Or Metastatic Cervical Cancer

Avastin/Alymsys/Avzivi/Mvasi/Vegzelma/Zirabev, in combination with paclitaxel and cisplatin or paclitaxel and topotecan, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.

Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

- Avastin/Mvasi/Vegzelma/Zirabev, in combination with carboplatin and paclitaxel, followed by Avastin/Mvasi/Vegzelma/Zirabev as a single agent, is indicated for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection.
- Avastin/Alymsys/Avzivi/Mvasi/Vegzelma/Zirabev, in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan, is indicated for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than 2 prior chemotherapy regimens.
- Avastin/Mvasi/Vegzelma/Zirabev, in combination with carboplatin and paclitaxel, or with carboplatin and gemcitabine, followed by Avastin/Mvasi/Vegzelma/Zirabev as a single agent, is indicated for the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Hepatocellular Carcinoma

Avastin, in combination with atezolizumab, is indicated for the treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

Compendial Uses[7-15]

- Advanced gastric cancer
- Advanced liver carcinoma
- Breast cancer
- Central nervous system (CNS) cancers
    - Circumscribed glioma
    - Diffuse high grade and high grade gliomas
    - Glioblastoma
    - IDH mutant astrocytoma (WHO Grade 2, 3, or 4)

  - Oligodendroglioma (WHO Grade 2 or 3)
  - Intracranial and spinal ependymoma (excludes subependymoma)
  - Medulloblastoma
  - Primary central nervous system lymphoma
  - Meningiomas
  - Limited and extensive brain metastases
  - Metastatic spine tumors
  - Primary spinal cord tumors
- Necrosis of central nervous system due to exposure to ionizing radiation
- Pleural mesothelioma, Peritoneal mesothelioma, Pericardial mesothelioma, Tunica vaginalis testis mesothelioma
- Ovarian cancer/Fallopian tube cancer/Primary peritoneal cancer
- Soft tissue sarcoma
  - Angiosarcoma
  - Solitary fibrous tumor/Hemangiopericytoma
- Uterine neoplasms/Endometrial carcinoma
- Vulvar carcinoma
- Vaginal cancer
- Cervical cancer
- Small bowel adenocarcinoma
- Ampullary adenocarcinoma
- Appendiceal adenocarcinoma
- Anal adenocarcinoma
- Renal cell carcinoma
- Hepatocellular carcinoma

Nationally Covered Indications[9,10]

CMS covers bevacizumab for use in specific clinical trials (NCI-CMS Pilot Project). Refer to the Appendix for a list of these covered clinical trials.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Colorectal Cancer[1-7,11-13]

Authorization of 12 months may be granted for treatment of colorectal cancer, including appendiceal adenocarcinoma and anal adenocarcinoma.

Non-Small Cell Lung Cancer[1-7]

Authorization of 12 months may be granted for treatment of symptomatic local, recurrent, unresectable, advanced or metastatic non-squamous non-small cell lung cancer.

Renal Cell Cancer[1-7]

Authorization of 12 months may be granted for treatment of relapsed or stage IV renal cell cancer.

Cervical Cancer[1-7]

Authorization of 12 months may be granted for treatment of persistent, recurrent, or metastatic cervical cancer.

Vaginal Cancer[7]

Authorization of 12 months may be granted for treatment of recurrent or metastatic vaginal cancer.

Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer[1-7]

Authorization of 12 months may be granted for treatment of epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, and malignant sex cord stromal tumors.

Hepatocellular Carcinoma[1,7,8]

Authorization of 12 months may be granted for treatment of unresectable, advanced or extrahepatic/metastatic hepatocellular carcinoma.

Authorization of 12 months may be granted for adjuvant treatment of operable hepatocellular carcinoma, when the member is at a high risk of recurrence and the requested medication will be used in combination with atezolizumab.

Gastric Cancer[8]

Authorization of 12 months may be granted for treatment of gastric cancer.

Central Nervous System (CNS) Cancer[1-7]

Authorization of 12 months may be granted for treatment of the following types of CNS cancer:

- Circumscribed glioma
- Diffuse high grade and high grade gliomas
- Glioblastoma
- IDH mutant astrocytoma (WHO Grade 2, 3, or 4)
- Oligodendroglioma (WHO Grade 2 or 3)
- Intracranial and spinal ependymoma (excluding subependymoma)
- Medulloblastoma
- Primary central nervous system lymphoma
- Meningiomas
- Limited and extensive brain metastases
- Metastatic spine tumors
- Primary spinal cord tumors

Necrosis of Central Nervous System Due to Exposure to Ionizing Radiation[8]

Authorization of 3 months may be granted for treatment of central nervous system necrosis due to exposure to ionizing radiation.

Uterine Neoplasms/Endometrial Carcinoma[7,14]

Authorization of 12 months may be granted for treatment of progressive, persistent, recurrent, or metastatic uterine neoplasms or endometrial carcinoma.

Mesothelioma[7,8]

Authorization of 12 months may be granted for treatment of pleural mesothelioma, peritoneal mesothelioma, pericardial mesothelioma, or tunica vaginalis testis mesothelioma when any of the following criteria are met:

- As first-line therapy in combination with pemetrexed and either cisplatin or carboplatin, followed by single-agent maintenance bevacizumab
- As subsequent therapy in combination with pemetrexed and either cisplatin or carboplatin if immunotherapy was administered as first-line treatment

Authorization of 12 months may be granted for treatment of peritoneal mesothelioma, pericardial mesothelioma, or tunica vaginalis testis mesothelioma when used in combination with atezolizumab as subsequent therapy.

Breast Cancer[8,14]

Authorization of 12 months may be granted for treatment of metastatic breast cancer.

Soft Tissue Sarcoma[7,15]

Authorization of 12 months may be granted for treatment of angiosarcoma, as single agent therapy.

Authorization of 12 months may be granted for treatment of solitary fibrous tumor or hemangiopericytoma, in combination with temozolomide.

Vulvar Carcinoma[7]

Authorization of 12 months may be granted for treatment of advanced, recurrent, or metastatic vulvar carcinoma, including squamous cell carcinoma and adenocarcinoma.

Small Bowel Adenocarcinoma[7]

Authorization of 12 months may be granted for treatment of small bowel adenocarcinoma.

Ampullary Adenocarcinoma[7]

Authorization of 12 months may be granted for treatment of intestinal-type ampullary adenocarcinoma that is progressive, unresectable, or metastatic.

NCD Indications[9,10]

Authorization of 12 months may be granted for treatment of patients enrolled in any of the studies listed in the Appendix section.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 3 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat central nervous system necrosis due to exposure to ionizing radiation.
- The member is receiving benefit from therapy.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section (excluding central nervous system necrosis due to exposure to ionizing radiation).
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen and
    - No evidence of disease progression while on the current regimen.

Appendix

NCI/CTEP-Sponsored Studies Selected for Inclusion in NCI-CMS Pilot Project (Studies in Various Stages of Development)

Study ID #	Study Title
C80405	Phase III Trial of Irinotecan/5-FU/Leucovorin or Oxaliplatin/5FU/Leucovorin with Bevacizumab, or Cetuximab, or with the combination of Bevacizumab and Cetuximab for Patients with Untreated Metastatic Adenocarcinoma of the Colon or Rectum
E2204	An Intergroup Randomized Phase II Study of Bevacizumab or Cetuximab in Combination with Gemcitabine and in Combination with Chemoradiation (Capecitabine and Radiation) in Patients with Completely-Resected Pancreatic Carcinoma
E4203	Phase II Study of Treatment Selection Based Upon Tumor Thymidylate Synthase Expression in Previously Untreated Patients with Metastatic Colorectal Cancer
E5202	Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers
E5204	Intergroup Randomized Phase III Study of Post-Operative Oxaliplatin, 5-Fluorouracil and Leucovorin with or without Bevacizumab in Patients with Stage II or III Rectal Cancer Receiving Pre-Operative Radiation and a 5-Fluorouracil-Based Regimen
NSABP-R-04	A Clinical Trial Comparing Preoperative Radiation Therapy and Capecitabine with or without Oxaliplatin with Preoperative Radiation Therapy and Continuous Intravenous Infusion 5-Fluorouracil with or without Oxaliplatin in the Treatment of Patients with Operable Carcinoma of the Rectum
RTOG-0522	Phase III Trial of Concurrent Accelerated Radiation & Cisplatin vs Concurrent Accelerated Radiation, Cisplatin, & Cetuximab (Followed by Surgery for Selected Patients) for Stage III & IV Head & Neck Carcinomas
S0502	Phase III Randomized Study of Imatinib, with or without Bevacizumab, in Patients with Metastatic or Unresectable Gastrointestinal Stromal Tumors
7325	Dose-Dense and Dose-Intense Alternating Irinotecan/Capecitabine & Oxaliplatin/Capecitabine: Phase I in Solid Tumors and Phase II with Bevacizumab as First-Line Therapy of Advanced Colorectal Cancer

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Avastin, Alymsys, Avzivi, Mvasi, Vegzelma, and Zirabev.
- The available compendium

  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)
  - Lexi-Drugs
  - Clinical Pharmacology
- NCCN Guideline: Vulvar cancer
- NCCN Guideline: Cervical cancer
- NCCN Guideline: Small bowel adenocarcinoma
- NCCN Guideline: Peritoneal mesothelioma
- NCCN Guideline: Pediatric central nervous system cancers
- NCCN Guideline: Pleural mesothelioma
- NCCN Guideline: Non-small cell lung cancer
- NCCN Guideline: Hepatocellular carcinoma
- NCCN Guideline: Central nervous system cancers
- NCCN Guideline: Ampullary adenocarcinoma
- NCCN Guideline: Ovarian cancer, including fallopian tube cancer and primary peritoneal cancer
- NCCN Guideline: Kidney cancer
- NCCN Guideline: Uterine neoplasms
- NCCN Guideline: Soft tissue sarcoma
- NCCN Guideline: Colon cancer
- NCCN Guideline: Rectal cancer
- NCCN Guideline: Vaginal cancer
- National Coverage Determination (NCD) for Anti-cancer Chemotherapy for Colorectal Cancer (110.17)
- NCI/CTEP-Sponsored Studies Selected for Inclusion in NCI-CMS Pilot Project

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Avastin, Alymsys, Avzivi, Mvasi, Vegzelma, and Zirabev are covered in addition to the following:

- Inclusion in NCI/CTEP-sponsored studies selected for inclusion in NCI-CMS pilot project
- Advanced gastric cancer
- Advanced liver carcinoma
- Breast cancer
- Central nervous system (CNS) cancers
  - Circumscribed glioma
  - Diffuse high grade and high grade gliomas
  - Glioblastoma
  - IDH mutant astrocytoma (WHO Grade 2, 3, or 4)
  - Oligodendroglioma (WHO Grade 2 or 3)

  - Intracranial and spinal ependymoma (excludes subependymoma)
  - Medulloblastoma
  - Primary central nervous system lymphoma
  - Meningiomas
  - Limited and extensive brain metastases
  - Metastatic spine tumors
  - Primary spinal cord tumors
- Necrosis of central nervous system due to exposure to ionizing radiation
- Pleural mesothelioma, Peritoneal mesothelioma, Pericardial mesothelioma, Tunica vaginalis testis mesothelioma
- Ovarian cancer/Fallopian tube cancer/Primary peritoneal cancer
- Soft tissue sarcoma
  - Angiosarcoma
  - Solitary fibrous tumor/Hemangiopericytoma
- Uterine neoplasms/Endometrial carcinoma
- Vulvar carcinoma
- Vaginal cancer
- Cervical cancer
- Small bowel adenocarcinoma
- Ampullary adenocarcinoma
- Appendiceal adenocarcinoma
- Anal adenocarcinoma
- Renal cell carcinoma
- Hepatocellular carcinoma

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using bevacizumab for the below listed indications can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

- Central nervous system (CNS) cancers
  - Circumscribed glioma
  - Diffuse high grade and high grade gliomas
  - Glioblastoma
  - IDH mutant astrocytoma (WHO Grade 2, 3, or 4)

  - Oligodendroglioma (WHO Grade 2 or 3)
  - Intracranial and spinal ependymoma (excludes subependymoma)
  - Medulloblastoma
  - Primary central nervous system lymphoma
  - Meningiomas
  - Limited and extensive brain metastases
  - Metastatic spine tumors
  - Primary spinal cord tumors
- Necrosis of central nervous system due to exposure to ionizing radiation
- Pleural mesothelioma, Peritoneal mesothelioma, Pericardial mesothelioma, Tunica vaginalis testis mesothelioma
- Ovarian cancer/Fallopian tube cancer/Primary peritoneal cancer
- Soft tissue sarcoma
  - Angiosarcoma
  - Solitary fibrous tumor/Hemangiopericytoma
- Uterine neoplasms/Endometrial carcinoma
- Vulvar carcinoma
- Vaginal cancer
- Cervical cancer
- Small bowel adenocarcinoma
- Ampullary adenocarcinoma
- Appendiceal adenocarcinoma
- Anal adenocarcinoma
- Renal cell carcinoma
- Hepatocellular carcinoma

Support for using bevacizumab for advanced gastric cancer, advanced liver carcinoma and breast cancer can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Use of bevacizumab in an NCI/CTE-sponsored study is covered according to the conditions outlined in National Coverage Determination Manual section 110.17 Anti-Cancer Chemotherapy for Colorectal Cancer.

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Reference number(s)
2509-A

Standard Medicare Part B Management Avastin

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Avastin	bevacizumab
Alymsys	bevacizumab-maly
Avzivi	bevacizumab-tnjn
Mvasi	bevacizumab-awwb
Vegzelma	bevacizumab-adcd
Zirabev	bevacizumab-bvzr
Ocular & Other	ocular & other

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Avastin/Alymsys/Avzivi/Mvasi/Vegzelma/Zirabev does not have FDA-approved non-oncology indications. For oncology indications, please see the Avastin/Alymsys/Avzivi/Mvasi/Vegzelma/Zirabev - Oncology MedB policy.

Compendial Uses

- Diabetic macular edema
- Neovascular (wet) age-related macular degeneration
- Retinal vein occlusion with macular edema
- Proliferative diabetic retinopathy

- Choroidal neovascularization
- Neovascular glaucoma
- Retinopathy of prematurity
- Epistaxis due to hereditary hemorrhagic telangiectasia syndrome

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Diabetic Macular Edema

Authorization of 12 months may be granted for the treatment of diabetic macular edema.

Neovascular (Wet) Age-Related Macular Degeneration

Authorization of 12 months may be granted for the treatment of neovascular (wet) age-related macular degeneration including polypoidal choroidopathy.

Macular Edema Following Retinal Vein Occlusion

Authorization of 12 months may be granted for the treatment of macular edema following retinal vein occlusion.

Proliferative Diabetic Retinopathy

Authorization of 12 months may be granted for the treatment of proliferative diabetic retinopathy.

Choroidal Neovascularization

Authorization of 12 months may be granted for the treatment of choroidal neovascularization.

Neovascular Glaucoma

Authorization of 12 months may be granted for the treatment of neovascular glaucoma.

Retinopathy of Prematurity

Authorization of 12 months may be granted for the treatment of retinopathy of prematurity.

Epistaxis Due to Hereditary Hemorrhagic Telangiectasia Syndrome[7]

Authorization of 12 months may be granted for the treatment of epistaxis due to hereditary hemorrhagic telangiectasia syndrome.

Reference number(s)
2509-A

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The medication has been effective for treating the diagnosis or condition.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Avastin, Alymsys, Avzivi, Mvasi, Vegzelma, and Zirabev. The prescribing information only contains oncology indications.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Diabetic Retinopathy.
- American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Age-Related Macular Degeneration.
- American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Retinal Vein Occlusions.

After reviewing the information in the above resources, the following indications are covered for Avastin, Alymsys, Avzivi, Mvasi, Vegzelma, and Zirbev:

- Diabetic macular edema
- Neovascular (Wet) age-related macular degeneration
- Retinal vein occlusion with macular edema
- Proliferative diabetic retinopathy
- Choroidal neovascularization
- Neovascular glaucoma
- Retinopathy of prematurity
- Epistaxis due to hereditary hemorrhagic telangiectasia syndrome

Explanation of Rationale

Support for diabetic macular edema can be found in a systematic review and network meta-analysis of 24 randomized trials in 6007 patients with diabetic macular edema, antiangiogenic therapy with anti-vascular endothelial growth factor (anti-VEGF) agents (aflibercept, bevacizumab, pegaptanib, ranibizumab) was significantly more effective compared with laser photocoagulation in improving vision at 1 year evaluated with the best-corrected visual acuity. Aflibercept significantly improved the likelihood of a gain of 3+ lines and mean BCVA change compared with ranibizumab and bevacizumab. There was no significant difference in functional outcomes at 1 year comparing ranibizumab and bevacizumab, but reduction in central retinal thickness was better with ranibizumab.

A single-center randomized clinical trial also demonstrated that intravitreal injection of bevacizumab every 6 weeks based on clinical response determined by OCT and visual acuity is superior to macular photocoagulation every 4 months (Michaelides et al, 2010). The authors reported the odds of gaining greater than or equal to 10 ETDRS letters over 12 months were 5.1 times greater in the bevacizumab group than in the laser group (adjusted odds ratio, 5.1; 95 % CI: 1.3 to 19.7; p = 0.019).

Support for neovascular (wet) age-related macular degeneration can be found in a multicenter, single-blind, noninferiority trial conducted by the CATT Research Group. The study randomly assigned 1208 patients with neovascular AMD to receive intravitreal injections of ranibizumab or bevacizumab on either a monthly schedule or as needed with monthly evaluation. The primary outcome was the mean change in visual acuity at 1 year, with a noninferiority limit of 5 letters on the eye chart. Bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 letters gained, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with 5.9 and 6.8 letters gained, respectively. Ranibizumab as needed was equivalent to monthly ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive. The mean decrease in central retinal thickness was greater in the ranibizumab-monthly group (196 µm) than in the other groups (152 to 168 µm, P=0.03 by analysis of variance). Rates of death, myocardial infarction, and stroke were similar for patients receiving either bevacizumab or ranibizumab (P>0.20). The proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern. At 1 year, bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same schedule. Ranibizumab given as needed with monthly evaluation had effects on vision that were equivalent to those of ranibizumab administered monthly. Differences in rates of serious adverse events require further study.

Support for branch retinal vein occlusion with macular edema can be found in a study by Russo et al. Thirty eyes of 30 consecutive patients with cystoid macular edema secondary to nonischemic branch retinal vein occlusion were assigned to either GLP group or to intravitreal bevacizumab (IB) group. Complete ophthalmologic examinations were performed just before GLP and IB injection at 1, 3, 6, and 12 months after treatment. Changes in logarithm of minimum angle of resolution (logMAR) best-corrected visual acuity (BCVA), central macular thickness (CMT) shown by optical coherence tomography-3 were evaluated. Baseline BCVA (logMAR) and CMT were, respectively, 0.89 +/- 0.13 and 650 +/- 140 microm for the GLP group, 0.87 +/- 0.16 and 690 +/- 120 microm for the IB group. After the treatment, at 1, 3, 6, and 12 months in the GLP group, BCVA had improved by 0.19, 0.22, 0.21, and 0.20 logMAR, CMT had decreased by 40%, 41.3%, 40.5%, and 42%. In the IB group, BCVA had improved by 0.31, 0.32, 0.30, and 0.31 logMAR and CMT had decreased by 59.5%, 59%, 60%, and 60.3%. The group receiving bevacizumab had better BCVA and lower CMT values at all time points (P < 0.05). Intravitreal bevacizumab injection improved BCVA and reduced CMT more than GLP. Intravitreal bevacizumab

injection was well tolerated and could be used as primary treatment in patients with cystoid macular edema secondary to perfused branch retinal vein occlusion.

Support for central retinal vein occlusion with macular edema can be found in the SCORE2 randomized clinical trial. Intravitreal bevacizumab was not inferior to aflibercept in mean change in visual acuity letter score (VALS) at 6 months (from 50.4 to 69.3 vs from 50.3 to 69.3) in the randomized SCORE-2 trial in patients with macular edema secondary to central retinal or hemiretinal vein occlusion (N=362). There were also no significant between-group differences at 6 months in the proportion of eyes with a VALS gain of at least 15 (61.3% vs 65.1%), a VALS decrease of at least 15 (1.7% each group) or mean decrease in central subfield thickness (387 vs 425 mcm). A post hoc analysis demonstrated that the likelihood of resolution of macular edema was significantly decreased by 72% with bevacizumab. Bevacizumab was associated with 1 case of endophthalmitis (culture negative) and 2 cases of intraocular pressure (IOP) greater than 35 mmHg. An IOP increase of more than 10 mmHg from baseline occurred in 4.9% of patients with bevacizumab and in 2.2% of patients with aflibercept. Intravitreal interventions included 6 months of bevacizumab 1.25 mg every 4 weeks or aflibercept 2 mg every 4 weeks.

In a 24-week, prospective, randomized, double-blind study (n=60 eyes) of patients with macular edema secondary to central retinal vein occlusion (CRVO), intravitreal injections of bevacizumab statistically significantly improved visual acuity compared with sham (Epstein et al). Patients with CRVO for up to 6 months, best corrected visual acuity (BCVA) of 15 to 65 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Snellen equivalent approximately 20/50 to 20/500), and a mean central subfield thickness of 300 micrometers (mcm) or greater were included in the study. Patients (mean age of 70.5 years [range, 52 to 93 years]) were randomized to receive either bevacizumab 1.25 mg/0.05 mL via intravitreal injection (n=30 eyes) via the plans plana or sham (n=30 eyes) injection using a needless syringe pressed to the globe every 6 weeks for 6 months (4 injections). The percentage of patients achieving a 15 or greater ETDRS letter improvement (primary endpoint) was 60% vs 20% (p=0.003) in the bevacizumab and sham arms, respectively. At the 24-week follow-up, visual acuity improved from baseline by a mean of 14.1 ETDRS letters in the bevacizumab arm compared with a mean decrease from baseline of 2 ETDRS letters in the sham arm, with a statistically significant treatment difference occurring from week 12 and beyond (p less than 0.01). There was a statistically significant improvement in the mean decrease in central retinal thickness (CRT; 426 vs 102 mcm), respectively, at all-time points up to week 24 (p less than 0.001). There was no residual edema (CRT less than 300 mcm) at 24 weeks in 86.7% in the bevacizumab arm compared with 20% in the sham arm (p less than 0.001). Iris rubeosis occurred at week 24 in 16.7% of patients in the sham arm and 0% in the bevacizumab arm (p=0.052). There were no reports of serious adverse events, endophthalmitis, or retinal tear or detachment.

Support for proliferative diabetic retinopathy can be found in a study by Mirshahi et al. A prospective, fellow-eye sham controlled clinical trial was conducted on 80 eyes of 40 high-risk characteristic proliferative diabetic retinopathy type II diabetics. All cases received standard laser treatment according to Early Treatment Diabetic Retinopathy Study protocol. Avastin-assigned eyes received 1.25 mg intravitreal bevacizumab on the first session of their laser treatments. Fluorescein angiography was performed at baseline and at weeks 6 and 16, and proliferative diabetic retinopathy regression was evaluated in a masked fashion. The median age was 52 years (range: 39-68) and 30% of the participants were male. All patients were followed for 16 weeks. A total of 87.5% of Avastin-injected eyes and 25% of sham group showed complete regression at week 6 of follow-up (p<0.005). However, at week 16, PDR recurred in a sizable number of the Avastin-treated eyes, and the complete regression rate in the two groups became identical (25%; p=1.000); partial regression rates were 70% vs 65%. In the subgroup of Avastin-treated eyes, multivariate analysis identified hemoglobin A1c as the strongest predictor of proliferative diabetic retinopathy recurrence (p=0.033). Intravitreal bevacizumab remarkably augmented the short-term response to scatter panretinal laser photocoagulation in high-risk characteristic proliferative diabetic retinopathy but the effect was short-lived, as many of the eyes showed rapid recurrence. Alternative dosing (multiple and/or periodic intravitreal Avastin injections) is recommended for further evaluation.

Support for choroidal neovascularization can be found in a study published by Wang et al. Treatment with anti-vascular endothelial growth factor injections was more effective compared with photodynamic therapy, with significant improvements in best corrected visual acuity and retinal thickness reduction. A systematic review identified 2 randomized trials of patients treated with bevacizumab or ranibizumab for myopic choroidal neovascularization (N=32 eyes, duration 6 months; N=48 eyes, duration 18 months), and a meta-analysis found no significant difference between these groups in best corrected visual acuity or retinal thickness reduction. In the 6-month study, the number of required injections did not significantly differ (2.8 vs 2.4); however, in the 18-month study, significantly more injections were required in the bevacizumab group compared with ranibizumab (4.7 vs 2.6).

Chan and colleagues conducted a prospective pilot study studying the 1-year results of intravitreal bevacizumab for myopic choroidal neovascularization. Twenty-nine eyes of 29 patients with myopic CNV were prospectively recruited to receive three initial monthly intravitreal bevacizumab injections. Three additional monthly injections were performed in eyes with persistent or recurrent CNV after 3 months. The mean spherical equivalent refractive error was -10.0 D. Sixteen eyes had previous photodynamic therapy (PDT) and 13 eyes had no prior PDT. All patients completed follow-up at 1 year. Following the initial three bevacizumab injections, 27 (93.1%) eyes had angiographic closure and two (6.9%) required further treatment. Two additional patients required re-treatment for CNV recurrence between 6 and 9 months. The mean baseline logarithm of the minimum angle of resolution (logMAR best-corrected visual acuity) was 0.62 (20/83), which improved to 0.38 (20/48) at 12 months ($p<0.001$). The mean visual improvement was 2.4 lines and 21 (72.4%) eyes had improvement of > or =2 lines. Optical coherence tomography showed significant reduction in central foveal thickness following treatment. Eyes without previous PDT were more likely to gain > or =2 lines after treatment than eyes that had previous PDT ($p = 0.010$). The 1-year outcomes confirmed the results of previous short-term studies that intravitreal bevacizumab is effective for myopic CNV, with a high proportion of patients sustaining visual gain after treatment.

Support for neovascular glaucoma can be found in a study by Yazdani et al. This randomized controlled trial included 26 eyes of 26 patients with neovascular glaucoma (NVG). All eyes received conventional treatment for NVG and were randomly allocated to three 2.5 mg intravitreal bevacizumab injections at 4-week intervals or a sham procedure (subconjunctival normal saline) at similar time intervals and in the same setting. Overall, 14 eyes of 14 patients received intravitreal bevacizumab and 12 eyes of 12 subjects were allocated to the sham procedure and followed for a mean period of 5.9+/-1.4 months. The intravitreal bevacizumab group demonstrated significant reduction in intraocular pressure from a baseline value of 33.4+/-14.5 mm Hg to 21.8+/-13.7 mm Hg (P=0.007), 25.1+/-20 mm Hg (P=0.058), and 23.9+/-18.7 mm Hg (P=0.047) at 1, 3, and 6 months after intervention, respectively. Iris neovascularization was also significantly reduced from a mean baseline value of 347+/-48 degrees to 206+/-185 degrees (P=0.01), 180+/-187 degrees (P=0.004), and 180+/-180 degrees (P=0.004) at 1, 3, and 6 months after intervention. In contrast, intraocular pressure and iris neovascularization remained unchanged or increased insignificantly at all follow-up intervals in the control group. No significant change in visual acuity was observed within the study groups at any time interval. The study groups were comparable in terms of requirement for additional interventions such as panretinal photocoagulation and cyclodestructive procedures.

Support for retinopathy of prematurity can be found in a study by the BEAT-ROP Cooperative Group. The BEAT-ROP Cooperative Group conducted a prospective, controlled, randomized, stratified, multicenter trial to assess intravitreal bevacizumab monotherapy for zone I or zone II posterior stage 3+ (i.e., stage 3 with plus disease) retinopathy of prematurity. Infants were randomly assigned to receive intravitreal bevacizumab (0.625 mg in 0.025 ml of solution) or conventional laser therapy, bilaterally. The primary ocular outcome was recurrence of retinopathy of prematurity in one or both eyes requiring retreatment before 54 weeks' postmenstrual age. One hundred and fifty infants were enrolled (total sample of 300 eyes); 143 infants survived to 54 weeks' postmenstrual age, and the 7 infants who died were not included in the primary-outcome analyses. Retinopathy of prematurity recurred in 4 infants in the bevacizumab group (6

of 140 eyes [4%]) and 19 infants in the laser-therapy group (32 of 146 eyes [22%], P=0.002). A significant treatment effect was found for zone I retinopathy of prematurity (P=0.003) but not for zone II disease (P=0.27). Intravitreal bevacizumab monotherapy, as compared with conventional laser therapy, in infants with stage 3+ retinopathy of prematurity showed a significant benefit for zone I but not zone II disease. Development of peripheral retinal vessels continued after treatment with intravitreal bevacizumab, but conventional laser therapy led to permanent destruction of the peripheral retina. This trial was too small to assess safety.

Support for using bevacizumab as an intranasal injection to treat epistaxis due to hereditary hemorrhagic telangiectasia syndrome can be found in two studies. Steineger and colleagues found repeated intranasal submucosal bevacizumab injections produced a continued positive response in 36.3% of patients with hereditary hemorrhagic telangiectasia in a single arm study (N=33). The mean duration from first to last injection in responders was 54 months (range, 33 to 66 months). A positive response was any reduction in the epistaxis severity score (ESS) and epistaxis intensity, frequency, and need for blood transfusion (IFT) score 6 to 8 weeks after the procedure. After the first intranasal bevacizumab procedure, 87.8% of patients had a positive response. With repeated injections, 33% of patients had a gradual shortening of the effect duration that resulted in treatment discontinuation when the effect duration was less than 8 weeks. Included patients had no benefit from repeated pulsed-dye laser, diode laser, argon plasma coagulation, and septodermoplasty in the previous 2 years or had contraindications to those therapies. During the 5.5 years of study observation, no local adverse events were reported. However, there was 1 case of bilateral osteonecrosis of the knees after eight 200-mg doses with a mean interval between treatments of 5.6 months. The bevacizumab dosage was 100 mg per procedure (50 mg in each side of the nose) initially and later increased to 200 mg per procedure (100 mg on each side). Injections were in the sphenopalatine area, upper part of the bony septum, upper part of the lateral nasal wall, and the anterior floor of the nose; injections were repeated as soon as the effect of the previous treatment diminished. The mean duration between injections was 5.1 +/- 2 months (range, 7 weeks to 11 months).

A prospective study by Karnezis et al found submucosal bevacizumab injection plus nasal spray significantly decreased epistaxis severity scores (ESS) over a 9- to 12-month follow-up period in patients with recalcitrant hereditary hemorrhagic telangiectasia epistaxis. Patients (n=19, mean age, 60 years) received an intranasal submucosal injection of bevacizumab 100 mg (25 mg/mL) at initial presentation. Injections were made along the lateral nasal wall, middle/inferior turbinates, nasal floor, and bony septum; there was intention for two-thirds of the injection to be placed in the anterior one-third of the nose. Over the 12-month follow-up, 6 of the 19 patients received 8 additional treatments with bevacizumab 100 mg nasal spray via a metered dose atomizer, which was given 3, 4, 6, 7, and 11 months after the original submucosal injection for increased bleeding. Following the submucosal injection, the ESS score significantly improved from a mean of 8.12 (severe disease) before treatment to a nadir of 2 (mild disease) at 2 months; in evaluable patients at month 11, the maximum mean ESS was 3.6.

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Reference number(s)
2746-A

Standard Medicare Part B Management bendamustine products

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Treanda	bendamustine
Bendeka	bendamustine
Belrapzo	bendamustine
Vivimusta	bendamustine

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

- Chronic lymphocytic leukemia (CLL)
- Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen

Compendial Uses

- Classic Hodgkin lymphoma (cHL)
- Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)
- Multiple myeloma (MM)
- Small lymphocytic lymphoma (SLL)
- B-cell lymphomas:
    - Human immunodeficiency virus (HIV)-related B-cell lymphoma
    - Diffuse large B-cell lymphoma (DLBCL)
    - Follicular lymphoma (FL)

    - Marginal zone lymphoma
        - Nodal marginal zone lymphoma
        - Gastric mucosa associated lymphoid tissue (MALT) lymphoma (extranodal marginal zone lymphoma of the stomach)
        - Nongastric MALT lymphoma (extranodal marginal zone lymphoma of nongastric sites)
        - Splenic marginal zone lymphoma
    - Mantle cell lymphoma (MCL)
    - Post-transplant lymphoproliferative disorders (PTLD)
    - Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
    - High grade B-cell lymphoma
- T-cell lymphomas:
    - Adult T-cell leukemia/lymphoma (ATLL)
    - Hepatosplenic T-Cell lymphoma
    - Peripheral T-cell lymphoma (PTCL)
    - Breast implant associated anaplastic large cell lymphoma (ALCL)
    - T-cell prolymphocytic leukemia
- Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma (WM/LL)/Bing-Neel syndrome
- Metastatic breast cancer
- Systemic light chain amyloidosis
- Hematopoietic cell transplantation
- Cold agglutinin disease
- Mycosis fungoides (MF) and Sezary syndrome (SS)

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

B-Cell Lymphoma

Authorization of 12 months may be granted for treatment of B-cell lymphoma with any of the following subtypes:

- Follicular lymphoma
- Diffuse large B-cell lymphoma (DLBCL) when all of the following criteria are met:
    - The requested drug is used as subsequent therapy
    - The requested drug is used in combination with polatuzumab vedotin-piiq with or without rituximab
    - The member is not a candidate for transplant or the requested drug will be used as a bridging option until CAR T-cell product is available
- Human immunodeficiency virus (HIV)-related B-cell lymphoma (HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, and human herpesvirus-8 (HHV8)-positive diffuse large B-cell lymphoma, plasmablastic lymphoma) when all of the following criteria are met:
    - The requested drug is used as subsequent therapy
    - The requested drug is used in combination with polatuzumab vedotin-piiq with or without rituximab

  - The member is not a candidate for transplant or the requested drug will be used as a bridging option until CAR T-cell product is available
- Marginal zone lymphoma
  - Nodal marginal zone lymphoma when used in combination with rituximab or obinutuzumab
  - Gastric mucosa-associated lymphoid tissue (MALT) lymphoma (extranodal marginal zone lymphoma of the stomach) when used in combination with rituximab or obinutuzumab
  - Nongastric MALT lymphoma (extranodal marginal zone lymphoma of nongastric sites) when used in combination with rituximab or obinutuzumab
  - Splenic marginal zone lymphoma when used in combination with rituximab or obinutuzumab
- Mantle cell lymphoma (MCL) when any of the following criteria are met:
  - The requested drug is used in combination with rituximab, or
  - The requested drug is used as a component of RBAC500 (rituximab, bendamustine, and cytarabine), or
  - The requested drug is used in combination with acalabrutinib and rituximab
- Post-transplant lymphoproliferative disorders (monomorphic PTLD B-cell type) when all of the following criteria are met:
  - The requested drug is used as subsequent therapy
  - The member is not a candidate for transplant or the requested drug will be used as a bridging option until CAR T-cell product is available
  - The requested drug will be used in combination with polatuzumab vedotin-piiq with or without rituximab
- Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma when all of the following criteria are met:
  - The requested drug is used in combination with polatuzumab vedotin-piiq with or without rituximab.
  - The member has received treatment with an anthracycline-based regimen (e.g., doxorubicin)
  - The member is not a candidate for transplant.
- High grade B-cell lymphoma when all of the following criteria are met:
  - The requested drug is used as subsequent therapy
  - The requested drug will be used in combination with polatuzumab vedotin-piiq with or without rituximab
  - The member is not a candidate for transplant or the requested drug will be used as a bridging option until CAR T-cell product is available.

T-Cell Lymphoma

Authorization of 12 months may be granted for treatment of T-cell lymphoma with any of the following subtypes:

- Adult T-cell leukemia/lymphoma (ATLL) when all of the following criteria are met:
  - The requested drug is used as a single agent
  - The requested drug is used as subsequent therapy
- Hepatosplenic T-Cell lymphoma when all of the following criteria are met:
  - The requested drug is used as a single agent or in combination with brentuximab vedotin
  - The requested drug is used for refractory disease after 2 first-line therapy regimens

- Peripheral T-cell lymphoma (PTCL) [including the following subtypes: anaplastic large cell lymphoma, peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, enteropathy associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, nodal peripheral T-cell lymphoma with TFH phenotype, or follicular T-cell lymphoma] when all of the following criteria are met:
    - The requested drug is used as a single agent or in combination with brentuximab vedotin
    - The requested drug is used as palliative or subsequent therapy
- Breast implant associated anaplastic large cell lymphoma (ALCL) when all of the following criteria are met:
    - The requested drug is used as a single agent or in combination with brentuximab vedotin
    - The requested drug is used as subsequent therapy
- T-cell prolymphocytic leukemia when used as a single agent for symptomatic disease

Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia (CLL/SLL)

Authorization of 12 months may be granted for treatment of CLL/SLL without chromosome 17p deletion or TP53 mutation

Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma (WM/LL)/Bing-Neel Syndrome

Authorization of 12 months may be granted for treatment of Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma or Bing-Neel syndrome when either of the following criteria are met:

- The requested drug will be used in combination with rituximab, or
- The requested will be used as a single agent

Multiple Myeloma (MM)

Authorization of 12 months may be granted for treatment of MM when all of the following criteria are met:

- The disease is relapsed or refractory and the member has tried more than 3 prior therapies, and
- The requested drug will be used in any of the following regimens:
    - In combination with lenalidomide and dexamethasone, or
    - In combination with bortezomib and dexamethasone, or
    - In combination with carfilzomib and dexamethasone, or
    - As a single agent

Classic Hodgkin Lymphoma (cHL)

Authorization of 12 months may be granted for treatment of cHL when all of the following criteria are met:

- The requested drug will be used as subsequent therapy or palliative therapy, and
- The requested drug will be used in any of the following regimens:
    - In combination with brentuximab vedotin, or
    - In combination with gemcitabine and vinorelbine, or
    - In combination with carboplatin and etoposide, or
    - As a single agent

Metastatic Breast Cancer

Authorization of 12 months may be granted for the treatment of metastatic breast cancer when used as a single agent or in combination with chemotherapy.

Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)

Authorization of 12 months may be granted for the treatment of nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) when all of the following criteria are met:

- The requested drug will be used as subsequent therapy
- The requested drug will be used in combination with rituximab

Systemic Light Chain Amyloidosis

Authorization of 12 months may be granted for the treatment of systemic light chain amyloidosis when all of the following criteria are met:

- The requested drug will be used in combination with dexamethasone
- The requested drug will be used to treat relapsed or refractory disease

Hematopoietic Cell Transplantation

Authorization of 12 months may be granted for use in hematopoietic cell transplantation when all of the following criteria are met:

- The requested drug will be used as conditioning for autologous transplant
- The requested drug will be used in combination with etoposide, cytarabine and melphalan

Cold Agglutinin Disease

Authorization of 12 months may be granted for treatment of cold agglutinin disease when used in combination with rituximab.

Mycosis Fungoides/Sezary Syndrome

Authorization of 12 months may be granted for treatment of mycosis fungoides/Sezary syndrome when used in combination with brentuximab vedotin.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested drug.

- The requested drug is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Treanda, Bendeka, Belrapzo, and Vivimusta.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN guideline: Waldenstrom macroglobulinemia/Lymphoplasmacytic lymphoma
- NCCN guideline: Systemic light chain amyloidosis
- NCCN guideline: Hodgkin lymphoma
- NCCN guideline: Multiple myeloma
- NCCN guideline: T-cell lymphomas
- NCCN guideline: Pediatric Hodgkin lymphoma
- NCCN guideline: Hematopoietic cell transplantation
- NCCN guideline: B-cell lymphomas
- NCCN guideline: Chronic lymphocytic leukemia/small lymphocytic lymphoma
- NCCN guideline: Primary cutaneous lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Treanda, Bendeka, Belrapzo and Vivimusta are covered in addition to the following:

- Classic Hodgkin lymphoma (cHL)
- Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)
- Multiple myeloma (MM)
- Small lymphocytic lymphoma (SLL)
- B-cell lymphomas:
    - Human immunodeficiency virus (HIV)-related B-cell lymphoma
    - Diffuse large B-cell lymphoma (DLBCL)
    - Follicular lymphoma (FL)
    - Marginal zone lymphoma
        - Nodal marginal zone lymphoma
        - Gastric mucosa associated lymphoid tissue (MALT) lymphoma (extranodal marginal zone lymphoma of the stomach)
        - Nongastric MALT lymphoma (extranodal marginal zone lymphoma of nongastric sites)
        - Splenic marginal zone lymphoma
    - Mantle cell lymphoma (MCL)

    - Post-transplant lymphoproliferative disorders
    - Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
    - High grade B-cell lymphoma
- T-cell lymphomas:
    - Adult T-cell leukemia/lymphoma (ATLL)
    - Hepatosplenic T-Cell lymphoma
    - Peripheral T-cell lymphoma (PTCL)
    - Breast implant associated anaplastic large cell lymphoma (ALCL)
    - T-cell prolymphocytic leukemia
- Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma (WM/LL)
- Metastatic breast cancer
- Systemic light chain amyloidosis
- Hematopoietic cell transplantation
- Cold agglutinin disease
- Mycosis fungoides/Sezary syndrome

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using the requested medication to treat the following indications can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

- Classic Hodgkin lymphoma (cHL)
- Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)
- Multiple myeloma (MM)
- Small lymphocytic lymphoma (SLL)
- B-cell lymphomas:
    - Human immunodeficiency virus (HIV)-related B-cell lymphoma
    - Diffuse large B-cell lymphoma (DLBCL)
    - Follicular lymphoma (FL)
    - Marginal zone lymphoma
        - Nodal marginal zone lymphoma
        - Gastric mucosa associated lymphoid tissue (MALT) lymphoma (extranodal marginal zone lymphoma of the stomach)
        - Nongastric MALT lymphoma (extranodal marginal zone lymphoma of nongastric sites)
        - Splenic marginal zone lymphoma
    - Mantle cell lymphoma (MCL)
    - Post-transplant lymphoproliferative disorders
    - Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
    - High grade B-cell lymphoma
- T-cell lymphomas:

  - Adult T-cell leukemia/lymphoma (ATLL)
  - Hepatosplenic T-Cell lymphoma
  - Peripheral T-cell lymphoma (PTCL)
  - Breast implant associated anaplastic large cell lymphoma (ALCL)
  - T-cell prolymphocytic leukemia
- Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma (WM/LL)
- Systemic light chain amyloidosis
- Hematopoietic cell transplantation
- Mycosis fungoides/Sezary syndrome

Support for using the requested medication for metastatic breast cancer can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen). In a multinational, randomized, phase 3 trial, first-line treatment with bendamustine, methotrexate, and 5-fluorouracil significantly increased the median time to progression (8.2 months) compared with cyclophosphamide, methotrexate, and 5-fluorouracil (6.7 months) in patients with metastatic breast cancer; although, overall response rates were not significantly different between the 2 treatment arms (confirmed response, 22.3% and 22.4%, respectively).

Support for using bendamustine to treat cold agglutinin disease can be found in the guidelines published by Jager et al. In patients with symptomatic, primary cold agglutinin disease, first-line treatment consists of rituximab alone, or rituximab plus bendamustine in fit patients. For second-line therapy, rituximab plus bendamustine should be given if not previously used, or in patients who responded to it as first-line therapy and at least 2 years have passed since treatment.

References

1. Treanda [package insert]. Parsippany, NJ: Teva Pharmaceuticals USA, Inc.; October 2022.
2. Bendeka [package insert]. Parsippany, NJ: Teva Pharmaceuticals USA, Inc.; January 2024.
3. Belrapzo [package insert]. Woodcliff Lake, NJ; Eagle Pharmaceuticals, Inc; January 2024.
4. Vivimusta [package insert]. Princeton, NJ; Slayback Pharma LLC; December 2022.
5. Bendamustine [package insert]. Durham, NC; Accord Healthcare Inc; November 2022.
6. The NCCN Drugs & Biologics Compendium® © 2025 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed February 3, 2025.
7. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at https://www.micromedexsolutions.com Accessed April 8, 2024.
8. Jager U, Barcellini W, Broome CM, et al: Diagnosis and treatment of autoimmune hemolytic anemia in adults: recommendations from the First International Consensus Meeting. Blood Rev 2020; 41:100648-.
9. Calquence [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; January 2025.

Reference number(s)
2502-A

Standard Medicare Part B Management Benlysta

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Benlysta	belimumab

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met, the member has no exclusions to the prescribed therapy, and the drug or biological is usually not self-administered. The criteria outlined in this policy is only applicable to drugs not usually self-administered and are furnished incident to a physician's service. Requests for drugs on a region's self-administered drug list are not covered. Members enrolled in Medicare Part D may seek coverage under their Medicare Part D plan.

FDA-Approved Indications

Benlysta is indicated for the treatment of:

- Patients aged 5 years and older with active systemic lupus erythematosus (SLE) who are receiving standard therapy, and
- Patients aged 5 years and older with active lupus nephritis who are receiving standard therapy.

Limitations of Use

The efficacy of Benlysta has not been evaluated in patients with severe active central nervous system (CNS) lupus. Use of Benlysta is not recommended in this situation.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- Initial requests: Medical records (e.g., chart notes, lab reports) documenting the presence of autoantibodies relevant to SLE (e.g., ANA, anti-ds DNA, anti-Sm, antiphospholipid antibodies, complement proteins), or kidney biopsy supporting diagnosis (where applicable).
- Continuation requests: Medical records (e.g., chart notes, lab reports) documenting disease stability or improvement.

Exclusions

Coverage will not be provided for members with any of the following exclusions:

- Severe active central nervous system (CNS) lupus (including seizures that are attributed to CNS lupus, psychosis, organic brain syndrome, cerebritis, or CNS vasculitis requiring therapeutic intervention within 60 days before initiation of belimumab) in a member initiating therapy with Benlysta.
- Member is using Benlysta in combination with other biologics.

Coverage Criteria

Systemic Lupus Erythematosus (SLE)

Authorization of 12 months may be granted for treatment of active SLE when all of the following criteria are met:

- Prior to initiating therapy, the member is positive for autoantibodies relevant to SLE (e.g., ANA, anti-ds DNA, anti-Sm, antiphospholipid antibodies, complement proteins)
- The member meets either of the following criteria:
    - The member is receiving a stable standard treatment for SLE with any of the following (alone or in combination):
        - Glucocorticoids (e.g., prednisone, methylprednisolone, dexamethasone)
        - Antimalarials (e.g., hydroxychloroquine)
        - Immunosuppressants (e.g., azathioprine, methotrexate, mycophenolate, cyclosporine, cyclophosphamide)
        - Nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., ibuprofen, naproxen)
    - The member has a clinical reason to avoid treatment with a standard treatment regimen.

Lupus Nephritis

Authorization of 12 months may be granted for treatment of active lupus nephritis when all of the following criteria are met:

- Prior to initiating therapy, the member is positive for autoantibodies relevant to SLE (e.g., ANA, anti-ds DNA, anti-Sm, antiphospholipid antibodies, complement proteins) or lupus nephritis was confirmed on kidney biopsy.
- Member is receiving a stable standard therapy regimen (e.g., cyclophosphamide, mycophenolate mofetil, azathioprine, corticosteroids) or has a clinical reason to avoid treatment with a standard therapy regimen.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication enumerated in the coverage criteria section.
- The member is receiving benefit from therapy. Benefit is defined as disease stability or improvement.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Benlysta.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- 2023 Update of the EULAR Recommendations for the Management of Systemic Lupus Erythematosus
- 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus
- Kidney Disease: Improving Global Outcomes (KDIGO) 2024 Clinical Practice Guideline for the Management of Glomerular Diseases
- The British Society for Rheumatology guideline for the management of systemic lupus erythematosus
- Derivation and Validation of Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Benlysta are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

The content of the exclusions can be found in the prescribing information.

The British Society for Rheumatology report that ANAs are present in about 95% of SLE patients. If the test for ANAs is negative, there is a low clinical probability of a member having SLE. The presence of anti-dsDNA antibodies, low complement levels or anti-Smith (Sm) antibodies are highly predictive of a diagnosis of SLE in patients with relevant clinical features. Anti-Ro/La and anti-RNP antibodies are less-specific markers of SLE as they are found in other autoimmune rheumatic disorders as well as SLE.

The SLICC group devised evidence-based classification criteria for lupus. These criteria introduced a requirement for at least one clinical and one immunological criterion and two others from an expanded list of items compared with the ACR criteria. They also allowed biopsy-proven lupus nephritis in the presence of ANA or anti-dsDNA antibodies to be

classified as lupus, without the need for other criteria. These classification criteria may be used to aid diagnosis.

THE EULAR/ACR classification criteria for SLE require ANA antibodies ≥1:80 on HEp-2 cells or an equivalent positive test and a classification threshold score of ≥ 10. The classification criteria should not be used as diagnostic criteria. Testing by immunofluorescence on HEp-2 cells or a solid-phase ANA screening immunoassay with at least equivalent performance is highly recommended.

According to the 2023 update of the EULAR recommendations for the management of systemic lupus erythematosus, the goal of treatment should be remission or low disease activity and prevention of flares in all organs. Hydroxychloroquine is recommended for all patients, unless contraindicated. Glucocorticoids (GC), if needed, can be used at doses and route of administration that depend on the type and severity of organ involvement and should be reduced to maintenance dose of less than or equal to 5 mg/day (prednisone equivalent). In patients not responding to hydroxychloroquine (alone or in combination with GC) or patients unable to reduce GC below doses acceptable for chronic use, addition of immunomodulating/immunosuppressive agents such as methotrexate, azathioprine, or mycophenolate and/or biological agents (e.g., belimumab or anifrolumab) should be considered. In patients with organ-threatening or life-threatening disease, cyclophosphamide should be considered.

References

1. Benlysta [package insert]. Philadelphia, PA: GlaxoSmithKline LLC; February 2023.
2. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2023 Update of the EULAR Recommendations for the Management of Systemic Lupus Erythematosus. Ann Rheum Dis. 2024; 83:15-29.
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4. Rovin BH, Adler SG, Barratt J, et al. 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(15):S1-S69.
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6. Petri M, Orbai A-M, Alarcon GS, et al. Derivation and Validation of Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheum. 2012; 64:2677-2686. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3409311/. Accessed January 4, 2024.
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12. Self-Administered Drug Exclusion List: (SAD List) (A52800). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.
13. Self-Administered Drug Exclusion List: (A53127). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.

14. Self-Administered Drug Exclusion List: (A53066). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.
15. Self-Administered Drug Exclusion List: Medical Policy Article (A53022). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.

Reference number(s)
3348-A

Standard Medicare Part B Management Beovu

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Beovu	brolucizumab-dbll

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

- Neovascular (wet) age-related macular degeneration
- Diabetic macular edema

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Neovascular (Wet) Age-Related Macular Degeneration[1,2]

Authorization of 12 months may be granted for treatment of neovascular (wet) age-related macular degeneration.

Diabetic Macular Edema[1]

Authorization of 12 months may be granted for treatment of diabetic macular edema.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member demonstrated a positive clinical response to therapy (e.g., improvement or maintenance in best corrected visual acuity [BCVA] or vision field, or a reduction in the rate of vision decline or the risk of more severe vision loss).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Beovu.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Beovu are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Beovu [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; September 2023.
2. Dugel PU, Koh A, Ogura Y et al. HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration. Ophthalmology. 2020; 127:72-84

Reference number(s)
6756-A

Standard Medicare Part B Management Bizengri

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Bizengri	zenocutuzumab-zbco

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

- Adults with advanced unresectable or metastatic non-small cell lung cancer (NSCLC) harboring a neuregulin 1 (NRG1) gene fusion with disease progression on or after prior systemic therapy.
- Adults with advanced unresectable or metastatic pancreatic adenocarcinoma harboring a NRG1 gene fusion with disease progression on or after prior systemic therapy.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

Submission of the following information must be available, upon request for initial approval: NRG1 gene fusion status.

Coverage Criteria

Non-Small Cell Lung Cancer (NSCLC)

Authorization of 12 months may be granted for treatment of advanced unresectable or metastatic NSCLC when both of the following criteria are met:

- Member has experienced disease progression on or after prior systemic therapy AND
- Member has neuregulin 1 (NRG1) gene fusion positive disease.

Pancreatic Adenocarcinoma

Authorization of 12 months may be granted for treatment of advanced unresectable or metastatic pancreatic adenocarcinoma when both of the following criteria are met:

- Member has experienced disease progression on or after prior systemic therapy AND
- Member has neuregulin 1 (NRG1) gene fusion positive disease.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat an indication listed in coverage criteria section
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen, and
    - No evidence of disease progression while on the current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Bizengri.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Bizengri are covered.

Reference number(s)
6756-A

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Bizengri [package insert]. Cambridge, MA: Merus US, Inc.; December 2024.

Reference number(s)
2624-A

Standard Medicare Part B Management Botulinum Toxins

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Botox	onabotulinumtoxinA
Dysport	abobotulinumtoxinA
Xeomin	incobotulinumtoxinA
Myobloc	rimabotulinumtoxinB
Daxxify	daxibotulinumtoxinA-lanm

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

Botox

FDA-Approved Indications

- Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication
- Treatment of urinary incontinence due to detrusor muscle overactivity associate with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication
- Prophylaxis of headaches in adult patients with chronic migraine (>15 days per month with a headache lasting 4 hours a day or longer)
- Treatment of spasticity in patients 2 years of age and older
- Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain

- Treatment of severe primary axillary hyperhidrosis that is inadequately managed by topical agents in adult patients
- Treatment of blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients > 12 years of age
- Treatment of strabismus in patients > 12 years of age
- Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication

Compendial Uses

- Achalasia
- Auriculotemporal syndrome
- Backache
- Benign prostatic hyperplasia
- Cervicogenic headache
- Chronic anal fissures
- Detrusor and sphincter dyssynergia
- Difficulty speaking after total laryngectomy
- Disorder of esophagus
- Epicondylitis
- Essential tremor disorder
- Excessive salivation secondary to advanced Parkinson’s disease
- Excessive salivation secondary to a disorder of the nervous system
- Excessive tear production
- Fibromyalgia
- Gilles de la Tourette's syndrome
- Granuloma of vocal cords which is refractory to conventional surgical and medical therapies
- Hemifacial spasm
- Infantile esotropia
- Isolated oromandibular dystonia
- Larynx closure as adjunct to surgical procedure
- Myofascial pain syndrome
- Neuropathic pain secondary to spinal cord injury
- Oculomotor nerve injury (acute)
- Organic voice tremor
- Palmar hyperhidrosis
- Pelvic floor dyssynergia
- Pharyngoesophageal segment spasm following total laryngectomy

- Refractory idiopathic trigeminal neuralgia
- Spastic dysphonia
- Stuttering
- Tardive dyskinesia
- Temporomandibular joint disorder
- Tension-type headache
- Thoracic outlet syndrome
- Whiplash injury to neck

Dysport

FDA-Approved Indications

- Treatment of adults with cervical dystonia
- Treatment of spasticity in patients 2 years of age and older

Compendial Uses

- Achalasia in patients who are surgical candidates
- Blepharospasm
- Hemifacial spasm

Xeomin

FDA-Approved Indications

- Treatment of chronic sialorrhea in patients 2 years of age and older
- Treatment of upper limb spasticity in adult patients
- Treatment of upper limb spasticity in pediatric patients 2 to 17 years of age, excluding spasticity caused by cerebral palsy
- Treatment of adults with cervical dystonia
- Treatment of adults with blepharospasm

Myobloc

FDA-Approved Indication

- Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia
- Treatment of chronic sialorrhea in adults

Compendial Uses

- Axillary hyperhidrosis
- Bladder muscle dysfunction leading to overactive bladder

- Bladder spasticity secondary to a spinal cord injury
- Blepharospasm
- Hemifacial spasm
- Palmar hyperhidrosis
- Spastic dysphonia
- Upper limb spasticity

Daxxify

FDA-Approved Indication

- The treatment of cervical dystonia in adult patients.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Exclusions

Coverage will not be provided for cosmetic use.

Coverage Criteria

Botox

Overactive Bladder with Urinary Incontinence

Authorization of 12 months may be granted for the treatment of overactive bladder in adults, 18 years of age and older with urinary incontinence.

Urinary Incontinence Associated with A Neurologic Condition

Authorization of 12 months may be granted for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., spinal cord injury, multiple sclerosis) when members are 5 years of age and older.

Chronic Migraine Prophylaxis

Authorization of 6 months (two injection cycles) may be granted for the treatment of chronic migraine headache when all of the following are met:

- Member has migraine headaches at least 15 days per month.
- Member is 18 years of age or older.

Limb Spasticity

Authorization of 12 months may be granted for the treatment of limb spasticity including hands and feet either as a primary diagnosis or as a symptom of a condition causing limb spasticity in members 2 years of age and older.

Cervical Dystonia

Authorization of 12 months may be granted for the treatment of adults with cervical dystonia (e.g., torticollis) when there is abnormal placement of the head with limited range of motion in the neck when members are 18 years of age or older.

Primary Axillary Hyperhidrosis

Authorization of 12 months may be granted for the treatment of primary axillary hyperhidrosis for members 18 years of age and older.

Blepharospasm

Authorization of 12 months may be granted for the treatment of blepharospasm, including blepharospasm associated with dystonia and benign essential blepharospasm or VII nerve disorders when the member is 12 years of age or older.

Strabismus

Authorization of 12 months may be granted for the treatment of strabismus when the member is 12 years of age or older.

Achalasia

Authorization of 12 months may be granted for the treatment of achalasia.

Auriculotemporal Syndrome

Authorization of 12 months may be granted for the treatment of auriculotemporal syndrome.

Backache

Authorization of 6 months may be granted for the treatment of chronic lower back pain.

Benign Prostatic Hyperplasia

Authorization of 12 months may be granted for the treatment of benign prostatic hyperplasia.

Cervicogenic Headache

Authorization of 12 months may be granted for the treatment of cervicogenic headache.

Chronic Anal Fissures

Authorization of 12 months may be granted for the treatment chronic anal fissures.

Detrusor (Including Neurogenic Detrusor Overactivity (NDO)) and Sphincter Dyssynergia

Authorization of 12 months may be granted for the treatment of detrusor (NDO) and sphincter dyssynergia.

Difficulty Speaking after total Laryngectomy

Authorization of 12 months may be granted for the treatment of difficulty speaking following a total laryngectomy.

Disorder of Esophagus

Authorization of 12 months may be granted for the treatment of disorder of the esophagus.

Epicondylitis

Authorization of 12 months may be granted for the treatment of epicondylitis.

Essential Tremor

Authorization of 12 months may be granted for the treatment of disorder of essential tremor.

Excessive Salivation Secondary to a Disorder of the Nervous System or Advanced Parkinson’s Disease

Authorization of 12 months may be granted for the treatment of excessive salivation secondary to a disorder of the nervous system or advanced Parkinson’s disease.

Excessive Tear Production

Authorization of 12 months may be granted for the treatment of excessive tear production

Fibromyalgia

Authorization of 12 months may be granted for the treatment of fibromyalgia.

Gilles De La Tourette's Syndrome

Authorization of 12 months may be granted for the treatment of Gilles de la Tourette's syndrome.

Granuloma of Vocal Cords

Authorization of 12 months may be granted for the treatment of granuloma of the vocal cords that is refractory to conventional surgical and medical therapies.

Hemifacial Spasm

Authorization of 12 months may be granted for the treatment of hemifacial spasm.

Idiopathic Trigeminal Neuralgia

Authorization of 12 months may be granted for the treatment of refractory idiopathic trigeminal neuralgia.

Infantile Esotropia

Authorization of 12 months may be granted for the treatment of infantile esotropia.

Isolated Oromandibular Dystonia

Authorization of 12 months may be granted for the treatment of isolated oromandibular dystonia.

Larynx Closure as Adjunct to Surgical Procedure

Authorization of 12 months may be granted for the treatment of larynx closure as adjunct to surgical procedure.

Myofascial Pain Syndrome

Authorization of 12 months may be granted for the treatment of myofascial pain syndrome.

Neuropathic Pain Secondary to Spinal Cord Injury

Authorization of 12 months may be granted for the treatment of neuropathic pain secondary to spinal cord injury.

Oculomotor Nerve Injury (acute)

Authorization of 12 months may be granted for the treatment of oculomotor nerve injury.

Organic Voice Tremor

Authorization of 12 months may be granted for the treatment of organic voice tremor.

Palmar Hyperhidrosis

Authorization of 12 months may be granted for the treatment of palmar hyperhidrosis.

Pelvic Floor Dyssynergia

Authorization of 12 months may be granted for the treatment of pelvic floor dyssynergia.

Pharyngoesophageal Segment Spasm Following total Laryngectomy

Authorization of 12 months may be granted for the treatment of pharyngoesophageal segment spasm following total laryngectomy.

Spastic Dysphonia

Authorization of 12 months may be granted for the treatment of spastic dysphonia.

Stuttering

Authorization of 12 months may be granted for the treatment of stuttering.

Tardive Dyskinesia

Authorization of 12 months may be granted for the treatment of tardive dyskinesia.

Temporomandibular Joint Disorder

Authorization of 12 months may be granted for the treatment of temporomandibular joint disorder.

Tension-Type Headache

Authorization of 12 months may be granted for the treatment of tension-type headache.

Thoracic Outlet Syndrome

Authorization for 12 months may be granted for the treatment of thoracic outlet syndrome.

Whiplash to the Neck

Authorization of 12 months may be granted for the treatment of whiplash to the neck.

Dysport

Cervical Dystonia

Authorization of 12 months may be granted for the treatment of adults 18 years of age and older with cervical dystonia (e.g., torticollis) when there is abnormal placement of the head with limited range of motion in the neck.

Limb Spasticity

Authorization of 12 months may be granted for the treatment of upper or lower limb spasticity either as a primary diagnosis or as a symptom of a condition causing limb spasticity in members 2 years of age or older.

Achalasia

Authorization of 12 months may be granted for the treatment of achalasia.

Blepharospasm

Authorization of 12 months may be granted for the treatment of blepharospasm, including blepharospasm associated with dystonia and benign essential blepharospasm.

Hemifacial Spasm

Authorization of 12 months may be granted for hemifacial spasm.

Xeomin

Blepharospasm

Authorization of 12 months may be granted for the treatment of blepharospasm, including blepharospasm associated with dystonia and benign essential blepharospasm in members 18 years of age or older.

Cervical Dystonia

Authorization of 12 months may be granted for the treatment of adults, aged 18 years and older with cervical dystonia (e.g., torticollis) when there is abnormal placement of the head with limited range of motion in the neck.

Upper Limb Spasticity

Authorization of 12 months may be granted for the treatment of upper limb spasticity when all of the following are met:

- Member has a diagnosis of upper limb spasticity either as a primary diagnosis or as a symptom of a condition causing limb spasticity
- Member meets one of the following criteria:
    - Member is 18 years of age or older
    - Member is 2 to 17 years of age and the spasticity is not caused by cerebral palsy.

Excessive salivation

Authorization of 12 months may be granted for the treatment of excessive salivation (chronic sialorrhea) for members 2 years of age and older.

Myobloc

Cervical dystonia

Authorization of 12 months may be granted for the treatment of adults, aged 18 years of age and older with cervical dystonia (e.g., torticollis) when there is abnormal placement of head and limited range of motion in the neck.

Axillary hyperhidrosis

Authorization of 12 months may be granted for the treatment of primary axillary hyperhidrosis.

Overactive bladder with urinary incontinence

Authorization of 12 months may be granted for the treatment of overactive bladder with urinary incontinence.

Bladder spasticity secondary to a spinal cord injury

Authorization for 12 months may be granted for the treatment of bladder spasticity secondary to a spinal cord injury.

Blepharospasm

Authorization of 12 months may be granted for the treatment of blepharospasm.

Excessive salivation

Authorization of 12 months may be granted for the treatment of excessive salivation (chronic sialorrhea) in adults aged 18 years and older.

Hemifacial spasm

Authorization of 12 months may be granted for hemifacial spasm.

Palmar hyperhidrosis

Authorization of 12 months may be granted for the treatment of palmar hyperhidrosis.

Spastic dysphonia

Authorization of 12 months may be granted for the treatment of spastic dysphonia.

Upper limb spasticity

Authorization of 12 months may be granted for the treatment of upper limb spasticity either as a primary diagnosis or as a symptom of a condition causing limb spasticity.

Daxxify

Cervical dystonia

Authorization of 12 months may be granted for the treatment of adults, aged 18 years of age and older with cervical dystonia (e.g., torticollis) when there is abnormal placement of head and limited range of motion in the neck.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 24 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested botulinum toxin drug.
- The botulinum toxin drug requested is for a diagnosis or condition in the coverage criteria section.
- The botulinum toxin drug requested has been effective for treating the diagnosis or condition.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Botox, Daxxify, Dysport, Myobloc, and Xeomin.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- European Academy of Neurology guideline on trigeminal neuralgia
- Practice guideline update: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adults spasticity, and headache: report of the guideline development subcommittee of the American Academy of Neurology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Botox, Daxxify, Dysport, Myobloc and Xeomin are covered in addition to the following:

Botox

- Achalasia
- Auriculotemporal syndrome
- Backache
- Benign prostatic hyperplasia
- Cervicogenic headache
- Chronic anal fissures
- Detrusor and sphincter dyssynergia
- Difficulty speaking after total laryngectomy
- Disorder of esophagus

- Epicondylitis
- Essential tremor disorder
- Excessive salivation secondary to advanced Parkinson’s disease
- Excessive salivation secondary to a disorder of the nervous system
- Excessive tear production
- Fibromyalgia
- Gilles de la Tourette's syndrome
- Granuloma of vocal cords which is refractory to conventional surgical and medical therapies
- Hemifacial spasm
- Infantile esotropia
- Isolated oromandibular dystonia
- Larynx closure as adjunct to surgical procedure
- Myofascial pain syndrome
- Oculomotor nerve injury (acute)
- Organic voice tremor
- Neuropathic pain secondary to spinal cord injury
- Palmar hyperhidrosis
- Pelvic floor dyssynergia
- Pharyngoesophageal segment spasm following total laryngectomy
- Refractory idiopathic trigeminal neuralgia
- Spastic dysphonia
- Stuttering
- Tardive dyskinesia
- Temporomandibular joint disorder
- Tension-type headache
- Thoracic outlet syndrome
- Whiplash injury to neck

Dysport

- Achalasia in patients who are surgical candidates
- Blepharospasm
- Hemifacial spasm

Myobloc

- Axillary hyperhidrosis

- Bladder muscle dysfunction leading to overactive bladder
- Bladder spasticity secondary to a spinal cord injury
- Blepharospasm
- Hemifacial spasm
- Palmar hyperhidrosis
- Spastic dysphonia
- Upper limb spasticity

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Botox to treat achalasia can be found in a trial by Annese and Bassotti. A double-blind, placebo-controlled trial verified the efficacy of botulinum toxin for previously untreated achalasia. Sixteen patients were randomized to placebo or botulinum toxin, endoscopically injected into multiple sites within the lower esophageal sphincter (total of 100 units as 0.5-mL aliquots of 12.5 units each). All patients in the botulinum group reported significantly improved mean symptom scores at the one-month visit. In contrast, all placebo-treated patients had unchanged symptom scores and required pneumatic dilation. When comparing pneumatic dilation to botulinum toxin, statistically similar reductions in symptom score, sphincter pressure and esophageal retention occurred. The beneficial effect of botulinum toxin lasted for a mean of 7.1 months and 10.8 months after the first and second injections, respectively.

Additionally, Kolbasnik and colleagues published one study of 30 consecutive patients. The authors reported an initial 77% response rate, with 30% of responders maintaining symptom relief after a single 80-unit injection for a mean of 21 months. Of the remaining 70% of responders who relapsed (at 11 months on average), 56% were successfully treated with additional injection(s). Those who failed the first botulinum toxin injection also failed subsequent injections. Reduction of lower esophageal sphincter pressure to less than 18 mmHg at one month postinjection was a significant predictor of symptomatic response.

Support for using Botox to treat auriculotemporal syndrome can be found in a study by Duluerov et al. Local infiltration of botulinum toxin was effective in reducing food-induced facial flushing and sweating in 15 patients with Frey syndrome. Patients received total doses of 15 to 75 units, given as 0.1-mL injections with a 1-cm inter-injection distance. An evaluation 2 weeks later demonstrated a significant reduction in sweat quantity as compared with baseline (p less than 0.05). Measurements of skin temperature and color (erythema) did not show a clear difference before and after treatment. Subjectively, symptoms were reported to disappear in all patients following treatment. No adverse effects were reported.

Support for using Botox to treat backache can be found in a study by Foster et al. Botulinum toxin type A administered paravertebrally was effective in relieving pain and improving function in patients with chronic lower back pain. Patients (n=31) were randomized to 200 units of Botox(R) (40 units per site at 5 lumbar paravertebral levels) on the side of maximum discomfort (n=15) or to placebo (n=16). At 3 weeks, 73.3% of patients receiving botulinum toxin had more than 50% pain relief compared with 25% in the placebo group (p equal to 0.012). At 8 weeks, 60% of the patients receiving botulinum toxin experienced relief compared with 12.5% in the placebo group (p equal to 0.009). A questionnaire on physical impairment and disability was given at 8 weeks and 66.7% patients in the botulinum toxin

group showed improvement compared with 18.8% in the placebo group (p equal to 0.011). There were no side effects reported.

Support for using Botox to treat benign prostatic hyperplasia can be found in a study by Maria et al. A randomized, double-blind study demonstrated that botulinum toxin type A (Botox(R)) was significantly more effective than placebo for the treatment of benign prostatic hyperplasia (BPH). Patients with symptomatic BPH who no longer responded to medication and refused surgical treatment were randomized to receive botulinum toxin A injection (n=15) or placebo injection (n=15). Inclusion criteria were: moderate to severe symptoms of urinary obstruction based on the American Urological Association (AUA) index, mean peak urinary flow rate less than 15 mL/sec with voided volume of at least 150 mL, and an enlarged prostate gland. Primary study endpoints were the AUA symptom score and peak urinary flow rate. Each patient received an injection of 4 mL of solution into the prostate (2 mL into each lobe of the gland); the placebo group received saline solution only and the botulinum toxin A group received 200 Units of botulinum toxin type A. At both the 1 month and 2 month evaluations, patients in the botulinum toxin A group demonstrated significant improvement in all measures compared with baseline and to the placebo group. At 1 month, 11 of 15 patients in the botulinum toxin A group and 2 of 15 in the placebo group had symptomatic relief. In the botulinum toxin A group, the mean AUA score decreased from 23.2 at baseline to 10.6 posttreatment (54% decrease; p=0.00001) and mean peak urinary flow rate increased from 8.1 mL/sec to 14.9 mL/sec (p=0.00001). At the 2-month evaluation, 13 patients in the botulinum toxin A group and 3 in the placebo group had symptomatic relief; the botulinum toxin A group had a 65% decrease in mean AUA score (p=0.00001) and the mean peak urinary flow rate was 15.4 mL/sec (p=0.00001). At both evaluation time points, these post-injection measures did not change significantly from baseline in the placebo group and were significantly different from the botulinum toxin A group (p not stated). For the patients who received a botulinum toxin A injection, improvements in all outcome measures were maintained at 6 and 12-month evaluations. No adverse events were reported during the follow-up period (average duration 19.6 months).

Support for using Botox to treat cervicogenic headache can be found in a study by Freund and Schwartz. In a randomized, double blind, placebo-controlled pilot study, the efficacy of botulinum toxin A in reducing the pain associated with cervicogenic headache was tested in 30 otherwise healthy subjects ranging in age from 29 to 75 years. Patients were included if they suffered from chronic headache unrelieved by other therapies secondary to a cervical whiplash injury which occurred within 2 years of study entry and which restricted range of motion in the neck. Each patient was given an injection of botulinum toxin A (100 units diluted in 1 mL saline) or an equivalent volume of saline placebo dispersed in the five most tender cervical muscular trigger points. At 2 and 4 weeks later, the patients were evaluated for neck range of motion and for pain using a 10-point visual analog scale. At 2 weeks, the range of motion had increased for the treatment group (no p value reported). There was no significant change in the placebo group. At 4 weeks, both median pain scores and range of motion degree measurements improved significantly from preinjection levels for the group treated with botulinum toxin A (p=0.01). No significant change from baseline was seen in the placebo group. A potential confounder in this study was the difference in pain scores between groups at baseline. The median headache pain score for the placebo group was 3 (on a scale from 0 to 10), while that of the treatment group was 6.5 (no statistics reported). Thus, the placebo group appeared to have less headache pain, and therefore less room to improve, at the start of the trial. No side effects attributable to botulinum toxin A were reported in this study.

Support for using Botox to treat chronic anal fissures can be found in several published studies. Mentes et al. found botulinum toxin type A had a lower, shorter-term healing rate but significantly better recovery and adverse effect profile than lateral internal sphincterotomy (LIS) for the treatment of chronic anal fissure. Patients with severe, chronic fissure with visible horizontal fibers in the base of the internal anal sphincter were randomly selected to receive botulinum toxin type A (Botox(R)) injection (n=61) or LIS (n=50). For the botulinum toxin group (BT), patients received 0.3 units per kg injected in equal volumes on either side of the anterior midline; treatment was repeated if there was non- or incomplete healing 2 months after the first injection. Healing rate, defined as complete healing of the fissure, was

significantly higher for the LIS group at 28 days (62.3% BT group vs 82% LIS group; p=0.023), 2 months (73.8% BT group vs 98% LIS group; p less then 0.0001), and 12 months posttreatment (75.4% BT group vs 94% LIS group; p=0.008). At 6 months posttreatment, healing rate was comparable between the groups (86.9% BT group vs 94% LIS group; p=0.212). Sixteen patients with incomplete healing in the BT group were offered repeat treatment; 6 refused due to satisfaction with pain relief from the first treatment and were considered incomplete healers in healing rate determinations. The BT group recovered from treatment significantly faster than the LIS group; return to daily activities averaged 1 day for the BT group and 14.8 days for the LIS group (p less than 0.0001). Complication rate was significantly different between the groups, no adverse events were reported in the BT group compared with 16% of patients in the LIS group reporting transient flatus incontinence (p less than 0.001).

Minguez et al successfully treated chronic anal fissure in a nonrandomized, prospective, dose-ranging trial (n=69). Dosing consisted of 5 units of botulinum toxin A on each side of the fissure (low dose: total 10 units), 5 units on each side of the fissure plus 5 units below the fissure (middle dose: total 15 units) or 7 units on each side of the fissure plus 7 units below the fissure (high dose: total 21 units). At 6 months follow-up, the overall rates of healing (83%, 78%, 90%), reinjection (52%, 30%, 37%) and sphincterotomy requirement (17%, 19%, 5%) did not differ statistically between the low, middle and high dose groups, respectively. Adverse effects included puncture site infection (n=1), perianal hematoma (n=1) and transient flatus or fecal incontinence (n=7). All subjects were fully continent at the end of follow-up.

Support for using Botox to treat infantile esotropia can be found in a study by Campos, Schiavi and Bellusci. Botulinum toxin type A was effective in patients (n=60) with esotropia if treated by age 7 months. A minimum dose of 2.5 units of botulinum toxin type A per muscle was initially used in 10 patients but it was discovered that 3 units per muscle produced better results; therefore the following 50 patients received the higher dose. The mean follow-up period was 5.2 years (2 to 9 years).

Support for using Botox to treat detrusor and sphincter dyssynergia can be found in a study by Gallien et al. Botulinum toxin A was not effective in treating detrusor sphincter dyssynergia (DSD) in patients with multiple sclerosis (MS) in a multicenter, double-blind, placebo-controlled clinical trial. Patients (n=86; mean age, 50 +/- 10 years) with DSD due to MS, who had post-voiding residual urine volumes between 100 and 500 mL were randomized to botulinum toxin A 100 units or placebo, administered as single transperineal injections using striated sphincter electromyography. Each patient was also started on an alpha-blocker (alfuzosin 5 mg slow-release twice daily) for 4 months. No significant differences were found in the primary endpoint, the post-voiding residual urine volume at day 30 (botulinum toxin A, 186 +/- 158 mL, n=43; placebo, 206 +/- 145 mL, n=40; p=0.45). Secondary endpoints that were assessed at day 30 included voiding variables (symptoms were assessed using 10 centimeter (cm) visual analogue scales) and urodynamic variables. Of the voiding variables, only the voiding volume was significantly improved (p=0.02) in the botulinum toxin A arm (197 +/- 143 mL; n=35) compared with the placebo arm (128 +/- 95 mL; n=34), while the other voiding variables (obstructive symptoms, pollakiuria, urgencies, incontinence, and International Prostatism Symptom Score) were no different between treatment groups. Urodynamic variables that were significantly improved in the botulinum toxin A arm compared with the placebo arm included pre-micturition detrusor pressure (botulinum toxin A, 24 +/- 11 cm of water, n=34; placebo, 34 +/- 18 cm of water, n=28; p=0.02) and maximal detrusor pressure (botulinum toxin A, 52 +/- 22 cm of water, n=35; placebo, 66 +/- 25 cm of water, n=32; p=0.02), while the other urodynamic variables (maximal and cloture urethral pressures, basal detrusor pressure, detrusor compliance, maximal bladder capacity, and maximal urinary flow) were no different between treatment groups. At time points between day 30 and day 120, few endpoints were significantly improved in the botulinum toxin A arm compared with the placebo arm; these included voiding volume (at days 30 and 60; p=0.05) and incontinence (between days 60 and 120; p=0.04). Adverse events were similar between treatment groups.

Support for using Botox to treat difficulty speaking after total laryngectomy can be found in two studies published by Blitzer and colleagues and Terrell and colleagues. Preliminary reports indicate that botulinum A toxin injection of the upper esophageal sphincter appears to be effective in the management of voice failure after tracheoesophageal puncture (TEP) and prosthesis placement in most patients after total laryngectomy. Persistent focal constrictor hypertonicity/spasm appears to be responsible for the patients' poor speech production or inability to speak with the prosthesis. Botulinum A toxin injections of the cricopharyngeal muscle complex may be used successfully both diagnostically and therapeutically in patients who have voice production difficulties after TEP.

Support for using Botox to treat disorder of esophagus can be found in two studies. Alberty, Oelerich and Ludwig published a prospective study of patients with dysphagia. Botulinum toxin was effective in the treatment of dysphagia resulting from pure upper esophageal sphincter (UES) dysfunction. Ten patients (aged 39 to 77 years) with incomplete opening (n=8), delayed opening (n=1), or premature closure (n=1) of the UES received botulinum toxin 30 units injected into the UES under brief general anesthesia. One month following treatment, videofluoroscopic studies showed significant improvement in the opening of the pharyngoesophageal segment (from a mean of 47% at baseline to 71%, p less than 0.01). In addition, clinical symptoms scores improved in 9 of 10 patients (mean 4.9 at baseline to 2.0 post-injection).

Miller, Parkman, and Schiano published a study of fifteen patients with nonachalasia esophageal motility disorder, unresponsive to medical therapy, underwent endoscopic injection of botulinum toxin A at the level of the gastroesophageal junction. Twenty-unit injections were used in each of four quadrants above the squamocolumnar junction. There was significant improvement in chest pain (p less than 0.01), dysphagia (p less than 0.01), and regurgitation (p less than 0.01). After one month 73% of patients had a good or excellent response, while at the last patient interview (mean of 10.6 months) 33% continued to have a good to excellent response.

Support for using Botox to treat epicondylitis can be found in a study by Keizer et al. Botulinum toxin injection was as effective as surgical treatment for lateral humeral epicondylitis (tennis elbow) for patients who did not respond to conventional treatment. In this randomized pilot study, 40 patients received an injection of 30 to 40 units of botulinum toxin type A (Botox(R)) into the extensor carpi radius brevis (n=20) or a surgical wrist extensor release (Hohmann operation; n=20). Eight patients with insufficient paresis by the 6-week follow up received a second injection of botulinum toxin (50 units). Four of these patients still had insufficient paresis and had a Hohmann operation 6 to 18 months after initial treatment; only 1 of the 4 had a good result after surgery. During the 2-year follow up, the only significant difference between the groups was in the amount of sick leave at the 3-month follow-up, which was less in the operative group compared with the botulinum toxin group (p=0.01). The operative group experienced more extension problems of the elbow; 3 of 20 in the operative group and no patients in the botulinum toxin group had an extension deficit at the end of the 2-year follow-up. The overall results (modified Verhaar scoring system) showed no differences between the groups; 16 of 20 in the botulinum toxin group (15 of 16 for patients in botulinum toxin corrected group, with nonresponders excluded) and 17 of 20 in the operative group had treatment ratings of good or excellent. Botulinum toxin type A injection may provide a less invasive alternative for the treatment of tennis elbow.

Support for using Botox to treat essential tremor disorder can be found in a study by Brin et al. Botulinum toxin type A resulted in limited functional efficacy for the treatment of essential hand tremor since it improved postural but not kinetic hand tremors. Patients (n=133) with essential hand tremor were randomized to low-dose (50 units) or high-dose (100 units) botulinum toxin type A (Botox(R)) or placebo. Injections were made into the wrist flexors and extensors. During a 16-week follow-up, both doses of botulinum toxin significantly reduced postural tremor after 6 to 16 weeks (p=0.0002 and 0.0001 for low-dose and high-dose, respectively, at 6 weeks). Kinetic tremor, however, significantly reduced only at the 6-week examination (p=0.03 and 0.005 for low-dose and high-dose, respectively, at 6 weeks). Measures of motor tasks and functional disability were not consistently improved with treatment. In addition, grip

strength was reduced for both doses of botulinum toxin type A compared with placebo. Dose-dependent hand weakness was the major adverse reaction reported.

Support for using Botox to treat excessive salivation secondary to advanced Parkinson's disease can be found in two studies. Lagalla et al conducted a double-blind, randomized, placebo-controlled study (n=32), botulinum toxin type A was safe and led to subjective and objective improvement in drooling in outpatients with Parkinson disease. Nobrega et al conducted a open-label, prospective study. Ultrasound-guided, intraparotid injections of botulinum toxin type A decreased the severity, and to a limited extent, the frequency of diurnal drooling in outpatients with advanced Parkinson disease (PD) in an open-label, prospective study. Patients with PD characterized by presence of bradykinesia associated with muscular rigidity, 4 to 6 Hertz rest tremor, or postural instability were evaluated for sialorrhea. The drooling score was based on the sum of the scores for severity (1 to 5 scale; 1=dry: never drools; 5=profuse: clothing, hands, and tray moist wet) and frequency (1 to 4 scale; 1=never drools; 4=constant drooling). Patients (n=21; 18 males; mean age, 70 years; range, 55 to 84 years) with a diurnal sialorrhea of grade 5 or higher were included. Patients with dementia, severe depression, who had received treatment with neuroleptics within 1 years prior to onset of symptoms, or who had previously received treatment for drooling or anticholinergic drugs were among those excluded. Study patients were injected with botulinum toxin type A 125 units (500 units diluted in 2.5 mL saline) in two points of the parotid gland using ultrasonography. Drooling was evaluated by a speech therapist at 15 and 30 days following the injection. All patients were on levodopa therapy with entacapone and/or pramipexole during the study. At 15 days posttreatment, 19 of 21 patients reported a decrease in drooling; of the remaining 2 patients, one had no substantial change while the other's condition worsened. The total drooling score decreased from a mean baseline score of 6.85 to 5.14 at 1 month following the injection (p less than 0.001). The mean pre- and 1-month posttreatment drooling severity scores were 3.42 and 2.14, respectively (p less than 0.001), and drooling frequency scores were 3.42 and 3, respectively (p=0.021). Overall, the severity of drooling decreased in 18 (86%) patients and the frequency of drooling decreased in 8 (38%) patients. The frequency of drooling remained unchanged in 11 (52%) patients. Among treatment-emergent adverse events, two patients experienced mild dry mouth lasting 1 month. One patient developed bilateral local edema, which was mild, self-limited, and resolved after 4 days.

Support for using Botox to treat excessive salivation secondary to a disorder of the nervous system can be found in two published studies. Porta and colleagues found that ultrasound guided botulinum toxin type A was safe and effective in the treatment of sialorrhea in patients with neurological disorders. Botulinum toxin type A (Botox(R)) was injected bilaterally into the parotid and submandibular glands at doses which were calculated based on patient weight and rate of salivation. The mean parotid dose was 27.7 units/gland and the mean submandibular dose was 11.9 units/gland (mean total dose was 76.6 units). After treatment, there was a subjective reduction in salivation reported for 9 patients and no improvement in 1 patient. Visual analogue scale scores showed a 55% decrease in mean rate of salivation for all patients and a 61% decrease for the responder group. No serious adverse events occurred.

Additionally, Giess et al found that injections of botulinum toxin into the salivary glands successfully ameliorated sialorrhea and improved quality of life without significant adverse effects in patients with bulbar amyotrophic lateral sclerosis. Five patients (mean age 64 years) received 6 to 20 mouse units of botulinum toxin A injected into each parotid gland in 3 divided doses. This was repeated 2 weeks later if, as judged by the patient, the clinical response was inadequate. Additional injections (5 units) into each submandibular gland were required in 2 patients. In 4 of 5 patients, botulinum toxin injections markedly reduced sialorrhea as measured by paper handkerchiefs used before and at 4 weeks after treatment (11 vs 3, p=0.068) and by a reduced radiotracer uptake in both parotid glands noted on salivary gland scintigraphy. At up to 3 months of follow-up, a slight increase of sialorrhea was noted in 1 patient. Quality of life was markedly improved in 3 patients, moderately improved in 1 patient, and not enhanced in the last.

Support for using Botox to treat excessive tear production can be found in a study by Whittaker et al. A small pilot study demonstrated the effectiveness of botulinum toxin type A in the treatment of functional epiphora. Patients (n=14) with symptoms of epiphora and a patent lacrimal system received a single injection of 2.5 to 5 units of botulinum toxin A (Botox(R)) into the palpebral lobe of the lacrimal gland on the worst affected side. Four patients received 5 units of botulinum toxin A, but 2 of the 4 patients experienced side effects, so the remaining 10 patients received 2.5 units of botulinum toxin A. Evaluation of efficacy was based on a 5-minute Schirmer test and subjective reports from the patients at week 1, week 4, and week 13. A reduction in epiphora was reported by 71.4%, 85.7%, and 72.7% of patients at week 1, week 4, and week 13, respectively. Based on Schirmer test results, a reduction in tearing occurred in 78.6%, 71.4%, and 54.5% at week 1, week 4 and week 13, respectively. Adverse effects were reported in 2 patients who received a 5-unit botulinum toxin A dose; 1 patient had a ptosis that resolved within 4 weeks and another patient had vertical diplopia for 3 weeks after the injection. Additional studies to determine the optimal dosage as well as the safety and effectiveness of multiple injections over a longer term are recommended.

Support for using Botox to treat fibromyalgia and myofascial pain syndrome can be found in a study by Porta (1999). Botulinum A toxin exhibited efficacy equivalent or superior to that of methylprednisolone in the treatment of myofascial pain syndrome in a randomized, single-blind trial (n=40). Along with adjunctive bupivacaine, Botox(R) 80 to 150 units or methylprednisolone 80 mg was injected into the piriformis, scalenus anterior, or iliopsoas muscle as confirmed by computed tomography. All subjects also entered an intensive physiotherapy program. Visual analogue scores (VAS) for pain decreased significantly in both groups at 30 days versus baseline. Botulinum recipients recorded statistically lower mean VAS (2.3) as compared with steroid recipients (4.9) at 60 days (p less than 0.0001). Neither regimen was associated with noteworthy adverse effects.

Support for using Botox to treat Gilles de la Tourette's syndrome can be found in a study by Kwak, Hanna and Jankovic. Botulinum toxin injections were effectively used to treat tics and associated premonitory symptoms in an open study of patients with Tourette syndrome. Thirty-five patients aged 8 to 69 years, who had a mean tic duration of 15 years, received an average of 120 units during each of 3 visits. The most common muscles injected were cervical, and those in the upper face, particularly the eyelids. During a mean follow-up period of 21 months (range 1.5 to 84 months), 29 patients experienced an improvement, with 23 of these patients demonstrating a marked improvement, based on a peak effect score of 3 or greater (0 to 4 scale). In addition, 21 (84%) of 25 patients with premonitory symptoms (described as discomfort, tingling, or tension preceding the tic) experienced significant relief from these symptoms. The duration of therapeutic benefits averaged 14 weeks. Adverse effects included neck weakness (n=4), ptosis (n=2), generalized weakness (n=1), dysphagia (n=2), fatigue (n=1), and nausea and vomiting (n=1).

Support for using Botox to treat granuloma of vocal cords which is refractory to conventional surgical and medical therapies can be found in a study by Orloff and Goldman. In a case series (n=8), botulinum A toxin (Botox(R)) was 100% effective in eradicating vocal fold granulomas that were refractory to conventional surgical and medical therapies. The toxin was injected under electromyographic guidance transcutaneously or during laryngoscopy into one or both thyroarytenoid muscles at an average dose of 10 units per site. All granulomas disappeared within 2 months. Four patients required early reinjection due to inadequate paresis. All patients remained free of recurrence throughout the follow-up period (11 to 41 months). Adverse effects included mild-to-moderate breathiness and reduced Valsalva effect in 7 and 1 patients, respectively. Depending on the etiology of vocal fold granuloma, treatment may also include voice therapy, behavioral modification and medication for contributory conditions (i.e., gastroesophageal reflux).

Support for using Botox to treat hemifacial spasm can be found in a retrospective chart review and open-label trial. In a retrospective chart review of 51 patients with benign essential blepharospasm (BEB, n=17), hemifacial spasm (HFS, n=17), or aberrant facial nerve regeneration synkinesis (AFR, n=17), and a minimum treatment period of 10 years, mean blepharospasm disability score (BDS) significantly improved from 6 to 3 at last review across all 3 groups, and

improvement was significantly greater in patients receiving flexible-interval injections compared to fixed-interval injections (Bladen et al, 2019). Mean BDS improved significantly in the BEB group with a trend to improvement in the HFS and AFR group, and BDS improvement mainly occurred in the first year with smaller fluctuations in following years. Mean duration of maximal effect was 10.5 weeks across the 3 groups but increased progressively only in the flexible-interval group. Patients (mean age, 63 years) received injections at a fixed, 12-week interval (n=14; mean annual injections, 4) or at flexible intervals (n=37; mean annual injections, 3.4). The cumulative complication rate was the same in the flexible- and fixed-interval groups and included ptosis, dry eye, and lagophthalmos.

In an open-label, time series in adults with hemifacial spasm (n=137), serial treatment with onabotulinumtoxinA led to an overall response rate of 88%. Patients with right- or left-sided hemifacial spasm refractory to other forms of therapy received treatment (mean age, 56.3 +/- 13 years; 55% female; mean disease duration, 5.6 +/- 6.4 years) (Chen, 1996). Patients with a history of previous peripheral facial palsy were excluded. Most patients received a total of 12 to 15 units of onabotulinumtoxinA per injection, which was injected as follows: 2.5 units each into the central and lateral orbicularis oculi of the lower eyelid, 2.5 to 5 units into the lateral orbicularis oculi of the upper eyelid, and 5 units divided into the buccolabial and/or platysma muscles. However, 20 patients received a total dose of 25 units. Efficacy was assessed both objectively and subjectively prior to each injection and at each follow-up (2 weeks after the initial injection, then monthly until the subsequent injection). Objective assessment involved grading of clinical severity of spasm, by 2 assessors, using a 5-point scale (0=no abnormality/normal blinking to 4=severe prolonged disfigurement/incapacitating social activities) and videotape recording. Subjective assessment involved patient-report degree of spasm relief using a 5-point scale (0=baseline, 1=25% improvement, 2=50%, 3=75%, 4=more than 90% improvement). A total of 228 treatments were administered, with an average of 1.7 treatments per patient. Based on both objective and subjective measures, the overall response rate was 88% (57% substantial improvement and 31% improvement), and the overall mean duration of spasm relief was 20 weeks (range, 2 to 52 weeks). Only 4 patients achieved complete remission after the first injection, with most patients requiring subsequent treatments on average every 3 to 4 months. No significant difference in response rate was observed among those who received doses less than 15 units and those who received 15 units or more. Additionally, analysis of the first 5 treatments did not reveal a significant difference in the duration of spasm relief based on severity of pretreatment spasm. Among 216 treatments, the most common adverse events included facial weakness in 95% of patients, which led to dynamic or static facial asymmetry in 37% of these patients, ptosis (29%), and diplopia (5%). Diplopia and ptosis resolved within 8 and 10 weeks, respectively, and the incidence decreased with consecutive treatments.

Support for using Botox to treat isolated oromandibular dystonia can be found in a several small open-label clinical trials. Jankovic and Hallett enrolled patients (n=96) who were diagnosed with jaw-closing OMD (n=51; 74.5% female), jaw-opening OMD (n=40; 67.5% female), or jaw-deviation OMD (n=5; 100% female) with over 70% of all cases considered idiopathic. Patients received botulinum toxin A (Botox(R)/Oculinum(R); Allergan Pharmaceuticals) into 3 to 5 sites of each involved muscle. Median doses for each muscle were 24.5 +/- 17.7 units (masseter; range, 2 to 100 units), 18.5 +/- 11.9 units (temporalis; range, 2 to 75 units), 16.3 +/- 8.1 units (medial pterygoid; range, 5 to 40 units), 15.9 +/- 8.7 (lateral pterygoid; range, 2.5 to 60 units), and 9.8 +/- 4.6 (anterior digastric; range, 3.75 to 30 units). Initial treatments were typically inadequate, and patients received an additional treatment of botulinum toxin A administered 2 to 4 weeks after the first dose. Patients rated their current condition using a linear, global clinical rating scale, with 0% defined as fully disabled/no useful function and 100% defined as normal. Patients with all 3 types of OMD reported statistically significant improvements, with improvements from 29.6% +/- 2.7% to 72% +/- 4.4% (p=0.0001) in the jaw-closing group, 30.8% +/- 4% to 73.8% +/- 4.2% (p=0.0001) in the jaw-opening group, and 38.8% +/- 9.2% to 75.8% +/- 12.2% (p=0.014) in the jaw-deviation group. Duration of benefit was 14.6 +/- 2.1 weeks, 11.8 +/- 2.1 weeks, and 10.8 +/- 5 weeks for the jaw-closing, jaw-opening, and jaw-deviation groups, respectively. Adverse effects occurred in 11.8% of

patients in the jaw-closing group, 17.5% of patients in the jaw-opening group, and no patients in the jaw-deviation group. The most common adverse effect was dysphagia (n=14). One patient developed antibodies to botulinum toxin A.

Additionally, Jankovic, Schwartz, and Donovan studied patients (n=62; mean age, 57.2 years; range, 14 to 78 years) with idiopathic OMD, who despite optimal pharmacological therapy, surgery, or both, were treated with botulinum toxin A every 3 to 6 months, injected into masseters, submental, temporalis, and pterygoids muscles. Doses were initiated at 25 units per muscle and increased to 50 units each into the masseters and temporalis muscles. Assessments consisted of severity of dystonia (0 to 4 scale with 0 as no spasm and 4 as severe, incapacitating spasm) rated in a patient diary, latency (interval between the injection and first sign of improvement), peak effect (maximum benefit obtained; determined from patient diary, interview of family or friends, and patient's perception rated as no effect (0), mild improvement (1), moderate improvement but no change in function (2), moderate improvement in severity and function (3), or marked improvement in severity and function (4)), and global rating (peak effect score minus one point for mild or moderate complications or minus 2 points for severe or disabling complications). Patients received a total of 407 injections during 186 visits. Favorable response (global rating of 2 or more) occurred in 73% of evaluable patients (n=45) with OMD. Mean global rating was 2.2 +/- 1.5, while peak effect was 2.4 +/- 1.6, latency to response was 4.6 +/- 5.6 days (range, 0 to 30 days), and total duration of response was 10.3 +/- 8.7 weeks (range, 0 to 54 weeks). Over half (55.6%) of patients failed (global rating of 1 or less) one or more visits. Overall, adverse events were observed on 37% of visits (n=115) with the most common adverse event of dysphagia occurring in 12% of patients.

Support for using Botox to treat neuropathic pain secondary to spinal cord injury can be found in a randomized, double blind, placebo-controlled, parallel group study by Han et al (2016). A 1-time, 200-unit, subcutaneous botulinum toxin type A dose was administered to the painful area in 40 patients with spinal cord injury-associated neuropathic pain. Patients in this study had spinal cord injury of any level, with daily neuropathic pain for at least 3 months, and a visual analog scale (VAS; 0-100mm) score of ≥ 40 at baseline. A total of 3 visits were scheduled over 8 weeks (baseline, 4 weeks, and 8 weeks after injection). The single administration of subcutaneous botulinum toxin A significantly reduced the VAS scale pain scores compared with placebo at both 4 weeks (18.6 +/- 16.8 vs 2.6 +/- 14.6) and 8 weeks (21.3 +/- 26.8 vs 0.3 +/- 19.5). Adverse effects included reports of pain during injection or triggering of spasticity, though there was no difference between the botulinum toxin treatment and placebo groups reported by the authors.

Support for using Botox to treat larynx closure as adjunct to surgical procedure can be found in a small study by Pototschnig et al (1996). In a small number of patients (n=6) requiring larynx closure, botulinum toxin A injections into the laryngeal musculature was effective at completely paralyzing the larynx and allowing for wound healing. Patients in this study all suffered from severe chronic aspiration caused by previous injury (e.g., stroke, tumor removal, and hypoxic trauma). Two weeks prior to surgery, patients were injected with 1 to 1.4 mL (200 to 280 units) of botulinum toxin A into the intrinsic laryngeal musculature (i.e., bilateral injections of posterior cricoarytenoid, aryepiglottic, medial thyroarytenoid, and lateral thyroarytenoid). Five of 6 patients had complete closure and the other patient had a thin fistula of the posterior commissure. This procedure reportedly preserves the ability of speech rehabilitation and can be performed in high-risk patients. Additional study is needed to further investigate the use of botulinum toxin A as adjunctive therapy to surgical procedures of the larynx.

Support for using Botox to treat oculomotor nerve injury can be found in a study by Talebnejad, Sharifi, and Nowroozzadeh. Botulinum toxin A injection was effective for treatment of trauma-induced, acute-phase, third nerve palsy (n=9). Additionally, Saad and Lee conducted a retrospective review of botulinum toxin A for the treatment of exotropia of third nerve palsy provides evidence that long-term efficacy may rely on pretreatment markers and that treatment is not a reliable predictor of surgical outcomes.

Support for using Botox to treat organic voice tremor can be found in a study Hertegard et al. Botulinum A toxin successfully ameliorated essential voice tremor in the majority of a case series (n=15, mean age 73 years). After injection

into the bilateral thyroarytenoid muscles (dose range 0.6 to 5 units of Botox(R), typically at 3-month intervals), 67% of patients reported positive subjective results. Depending on the method of evaluation, the treatment was effective in 50% to 60% of patients. Adverse effects included transient breathiness, hoarseness and mild dysphagia.

Support for using Botox to treat palmar hyperhidrosis can be found in a study by Naver, Swartling and Aquilonius. Twenty-eight patients with palmar (n = 19) and/or axillary (n = 13) hyperhidrosis were treated with intracutaneous injections of botulinum toxin (Botox(R)) 2 U/4 cm2. Sweat function was studied clinically and by objective measurements after treatment of one side. Treated and untreated sides, and pre- and post-treatment skin areas were compared. Subjective evaluation was performed after treatment of one side and 2-5 months after treatment of both sides. Duration of effect was controlled by a one-year follow-up. Sweating disappeared in eight out of 13 patients with axillary and in five out of 19 with palmar hyperhidrosis, and was reduced markedly in another five out of 13 and 10 out of 19 patients. Two-thirds of those treated for hand sweat noticed a slight and transient reduction of power of finger grip. No side-effects were noticed after treatment of axillary hyperhidrosis.

Support for using Botox to treat pelvic floor dyssynergia can be found in a study by Hallan et al. The group conducted an uncontrolled study involving 7 patients with constipation has suggested benefits of botulinum A toxin in the treatment of anismus in intractable constipation. Botulinum A toxin was injected into the puborectalis muscle (bilaterally), at a dose of 3 nanograms (ng) (1.5 ng on each side of the muscle). At 4 weeks following treatment, total symptoms scores improved significantly, and were correlated with a reduction in the maximum voluntary squeeze anal canal pressure and an increase in the anorectal angle upon straining. Clinical response was considered excellent in 4 of the patients, with repeat injections being given at 8 to 10 weeks. There was one complete failure and 2 partial failures. More studies are required under controlled conditions to evaluate the efficacy of botulinum A toxin in anismus, and to evaluate the efficacy and safety of administering the toxin over prolonged periods.

Support for using Botox to treat pharyngoesophageal segment spasm following total laryngectomy can be found in a study by Bartolomei et al. Treatment with botulinum A toxin plus participation in a voice therapy program led to improved phonation in a published case series of 34 patients with pharyngoesophageal segment spasm after laryngectomy. After the first patient failed to demonstrate a response with a dose of 20 units (who then received a repeat injection of 100 units), 26 patients received 100 units of botulinum A toxin, 3 patients with minor spasm received 50 units, 3 patients received 30 units, and 1 patient received 60 units. Doses were administered in 1 injection unilaterally (n=29) or bilaterally (n=1), or unilaterally in 6 to 7 divided injections (n=4). Electromyography was used to guide the injections in the pharyngeal constrictor muscles. Benefit was seen in all but 2 patients at 72 hours postinjection, and patients were able to count to 9, say their name, and speak short sentences. Rapid decline occurred in 8 patients, requiring botulinum A toxin injection every 3 months, while the other patients demonstrated long-lasting benefit. No adverse effects were reported except for mild dysphagia in 1 patient.

Support for using Botox to treat refractory idiopathic trigeminal neuralgia can be found in the European Academy of Neurology (Bendtsen, 2019). A weak recommendation for the addition of botulinum toxin type A to other medications for medium-term treatment of trigeminal neuralgia is based on very low-quality evidence.

Liu et al published a study where botulinum toxin A significantly reduced visual analogue scale (VAS) pain scores from 8.5 to 4.5 in patients aged 80 years and older (n=14; mean age 82.6), and from 8 to 5 in patients less than 60-years-old (n=29; mean age 49.5). Patients were examined at baseline and at 1 month after treatment; median VAS scores were significantly lower at 1 month compared to baseline but did not differ significantly between groups. Drug administration was guided by pain and trigger zones, and delivered transdermally and/or submucosally. Botulinum toxin A dosages were 45 to 150 units in the older group (mean, 91.3 units) and 30 to 200 units (mean, 71.8 units) in the younger group. Transient mild side effects occurred in 2 patients in each group and resolved spontaneously within 3 weeks.

Support for using Botox to treat spastic dysphonia can be found in a study published by Blitzer, Brin and Stewart. Based on 12 years of experience treating spasmodic dysphonia (6300 injections in 901 patients), botulinum A toxin is considered to be the treatment of choice. The types of dysphonia included adductor (82%), abductor (17%), and adductor breathing or paradoxical vocal fold motion (1%). Dosing of Botox(R) was individualized. For adductor dystonia, the average onset and duration were 2.4 days and 15 weeks, respectively, with patients achieving 90% of normal function. Corresponding values for abductor dystonia were 4 days, 10.5 weeks and 67%, respectively. Patients with adductor breathing dystonia returned to 82% of normal functioning for a mean of 14 weeks. Botulinum A toxin was generally well-tolerated with a few patients developing mild and transient adverse effects such as breathiness, exertional wheezing/stridor and dysphagia.

Support for using Botox to treat stuttering can be found in a study by Brin, Stewart, and Blitzer. Botulinum A toxin 1.25 units (Botox(R)/Oculinum(R)) into each thyroarytenoid muscle has been shown to be effective in the treatment of stuttering with glottal block, resulting in a moderate improvement in fluency.

Support for using Botox to treat tardive dyskinesia can be found in an open-label study conducted by Rappaport et al. In an open-label study, the administration of botulinum toxin was effective and safe in the treatment of oro-facial-lingual-masticatory tardive dyskinesia due to dopamine receptor blocking agents. In this study, 12 psychiatric patients (mean age 74 years), who had received long-term treatment with phenothiazines or butyrophenones and were resistant to at least 1 prior treatment for dyskinesias, received 80 units of botulinum toxin injected subcutaneous into 4 facial sites (Lateral to the buccal commissures, midpoint of the upper lip, and the mid-central area of the chin). As assessed by the Tardive Dyskinesia Rating Scale, a significant improvement in dyskinesias was noted at 1, 5, and 8 weeks following treatment. A significant response was observed for pouting, grimacing, and dysarthria, while a trend for improvement was noted for puckering and choreoathetoid movements of the tongue. No adverse effects were observed.

Support for using Botox to treat temporomandibular joint disorder can be found in a study conducted by Freund, Schwartz, and Symington. A small, uncontrolled trial (n=15) provides preliminary evidence suggesting efficacy and safety of botulinum A toxin (Botox(R)) for chronic temporomandibular joint disorders. Subjects received a total of 150 units administered with electromyographic guidance to the masseter and temporalis muscles. When assessed every 2 weeks through week 8, average scores for pain, functional disability index, mouth opening, and tenderness improved from pretreatment values (p=0.05). Mean bite force did not change appreciably. Botulinum toxin therapy did not induce adverse effects or complications.

Support for using Botox to treat tension-type headache can be found in a several small trials. Porta (1999) reported headache pain scores were decreased by botulinum toxin to a greater extent than with methylprednisolone in a randomized, single-blind, comparative trial conducted in 20 patients ranging in age from 18 to 70 years. The subjects were recruited if they presented with a history of 2 or more tension-headache episodes per month for at least the past 3 months. They were then randomized to receive an IM injection of either 40 mg of methylprednisolone or multiple IM injections of 5 to 15 units per site of botulinum toxin A (Botox(R)) into various tender points on the head identified using algometry. The amount of botulinum toxin A varied with each patient. Visual analog pain scores were assessed at baseline and 30 and 60 days posttreatment for all patients. Quantitative algometry was performed in 5 patients at these same time points. At baseline and 30 days there was no difference in pain severity scores between the 2 groups (p=0.94 and p=0.67, respectively). However, at 60 days posttreatment there was a statistically significant difference in the median visual analog pain scores between the two groups, with the botulinum toxin A group experiencing less pain (p=0.0003). No adverse events were reported.

A study by Smuts et al addressed the use of botulinum toxin A for the prophylaxis of chronic tension-type headache (TTH). Investigators recruited 41 patients meeting the International Headache Society criteria for chronic TTH who had failed prior prophylactic drug therapy. Using a double-blind, placebo-controlled design, patients were randomized to

receive either IM injections of 100 units botulinum toxin A (Botox(R)) or an equivalent volume of normal saline. The injections were given in 2 sites in the temporal muscles and 4 sites in the cervical muscles bilaterally. Patients kept a headache diary for 4 weeks prior to treatment, and for 3 months afterwards. Headache pain was recorded using a 6-point scale, and a chronic pain index was used as an indirect quality-of-life measurement. The authors noted a statistically significant improvement in headache pain and headache-free days in the botulinum toxin A group compared with baseline values after 3 months. The botulinum toxin A group also experienced a statistically significant improvement in chronic pain index scores from baseline by month 3 (p=0.001). No between-group differences were noted with respect to adverse effects.

Support for using Botox to treat thoracic outlet syndrome can be found in a study by Jordan et al. Chemodenervation of the scalene muscles using botulinum toxin injections has been associated with substantial relief of symptoms related to thoracic outlet syndrome. In a study of 22 patients unresponsive to physical therapy and suboptimally managed with anesthetic and steroid injections, botulinum toxin 100 units was administered, under electrophysiologic and fluoroscopic guidance (12 units each into the anterior and middle scalene muscles, 76 units into the ipsilateral trapezius muscle). During a 6-month follow-up period, 14 of 22 (64%) patients reported greater than 50% relief of pain, numbness, and fatigue of the treated upper extremity. This improvement lasted for an average of 88 days (range 30 to 180 days). In contrast, only 4 of 22 patients responded similarly following lidocaine and steroid injections (p=0.0051). The positive, long-lasting response associated with botulinum toxin is useful for patients awaiting surgical decompression for this disorder.

Support for using Botox to treat whiplash injury to neck can be found in a study by Freund and Schwartz. Botulinum A toxin (Botox(R)) as a total of 100 units injected into five tender cervical muscle trigger points decreased subjective neck pain with resultant increase in range of motion, but had only equivocal effects on functioning in a randomized, double-blind, placebo-controlled trial (n=26). Subjects had chronic whiplash-associated neck pain following a motor vehicle accident that occurred an average of 3 years prior to baseline. At 4 weeks post-injection, the composite visual analogue scale (VAS) score for neck pain, headache and shoulder pain was significantly lower and total range of neck motion was significantly greater in the botulinum group as compared with the saline group (p less than 0.01). However, the Vernon-Mior score revealed no statistical difference in subjective functioning. Botulinum A toxin did not induce adverse effects.

Support for using Dysport to treat achalasia in a patient who is not a surgical candidate can be found in a study by Mikaeli et al. There was no significant difference between adjunctive treatment with abobotulinumtoxinA before pneumatic dilatation compared with pneumatic dilatation alone for the treatment of newly diagnosed achalasia in a prospective, randomized, controlled trial (n=52). Adults (18 years (yr) or older) with symptomatic, treatment-naïve achalasia were eligible and enrolled consecutively. Patients with functional class 3 or 4 cardiovascular disability and coagulopathy were excluded. Patients were randomly assigned to receive two 50-unit aliquots (0.5 milliliters) of abobotulinumtoxinA (400 units total dose) injections to each quadrant of the lower esophageal sphincter 1 month before pneumatic dilatation (PD) (n=26; median age 38 yr; interquartile range (IQR), 26 to 49 yr; 62% male) or PD-alone (n=26; median age 30 yr; IQR, 24 to 45 yr; 46% male). PD was performed with a 30 millimeter (mm) balloon, gradually inflated up to 10 pounds per square inch in 30 seconds (sec) and maintained for another 60 sec for all patients. Clinical evaluation was performed at baseline, 1-month after treatment, and every 6 months thereafter for 1 year. Clinical response was defined as a symptomatic total score less than 4 and relapse was defined as a symptomatic total score of 4 or greater. The symptomatic total score was based on 5 symptoms: dysphagia with solids, dysphagia with liquids, and active regurgitation, ranked as 0=none, 1=weekly, 2=daily and 3=with each meal, and passive regurgitation and chest pain, ranked as 0=none, 1=monthly, 2=weekly, and 3=daily. Despite significant reductions in total symptom scores within treatment groups at 1 month, which were sustained at 12 months (p less than 0.001), the cumulative remission (response) rate at 12 months was not significantly different between treatment groups. At 12 months, after a single treatment with abobotulinumtoxinA before PD, the cumulative remission rate was 77% (95% CI, 68% to 86%) compared

with 62% (95% CI, 52% to 72%; p log rank=0.1) with PD-alone. Relapse occurred in 23% (6/26) of evaluable patients in the abobotulinumtoxinA before PD group and 38% (10/26) of evaluable patients in the PD-alone group. Relapse patients received a second treatment of PD-alone with a 35 mm balloon. After retreatment, 100% of patients in the abobotulinumtoxinA before PD group and 85% of patients in the PD-alone group had symptomatic remission at 12 months from initial treatment. The cumulative remission rate was significantly higher in the abobotulinumtoxinA before PD group compared with PD-alone group after retreatment (p less than 0.05). No significant bleeding, perforation or aspiration occurred in either group and no confounding factor was found to be a predictor of treatment response.

Additionally, Kroupa et al (2010) found adjuvant therapy with abobotulinumtoxinA prior to pneumatic dilatation did not offer additional benefit compared with pneumatic dilatation alone for the treatment of esophageal achalasia in a prospective, historical-controlled study (n=91). Treatment-experienced and -naive adults with achalasia who underwent combined treatment (n=51; mean age 49.7 years (yr); range 24 to 83 yr; 39% male) were compared with historical controls who received PD-alone using the same procedural method and time protocol for evaluation (n=40; age range 26 to 80 yr; 40% male). Prior interventions among treatment-experienced patients included pharmacological treatment with nitrates or nifedipine (46/51), surgical myotomy (3/51), and at least 1 pneumatic dilatation (6/51) Eight days prior to pneumatic dilatation (PD), the adjuvant-therapy group received abobotulinumtoxinA 200 international units (IU) total dose injected in 0.5 milliliter aliquots in the z-line area of each quadrant of the lower esophageal sphincter (LES). PD was performed with a 30 millimeter (mm) balloon for dilatation 1, and a 35 mm balloon for subsequent dilatations. Repeat dilatations were indicated for patients with insufficient cardia relaxation after dilatation 1 as evident upon X-ray verification. Follow-up was conducted every 3 months (mo) for the first year, then annually thereafter; with a mean follow-up duration of 48 mo (range, 12 to 96 mo) and 42 mo (range, 12 to 96 mo) in the adjuvant therapy and control groups, respectively. Efficacy was assessed by application of a grading scale (1=excellent to 5=failure/complete relapse) for symptoms of dysphagia with liquids and solids, heartburn, regurgitation, chest pain or pressure, and weight change. Remission was defined as no or mild dysphagia, and acceptable individual symptoms as compared with baseline levels. About 3 to 4 days following the initial PD, 13 patients required 2 dilatations and 4 patients required 3 dilatations. For the adjuvant-therapy group, baseline measurements were 4.6 points (95% CI, 3.8 to 5.4 points) and 29 mmHg (range, 10 to 80 mmHg) for mean symptom score and median LES pressure, respectively. The initial treatment effect was observed in 91% (43/47) of patients (4 patients were lost to follow-up). After 3 months, the mean symptom score improved to 2.1 points (95% CI, 0.8 to 3.4 points) and the median LES pressure significantly improved to 14 mmHg (range, 5 to 26 mmHg; p less than 0.001). However, LES pressure slightly increased to 17 mmHg (range 8 to 40 mmHg) and 19 mmHg (9 to 38 mmHg) after 2 and 5 yr since initial treatment, respectively. Treatment durability was sustained in 75% (31/41) of patients with greater than 2-yr follow-up, and 70% (12/17) of patients with greater than 5 yr follow-up. The cumulative remission rate at the end of 5 yr was not significantly different between the adjuvant-therapy group (69%; 95% CI, 61% to 77%) and the historical control groups 50% (95% CI, 41% to 59%; p=0.07). Of 17% (8/47) of patients with relapse dysphagia, laparoscopic Heller myotomy was performed without complications. The most common adverse event was heartburn (36%), which was treated with proton pump inhibitors.

Support for using Dysport to treat blepharospasm can be found in a study by Truong et al. In a multicenter, phase 2, randomized, double-blind, placebo-controlled, parallel-group trial (n=120), a single injection of abobotulinumtoxinA 40 units, 80 units, or 120 units per eye was superior to placebo for the treatment of benign essential blepharospasm (BEB). Adults (age range, 33 to 91 years (yr)) with bilateral BEB for at least 6 months and who scored at least 8 points on the Blepharospasm Disability Scale (BDS; range, 0 to 26 points; higher score indicates greater disability) were eligible. Receipt of botulinum toxin prior to study entry was allowed provided a minimum of 12 weeks had elapsed since the last injection. Use of concomitant medications (e.g., benzodiazepines) that could potentially compromise evaluation of study outcomes was not permitted; however, concomitant use of antispasmodics, muscle relaxants, or other medications affecting the neuromuscular junction was allowed provided doses were stable during the study period. Patients were

randomized to receive a total dose per eye of either abobotulinumtoxinA 40 units (n=30; median age, 66 yr; 68% female), 80 units (n=31; median age, 67 yr; 77% female), 120 units (n=31; median age, 62 yr; 81% female) or placebo (n=28; median age 62 yr; 68% female) injected subcutaneously in 0.1 milliliter (mL) aliquots into 6 areas of the orbicularis oculi muscle (0.6 mL total volume/eye). The primary outcome was improvement in functional disability, measured as the difference in the median percentage of normal activity on the BDS between active treatment and placebo at week 4. Notably, 50% of patients in placebo group dropped out of the study citing lack of efficacy compared with 20%, 16%, and 10% of patients in the abobotulinumtoxinA 40-, 80-, and 120-unit dose groups, respectively. An intent-to-treat analysis at week 4 showed significant improvement in functional disability with all abobotulinumtoxinA doses compared with placebo (p less than 0.01); improvement was dose-related and was sustained through week 12. Among secondary outcomes, the frequency of involuntary movements (FIM; measured using a modified FIM scale; range, 0 (no involuntary movements) to 5 (movements present greater than 75% of the time)) and the severity of oculofacial spasm (measured using the Severity Rating Scale) significantly improved at weeks 4, 8, and 12 with all doses of abobotulinumtoxinA compared with placebo. Median differences over placebo in FIM scores at week 4 were -2 (95% confidence interval (CI), -3 to -1), -3 (95% CI, -4 to -2), and -3 (95% CI, -4 to -1) for the 40-unit, 80-unit, and 120-unit dose groups, respectively (p less than 0.001 for all); correspondingly, median differences over placebo in the severity of oculofacial spasm scores were -1 (95% CI, -2 to -1), -2 (95% CI, -2 to -1) and -2 (95% CI, -2 to -1), respectively (p less than 0.001 for all). Improvements in the primary and secondary outcomes were maintained through week 16 only in the 80- and 120-unit groups (p less than 0.05). AbobotulinumtoxinA was well tolerated, with dose-related treatment events that were mild to moderate in severity and resolved without sequelae. Common events included eyelid ptosis, blurred vision, lagophthalmos, diplopia, increased lacrimation, and aggravated dry eyes.

Support for using Dysport to treat hemifacial spasm can be found in a study by Jitpimolmard, Tiamkao, and Laopaiboon. The authors conducted a long-term, prospective, descriptive study (n=158), serial abobotulinumtoxinA injections were effective and led to sustained improvement of hemifacial spasm in adults. Over a 7-year period, 175 consecutive patients with idiopathic hemifacial spasm received abobotulinumtoxinA subcutaneous injections, with the dose ranging from 28 to 220 units per treatment session based on sites and severity of the spasm. The primary injection sites were the medial and lateral lower eyelid; and the lateral junction area of the orbital and preseptal orbicularis oculi, below the lateral eyebrow and orbital area of the upper eyelid. The upper eyelid injection site was later shifted to the lateral orbital orbicularis oculi above the lateral eyebrow to reduce the incidence of ptosis. Subsequent injections were administered upon recurrence of spasm and if patient perception of the spasm was severe enough to request additional treatment. Efficacy assessments, which included peak improvement (measured using a visual analog scale; range, 0% to 100%) and duration of improvement, were conducted for 855 treatments administered to 158 patients (mean age, 49.1 +/- 11.39 years; 75% female). The median number of treatments was 4 (range, 1 to 19) and the mean follow-up period was 2.39 years (range, 3 to 80 months). The median duration of hemifacial spasm prior to receiving treatment was 4 years (range, 0.25 to 25 years). Among the 855 treatments, the response rate was 97%, with an adjusted mean peak improvement of 77.2% (95% confidence interval (CI), 74.7% to 79.4%); 70% of the treatments were rated as 75% to 100% improved. The adjusted duration of improvement was 3.4 months (95% CI, 3.2 to 3.6 months). Analysis of serial injections from treatment 1 up to treatment 12 revealed sustained effects for mean peak improvement (range, 72.07% to 80.17%) and duration of improvement (range, 2.93 to 3.71 months), but there was no additional benefit in either parameter over the series of treatments (p=0.4 and p=0.87, respectively). Of 26 treatment failures (peak improvement of less than 20%) occurring in 23 patients, subsequent treatments at the same dose (n=12) or higher dose (n=6) resulted in satisfactory improvements. Over 855 treatments, the most common adverse events were ptosis (22.1%) and drooping of the mouth (8.38%). Ptosis resolved in a mean of 2.64 weeks (range, 1 to 4 weeks). Following the change in site of upper eyelid administration, the incidence of ptosis significantly reduced from 27.17% (138 treatments) to 9.67% (21 treatments; p less than 0.001), with no significant difference in mean peak improvement or duration of improvement.

Support for using Myobloc to treat axillary hyperhidrosis can be found in a study by Hecht, Birklein, and Winterholler. Botulinum toxin type B effectively treated axillary hyperhidrosis in 4 patients. Patients received 250 mouse units (diluted in 2.5 milliliters saline) of botulinum toxin type B injected subcutaneously into 10 to 15 sites in each axilla. Using gravimetry, the mean pretreatment axillary sweating was 212.5 milligrams (mg) and 161.3 mg on the right and left sides, respectively. Three weeks after the botulinum toxin type B injections, 3 of 4 patients had axillary anhidrosis. In the other patient axillary sweating had decreased from 585 mg on the right side and 408 mg on the left side to 27 mg and 10 mg on the right and left sides, respectively. The effect duration ranged from 1 to 3 months. No adverse effects were reported.

Support for using Myobloc to treat bladder muscle dysfunction leading to overactive bladder can be found in a study by Dykstra, Enriquez, and Valley. The results of a prospective, open-label, dose-escalation study suggest that botulinum toxin type B (Myobloc(R)) is effective for overactive bladder and the effect duration may be dose related. All patients (n=15) were female, had symptoms of overactive bladder for at least 6 months, and urinary frequency of 8 or more micturitions per 24 hours with or without incontinence. Botulinum toxin type B was injected into the bladder wall at 10 different sites (trigone was avoided) at doses of 2500 Units (n=5), 3750 Units (n=4), 5000 Units (n=2), 10,000 Units (n=2), or 15,000 Units (n=3). Fourteen of 15 patients responded to treatment with decreased frequency, urgency, and no incontinence; the average decrease in the number of frequency episodes per day was 5.27 (p less than 0.001). There was a correlation between the dosage and the response duration (correlation coefficient=0.96, p less than 0.001). The shortest response duration (approximately 3 weeks) occurred at the 2500 Unit dose while the longest response duration (approximately 3 months) occurred in the patients who received 10,000 Unit and 15,000 Unit doses. Five patients experienced mild, transient injection site discomfort and 2 patients in the 15,000 Unit group reported mild general malaise and dry mouth.

Support for using Myobloc to treat bladder spasticity to a spinal cord injury can be found in a publication by Pistolesi et al. In a case report, botulinum toxin type B (NeuroBloc(R)) effectively treated bladder spasticity in a spinal cord injury patient with demonstrated resistance to botulinum toxin type A. The patient received an injection of 5000 International Units of botulinum toxin type B at 20 detrusor muscle sites (the trigone was spared). Four days after injection, the patient was continent and had increased bladder capacity. One month postinjection, the increased bladder capacity persisted and the maximum detrusor pressure had decreased. Dry mouth and dry eyes were the only reported adverse events, which resolved by day 20.

Support for using Myobloc to treat blepharospasm and hemifacial spasm can be found in the American Hospital Formulary System- Drug Information resource. Myobloc has been used in the management of blepharospasm. The available published studies are in patients who have responded previously to onabotulinumtoxinA. The American Academy of Neurology (AAN) states that onabotulinumtoxinA and incobotulinumtoxinA should be considered as treatment options, and abobotulinumtoxinA may be considered for the treatment, of blepharospasm; AAN does not make a recommendation regarding rimabotulinumtoxinB for this use due to lack of data (Simpson, 2016).

Support for using Myobloc to treat palmar hyperhidrosis can be found in a study by Baumann et al. Twenty participants (10 men, 10 women) diagnosed with palmar hyperhidrosis were injected with either Myobloc (5,000 U per palm) or a 1.0 mL vehicle (100 mM NaCl, 10 mM succinate, and 0.5 mg/mL human albumin) into bilateral palms (15 Myobloc, 5 placebo). The participants were followed until sweating returned to baseline levels. The main outcome measures were safety, efficacy versus placebo, and duration of effect. A significant difference was found in treatment response at day 30, as determined by participant assessments, between 15 participants injected with Myobloc and 3 participants injected with placebo. The duration of action, calculated in the 17 participants who received Myobloc injections and completed the study, ranged from 2.3 to 4.9 months, with a mean duration of 3.8 months. The single most reported adverse event was dry mouth or throat, which was reported by 18 of 20 participants. The adverse event profile also

included indigestion or heartburn (60%), excessively dry hands (60%), muscle weakness (60%), and decreased grip strength (50%). Myobloc proved to be efficacious for the treatment of palmar hyperhidrosis. Myobloc had a rapid onset, with most participants responding within 1 week. The duration of action ranged from 2.3 to 4.9 months, with a mean of 3.8 months. The adverse event profile included dry mouth, indigestion or heartburn, excessively dry hands, muscle weakness, and decreased grip strength.

Support for using Myobloc to treat spastic dysphonia can be found in a case report by Sataloff et al. Botulinum toxin type B was an effective treatment for spasmodic dysphonia for a patient who had developed resistance to botulinum toxin type A. The 49-year old patient received an injection of 750 mouse units of botulinum toxin type B in the left thyroarytenoid muscle and 500 mouse units of botulinum toxin type B in the right thyroarytenoid muscle. Improvement was reported 8 days after the injection; the response lasted approximately 14 weeks.

Support for using Myobloc to treat upper limb spasticity can be found in a study by Brashear et al. The authors conducted a double-blind, placebo-controlled, randomized trial. 10,000 units of botulinum toxin type B was administered over a 16-week treatment period was not found to be beneficial in lowering muscle tone in the elbow, wrist, or finger flexors when compared to placebo of post-stroke patients. However, in the open-label portion of the trial, Botulinum toxin type B at four weeks showed statistically significant improvements in muscle tone in the elbow (p=0.039), wrist (p=0.002), finger (p=0.001), and thumb flexors (p=0.002). Fifteen patients (8 male) were enrolled into the double-blinded trial with ten patients randomized to the botulinum toxin type B arm. Following 16 weeks of therapy, thirteen patients continued into the open-label trial. Efficacy was measured with the 5-point Ashworth Scale, which is designed to measure the degree of spasticity in the muscle. While global assessment of change (GAC) did not reach significance in the double-blind trial, GAC did show statistically significant improvement with botulinum toxin type B in the open-label trial as reported on the physician, patient, and occupational therapist GAC scales. No improvements were seen with regards to function and pain (via a Jebsen test, 9-hole peg test, or pain assessment) in either trial. Overall, botulinum toxin type B produced mild side effects; vital signs were not shown to have changed significantly with treatment. The most commonly reported adverse effect was dry mouth, which occurred in 89% of the treatment group versus 20% of the placebo group. The researchers noted that the high prevalence of dry mouth with botulinum toxin type B treatment could have led to possible unblinding. Ten subjects also experienced dry mouth in the open label trial, but all subjects had complete resolution of dryness by week 12 of the trial. One patient with a history of stroke and atrial fibrillation in the double-blind trial died of a large stroke following his week 4 follow-up visit; this serious adverse effect did not appear to be related to botulinum toxin type B. The authors conclude small sample size may have accounted for why the primary endpoint was not found to be statistically significant in the double-blinded trial, and that the disparity in results between the double-blind and open-label study may have resulted from rater bias.

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Reference number(s)
5738-A

Standard Medicare Part B Management Briumvi

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Briumvi	ublituximab-xiiy

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication[1]

Briumvi 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.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Relapsing Forms of Multiple Sclerosis[1]

Authorization of 12 months may be granted to members who have been diagnosed with a relapsing form of multiple sclerosis (including relapsing-remitting and secondary progressive disease for those who continue to experience relapse).

Clinically Isolated Syndrome[1]

Authorization of 12 months may be granted to members for the treatment of clinically isolated syndrome of multiple sclerosis.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Briumvi.
- Briumvi is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Briumvi.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Briumvi are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Reference number(s)
5738-A

Reference

1. Briumvi [package insert]. Morrisville, NC: TG Therapeutics, Inc.; December 2022.

Reference number(s)
4703-A

Standard Medicare Part B Management
Cimzia

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-The-Counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Cimzia	certolizumab pegol

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

- Reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- Treatment of adults with moderately to severely active rheumatoid arthritis.
- Treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.
- Treatment of adult patients with active psoriatic arthritis.
- Treatment of adults with active ankylosing spondylitis.
- Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation.
- Treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Compendial Uses

Immune checkpoint inhibitor-related toxicity – inflammatory arthritis

Reference number(s)
4703-A

Documentation

The following documentation must be available, upon request, for all submissions:

Crohn's disease (CD), rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA), plaque psoriasis (PsO), and immune checkpoint inhibitor-related toxicity

For continuation requests: Chart notes or medical record documentation supporting benefit of therapy.

Coverage Criteria

Crohn's Disease (CD)

Authorization of 12 months may be granted for treatment of moderately to severely active Crohn's disease.

Rheumatoid Arthritis (RA)

Authorization of 12 months may be granted for treatment of moderately to severely active rheumatoid arthritis.

Polyarticular juvenile idiopathic arthritis (pJIA)

Authorization of 12 months may be granted for treatment of active polyarticular juvenile idiopathic arthritis.

Psoriatic Arthritis (PsA)

Authorization of 12 months may be granted for treatment of active psoriatic arthritis.

Ankylosing Spondylitis (AS) and Non-Radiographic Axial Spondyloarthritis (nr-axSpA)

Authorization of 12 months may be granted for treatment of active ankylosing spondylitis and active non-radiographic axial spondyloarthritis.

Plaque Psoriasis (PsO)

Authorization of 12 months may be granted for treatment of moderate to severe plaque psoriasis.

Immune Checkpoint Inhibitor-Related Toxicity

Authorization of 12 months may be granted for treatment of immune checkpoint inhibitor-related toxicity when the member has moderate or severe immunotherapy-related inflammatory arthritis.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

All Indications

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Cimzia.
- Cimzia is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Cimzia.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- 2016 Update of the international ASAS-EULAR management recommendations for axial spondyloarthritis.
- EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update.
- 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis.
- American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis.
- Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 6: Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions.
- European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies; 2019 update.
- Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021.
- 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis.
- 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.

- An evidence-based systematic review on medical therapies for inflammatory bowel disease.
- ACG Clinical Guideline: Management of Crohn's Disease in Adults.
- Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics.
- 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis.
- Joint AAD-NPF guidelines of care for the management and treatment of psoriasis in pediatric patients.
- Joint AAD-NPF guidelines of care for the management of psoriasis with systemic nonbiologic therapies.
- 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative.
- AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease.
- Guidelines of Care for the Management and Treatment of Psoriasis with Topical Therapy and Alternative Medicine Modalities for Psoriasis Severity Measures.
- 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis.
- 2019 American College of Rheumatology/Arthritis Foundation guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis.
- 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Cimzia are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

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Reference number(s)
2065-A

Standard Medicare Part B Management
Cinqair

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Cinqair	reslizumab

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Cinqair is indicated for the add-on maintenance treatment of patients with severe asthma aged 18 years and older with an eosinophilic phenotype.

Limitations of Use:

- Nor for treatment of other eosinophilic conditions
- Not for relief of acute bronchospasm or status asthmaticus

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

For initial requests:

- Chart notes or medical record documentation showing baseline blood eosinophil count, or dependance on inhaled corticosteroids, if applicable.
- Chart notes, medical record documentation, or claims history supporting previous medications tried including drug, dose, frequency and duration.

For continuation requests:

- Chart notes or medical record documentation supporting improvement in asthma control.

Coverage Criteria

Eosinophilic Asthma[1-4]

Authorization of 12 months may be granted for treatment of eosinophilic asthma when all of the following criteria are met:`

- Member is 18 years of age or older.
- Member has a baseline (pre-treatment with a biologic indicated for asthma) blood eosinophil count of at least 400 cells per microliter.
- Member has a history of severe asthma despite current treatment with both of the following medications at optimized doses, unless the member has a clinical reason to avoid these therapies:
    - Inhaled corticosteroid
    - Additional controller (i.e., long-acting beta$_2$-agonist, long-acting muscarinic antagonist, leukotriene modifier, or sustained-release theophylline)
- Member will not use the requested medication concomitantly with other biologics indicated for asthma (e.g., Dupixent, Fasenra, Nucala, Tezspire, or Xolair).

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication.

Authorization for 12 months may be granted when all of the following criteria are met:

- Member is 18 years of age or older.
- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy as defined by a reduction in the frequency and/or severity of symptoms and exacerbations.

- Member will not use the requested medication concomitantly with other biologics indicated for asthma (e.g., Dupixent, Fasenra, Nucala, Tezspire, or Xolair).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Cinqair.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2023 update.
- Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Cinqair are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Cinqair to treat severe asthma can be found in the Global Initiative for Asthma (GINA) guidelines. For adults, add-on interleukin-5 antagonists can be a drug used when either medium dose maintenance inhaled corticosteroids with formoterol or medium to high dose maintenance inhaled corticosteroids with long-acting beta2-agonists are not controlling the patient's asthma.

References

1. Cinqair [package insert]. West Chester, PA: Teva Respiratory, LLC; June 2020.
2. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med. 2015;3(5):355-366.
3. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2023 update. Available at: https://ginasthma.org/wp-content/uploads/2023/07/GINA-Full-Report-23_07_06-WMS.pdf. Accessed March 7, 2024.
4. Cloutier MM, Dixon AE, Krishnan JA, et al. Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program. JAMA. 2020;324(22): 2301-2317.

Reference number(s)
2189-A

Standard Medicare Part B Management
Cinryze

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Cinryze	C1 esterase inhibitor [human]

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

Cinryze is indicated for routine prophylaxis against angioedema attacks in adults, adolescents, and pediatric patients (6 years of age and older) with hereditary angioedema (HAE).

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- For initial authorization:
  - C1 inhibitor functional and antigenic protein levels
  - F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation testing, if applicable
  - Chart notes confirming family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy, if applicable
- For continuation of therapy, chart notes demonstrating a reduction in frequency of attacks

Reference number(s)
2189-A

Coverage Criteria

Hereditary Angioedema (HAE)[1-14]

Authorization of 12 months may be granted for prevention of HAE attacks when either of the following criteria is met at the time of diagnosis:

- Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
  - C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test, or
  - Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test).
- Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
  - Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
  - Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy (i.e., cetirizine at 40 mg per day or the equivalent) for at least one month.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for prevention of HAE attacks when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy. Benefit is defined as:
  - A significant reduction in frequency of attacks (e.g., ≥ 50%) since starting treatment, and
  - A reduction in the use of medications to treat acute attacks since starting treatment.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Cinryze.
- The available compendium
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)

  - Lexi-Drugs
  - Clinical Pharmacology
- 2010 International consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema.
- Hereditary Angioedema International Working Group. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group.
- US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema.
- Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel.
- The international WAO/EAACI guideline for the management of hereditary angioedema – the 2021 revision and update.
- International consensus on hereditary and acquired angioedema.
- Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group.
- Hereditary angioedema: beyond international consensus – The Canadian Society of Allergy and Clinical Immunology.
- International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency.
- Diagnosis and screening of patients with hereditary angioedema in primary care.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Cinryze are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the above diagnostic criteria can be found in the US HAEA Medical Advisory Board Guidelines for the Management of Hereditary Angioedema. When HAE is suspected based on the clinical presentation, the provider should test serum C4, C1INH antigenic level, and C1INH functional level. Low C4 and low C1INH antigenic or functional levels are consistent with a diagnosis of HAE with an abnormal C1INH.

When a diagnosis of HAE with normal C1INH is suspected, additional genetic tests for factor XII, plasminogen, angiopoietin-1, and kininogen mutations should be performed. If the genetic testing is unable to be performed or a known mutation is not found, the US HAEA guidelines indicate a positive family history of recurrent angioedema and a documented lack of efficacy of high-dose antihistamine therapy for at least 1 month or an interval expected to be associated with three or more attacks of angioedema, whichever is longer, can be used as clinical criteria to support the diagnosis. The understanding of the genetic mutations associated with HAE is evolving. Veronez et al have identified additional genetic mutations not mentioned in the US HAEA guidelines. There are five new genes associated with HAE and a normal C1-INH: ANGPT1 (angiopoietin-1), PLG (plasminogen), KNG1 (kininogen), MYOF (myoferlin), and HS3ST6 (heparan sulfate-glucosamine 3-O-sulfotransferase 6).

References

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Reference number(s)
4849-A

Standard Medicare Part B Management Coagadex (coagulation factor X [human])

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Coagadex	coagulation factor X [human]

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

Coagadex is indicated in adults and children with hereditary Factor X deficiency for:

- Routine prophylaxis to reduce the frequency of bleeding episodes
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding in patients with mild, moderate, and severe hereditary Factor X deficiency.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Hereditary Factor X Deficiency[1-4]

Authorization of 12 months may be granted for treatment of hereditary Factor X deficiency when used in either of the following settings:

- Prophylaxis to reduce the frequency of bleeding episodes
- On-demand treatment and control of bleeding episodes

Authorization of 1 month may be granted for perioperative management of bleeding in members with mild, moderate, or severe hereditary Factor X deficiency.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Perioperative Management of Bleeding

All members (including new members) requesting authorization for continuation of therapy must meet all requirements in the coverage criteria section.

All Other Indications

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat an indication in the coverage criteria section
- The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Coagadex.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service-Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- MASAC recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system.
- Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Coagadex are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Coagadex [package insert]. Durham, NC: Bio Products Laboratory USA, Inc.; April 2023.
2. National Hemophilia Foundation. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised April 2024. MASAC Document #284. https://www.bleeding.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed October 15, 2024.
3. Mumford AD, Ackroyd S, Alikhan R, et al. Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology. Br J Haematol. 2014;167(3):304-26.
4. Brown DL, Kouides PA. Diagnosis and treatment of inherited factor X deficiency. Haemophilia. 2008;14(6):1176-82.

Reference number(s)
6023-A

Standard Medicare Part B Management Columvi

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Columvi	glofitamab-gxbm

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Columvi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) or large B-cell lymphoma (LBCL) arising from follicular lymphoma, after two or more lines of systemic therapy.

Compendial Uses

B-Cell Lymphomas

- Diffuse Large B-Cell Lymphoma
- High Grade B-Cell Lymphoma
- Histologic Transformation of Indolent Lymphoma to Diffuse Large B-Cell Lymphoma
- Human Immunodeficiency Virus (HIV)-Related B-Cell Lymphoma
    - HIV- Related Diffuse Large B-cell Lymphoma
    - Primary Effusion Lymphoma
    - Human Herpes Virus Type 8 (HHV8)-Positive Diffuse Large B-cell Lymphoma
- Monomorphic Post-Transplant Lymphoproliferative Disorder

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

B-cell Lymphoma

Authorization of 12 months may be granted for treatment of B-cell lymphoma as a single agent after at least 2 prior lines of systemic therapy when the member has partial response, no response, progressive, relapsed or refractory disease and both of the following criteria are met:

- The member has any of the following subtypes
  - Diffuse Large B-Cell Lymphoma (DLBCL)
  - High Grade B-Cell Lymphoma
  - Histologic Transformation of Indolent Lymphoma to DLBCL
  - HIV-Related B-Cell Lymphoma including HIV-related DLBCL, primary effusion lymphoma, and HHV8-positive DLBCL, not otherwise specified as a single agent
  - Monomorphic Post-Transplant Lymphoproliferative Disorder (B-cell type)
- The member will be pretreated with a single dose of obinutuzumab (Gazyva) 7 days before initiation with the requested medication.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication.

Authorization for 12 months (up to a maximum of 12 cycles) may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat an indication in the coverage criteria section
- The member is receiving benefit from therapy. Benefit is defined as:
  - No evidence of unacceptable toxicity while on the current regimen AND
  - No evidence of disease progression while on the current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Columvi.
- The available compendium
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)

  - Lexi-Drugs
  - Clinical Pharmacology
- NCCN Guideline: B-cell lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Columvi are covered in addition to the following:

- Diffuse Large B-Cell Lymphoma
- High Grade B-Cell Lymphoma
- Histologic Transformation of Indolent Lymphoma to Diffuse Large B-Cell Lymphoma
- Human Immunodeficiency Virus (HIV)-Related B-Cell Lymphoma
  - HIV- Related Diffuse Large B-cell Lymphoma
  - Primary Effusion Lymphoma
  - Human Herpes Virus Type 8 (HHV8)-Positive Diffuse Large B-cell Lymphoma
- Monomorphic Post-Transplant Lymphoproliferative Disorder

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Columvi to treat all indications listed in section IV can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

References

1. Columvi [package insert]. South San Francisco, CA: Genentech, Inc.; June 2023.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed April 1, 2024.

Reference number(s)
4851-A

Standard Medicare Part B Management
Corifact

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Corifact	factor XIII concentrate [human]

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

Corifact is indicated in adult and pediatric patients with congenital Factor XIII deficiency for routine prophylactic treatment and peri-operative management of surgical bleeding.

Compendial Uses[3,4]

Acquired factor XIII deficiency

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Factor XIII Deficiency[1-4]

Authorization of 12 months may be granted for treatment of factor XIII deficiency.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat an indication in the coverage criteria section
- The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds)

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Corifact.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service-Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- MASAC recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system.
- Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Corifact are covered in addition to acquired factor XIII deficiency.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer’s prescribing information.

Support for using Corifact to treat acquired factor XIII deficiency can be found in the Guideline for the Diagnosis and Management of Rare Coagulation Disorders published by the United Kingdom Haemophilia Centre Doctors’ Organization. Acquired factor XIII deficiency has been reported in patients with cardiac surgery, inflammatory bowel disease and Henoch-Schonlein purpura and is rarely associated with de novo FXIII inhibitors. Corifact is listed as an appropriate treatment for acquired factor XIII deficiency, which follows the same recommendations as congenital factor XIII deficiency.

References

1. Corifact [package insert]. Kankakee, IL: CSL Behring LLC; September 2020.
2. National Hemophilia Foundation. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised April 2024. MASAC Document #284. https://www.bleeding.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed October 15, 2024.
3. Mumford AD, Ackroyd S, Alikhan R, et al. Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology. Br J Haematol. 2014;167(3):304-26.
4. AHFS DI (Adult and Pediatric) [database online]. Bethesda, MD. American Society of Health System Pharmacists, Inc. Electronic version. Updated October 2, 2024. Available with subscription. URL: http://online.lexi.com/lco. Accessed October 15, 2024.

Reference number(s)
4548-A

Standard Medicare Part B Management
Cosela

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Cosela	trilaciclib

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications [1]

COSELA is indicated to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

Compendial Uses [2]

Prophylaxis of chemotherapy-induced anemia

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Reference number(s)
4548-A

Coverage Criteria

Extensive-stage Small Cell Lung Cancer

Authorization of 6 months may be granted to decrease the incidence of chemotherapy-induced myelosuppression or anemia and red blood cell transfusions in adult patients with extensive-stage small cell lung cancer when all of the following criteria are met:

- The member will be receiving either of the following chemotherapeutic regimens:
    - A platinum/etoposide-containing regimen.
    - A topotecan-containing regimen.
- The requested medication will be given within 4 hours prior to the start of chemotherapy on each day chemotherapy is administered.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 6 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication enumerated in Section II.
- The member is receiving benefit from therapy.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Cosela
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Hematopoietic growth factors

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Cosela are covered as well as prophylaxis of chemotherapy-induced anemia in patients who will receive a platinum/etoposide-containing regimen or topotecan-containing regimen for ES-SCLC.

Reference number(s)
4548-A

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Cosela to decrease the incidence of anemia from chemotherapy can be found in the National Comprehensive Cancer Network's guideline for hematopoietic growth factors. The NCCN Guideline supports the use of Cosela as a prophylactic option to decrease the incidence of anemia and red blood cell transfusions when administered before platinum/etoposide ± immune checkpoint inhibitor-containing regimens or a topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

References

1. Cosela [package insert]. Durham, NC: G1 Therapeutics, Inc; August 2023.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed January 3, 2024.

Reference number(s)
6360-A

Standard Medicare Part B Management Cosentyx

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Cosentyx	secukinumab

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met, the member has no exclusions to the prescribed therapy, and the drug or biological is usually not self-administered. The criteria outlined in this document is only applicable to drugs not usually self-administered and are furnished incident to a physician's service. Requests for drugs on a region's self-administered drug list are not covered. Members enrolled in Medicare Part D may seek coverage under their Medicare Part D plan.

FDA-approved Indications [1]

- Adults with active psoriatic arthritis (PsA)
- Adults with active ankylosing spondylitis (AS)
- Adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation

The following indications are FDA-approved but the drug approved to treat the indication is usually self-administered and thus not covered by this document.

- Moderate to severe plaque psoriasis (PsO) in patients 6 years of age and older who are candidates for systemic therapy or phototherapy
- Active enthesitis-related arthritis (ERA) in patients 4 years of age and older
- Adults with moderate to severe hidradenitis suppurativa (HS)
- Active psoriatic arthritis in pediatric patients 2 years of age and older

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Reference number(s)
6360-A

Documentation

The following documentation must be available, upon request, for all submissions:

For continuation requests: Chart notes or medical record documentation supporting benefit of therapy.

Coverage Criteria

Psoriatic arthritis (PsA)[1]

Authorization of 12 months may be granted for treatment of active psoriatic arthritis.

Ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA)[1]

Authorization of 12 months may be granted for treatment of active ankylosing spondylitis and active non-radiographic axial spondyloarthritis.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

All indications

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Cosentyx.
- Cosentyx is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy.

Summary of Evidence

The contents of this document were created after examining the following resources:

- The prescribing information for Cosentyx.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)

  - Lexi-Drugs
  - Clinical Pharmacology
- 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.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Cosentyx are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Cosentyx [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; November 2023.

Reference number(s)
4234-A

Standard Medicare Part B Management
Crysvita

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-The-Counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Crysvita	burosumab-twza

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Crysvita is indicated for the treatment of:

- X-linked hypophosphatemia (XLH) in adult and pediatric patients 6 months of age and older.
- Fibroblast growth factor 23 (FGF23)-related hypophosphatemia in tumor-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in adult and pediatric patients 2 years of age and older.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

X-linked hypophosphatemia (XLH)

Initial requests:

- Radiographic evidence of rickets or other bone disease attributed to XLH
- At least one of the following:
    - Genetic testing results confirming the member has a PHEX (phosphate regulating gene with homology to endopeptidases located on the X chromosome) mutation
    - Genetic testing results confirming a PHEX mutation in a directly related family member with appropriate X-linked inheritance
    - Lab test results confirming the member's serum fibroblast growth factor 23 (FGF23) level is above the upper limit of normal or abnormal for the assay

Continuation requests:

- Chart notes or medical record documentation showing beneficial response to therapy

Tumor induced osteomalacia (TIO)

Initial requests:

- Lab test results confirming the member's serum fibroblast growth factor 23 (FGF23) level is above the upper limit of normal or abnormal for the assay
- Fasting serum phosphorus level
- Ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR)

Continuation requests:

- Chart notes or medical record documentation showing beneficial response to therapy

Coverage Criteria

X-linked hypophosphatemia (XLH)[1-4,7]

Authorization of 12 months may be granted for treatment of X-linked hypophosphatemia when both of the following criteria are met:

- Member meets one of the following criteria:
    - Genetic testing was conducted to confirm a PHEX mutation in the member.
    - Genetic testing was conducted to confirm a PHEX mutation in a directly related family member with appropriate X-linked inheritance.
    - Member's FGF23 level is above the upper limit of normal or abnormal for the assay.
- Member has radiographic evidence of rickets or other bone disease attributed to XLH.

Tumor-induced osteomalacia (TIO)[1,5-7]

Authorization of 12 months may be granted for treatment of tumor-induced osteomalacia (TIO) when both of the following criteria are met:

- Member's diagnosis is confirmed by ALL of the following:
  - Member's FGF23 level is above the upper limit of normal or abnormal for the assay.
  - Member's fasting serum phosphorus levels are less than 2.5 mg/dL.
  - Member's ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) is less than 2.5 mg/dL.
- Member's disease is associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication listed in the coverage criteria section.
- The member is receiving benefit from therapy (e.g., increase or normalization in serum phosphate, improvement in bone and joint pain, reduction in fractures, improvement in skeletal deformities).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Crysvita.
- The available compendium
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)
  - Lexi-Drugs
  - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Crysvita are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the diagnostic criteria listed above for X-linked hypophosphatemia (XLH) can be found in the design of the confirmational trials. To be eligible for inclusion, the diagnosis of XLH must have been supported by confirmation of phosphate regulating gene with homology to endopeptidases located on the X chromosome (PHEX) mutation in the patient or a directly related family member with appropriate X-linked inheritance, or a serum FGF23 level of greater than 30 pg/mL.

Support for the diagnostic criteria listed above for FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO) can be found in the design of the confirmational trials. To be eligible for inclusion, the diagnosis of TIO must have been confirmed by a fasting serum phosphorus level less than 2.5 mg/dL, have an FGF23 level greater than or equal to 100 pg/mL, and have a ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) of less than 2.5 mg/dL.

References

1. Crysvita [package insert]. Princeton, NJ: Kyowa Kirin, Inc.; March 2023.
2. Linglart A, Imel EA, Whyte MP, et al. Sustained Efficacy and Safety of Burosumab, a Monoclonal Antibody to FGF23, in Children With X-Linked Hypophosphatemia. J Clin Endocrinol Metab. 2022;107(3):813-824.
3. Insogna KL, Briot K, Imel EA, et al. A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial Evaluating the Efficacy of Burosumab, an Anti-FGF23 Antibody, in Adults With X-Linked Hypophosphatemia: Week 24 Primary Analysis. J Bone Miner Res. 2018;33(8):1383-1393.
4. Dieter, H., Emma, F., Eastwood, D.M., et.al. Clinical Practice Recommendations for the Diagnosis and Management of X-linked Hypophosphataemia. Nature Reviews Nephrology. 2019;15(7):435-455.
5. ClinicalTrials.gov. National Library of Medicine (US). Identifier NCT02304367. Study of Burosumab (KRN23) in Adults with Tumor-Induced Osteomalacia (TIO) or Epidermal Nevus Syndrome (ENS). 2020 June 30. Available from: http://clinicaltrials.gov/ct2/show/NCT02304367.
6. Chong WH, Molinolo AA, Chen CC, et.al Tumor-induced Osteomalacia. Endocrine Related Cancer. 2011;18(3):R53-R77.
7. Fauconnier C, Roy T, Gillerot G, et al. FGF23: Clinical usefulness and analytical evolution. Clin Biochem. 2019;66:1-12.

Reference number(s)
6817-A

Standard Medicare Part B Management Datroway

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Datroway	datopotamab deruxtecan-dlnk

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Datroway is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received endocrine based therapy and chemotherapy for unresectable or metastatic disease.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Test results confirming status of the following receptors:

- Human epidermal growth factor receptor 2 (HER2)
- Estrogen
- Progesterone

Reference number(s)
6817-A

Coverage Criteria

Breast cancer[1]

Authorization of 12 months may be granted for treatment of breast cancer when all of the following criteria are met:

- The disease is unresectable or metastatic
- The cancer cells are hormone receptor positive and HER2-negative.
- The member has received prior treatment including endocrine based therapy and chemotherapy for unresectable or metastatic disease

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication listed in the Coverage Criteria section.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen and
    - No evidence of disease progression while on the current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Datroway
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Datroway are covered.

Reference number(s)
6817-A

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Datroway [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc; January 2025.

Reference number(s)
5671-A

Standard Medicare Part B Management Elahere

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Elahere	mirvetuximab soravtansine-gynx

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Elahere is indicated for the treatment of adult patients with folate receptor-alpha positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens.

Compendial Use

Persistent or recurrent folate receptor-alpha positive, platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Documentation of testing or laboratory results confirming folate receptor-alpha status, where applicable.

Reference number(s)
5671-A

Coverage Criteria

Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Authorization of 12 months may be granted for treatment of folate receptor-alpha positive epithelial ovarian, fallopian tube, or primary peritoneal cancer when either of the following criteria are met:

- Member has platinum-resistant disease and all of the following criteria are met:
  - Member has received at least one prior systemic therapy
  - Requested medication will be used as a single agent or in combination with bevacizumab
- Member has persistent or recurrent platinum-sensitive disease, and the requested medication will be used in combination with bevacizumab

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat an indication listed in the coverage criteria
- The member is receiving benefit from therapy. Benefit is defined as:
  - No evidence of unacceptable toxicity while on the current regimen and
  - No evidence of disase progression while on the current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Elahere.
- The available compendium
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)
  - Lexi-Drugs
  - Clinical Pharmacology
- NCCN Guidelines: Ovarian cancer including fallopian tube cancer and primary peritoneal cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Elahere are covered in addition to using Elahere to treat and persistent or recurrent folate receptor-alpha positive, platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Reference number(s)
5671-A

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Elahere to treat epithelial ovarian, fallopian tube, or primary peritoneal cancer with Elahere in combination with bevacizumab and persistent or recurrent folate receptor-alpha positive, platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

References

1. Elahere [package insert]. Waltham, MA: ImmunoGen, Inc.; March 2024.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed August 21, 2024.

Reference number(s)
5935-A

Standard Medicare Part B Management Elfabrio

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Elfabrio	pegunigalsidase alfa-iwxj

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

Elfabrio is indicated for the treatment of adults with confirmed Fabry disease.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- Initial requests: alpha-galactosidase enzyme assay or genetic testing results supporting diagnosis. In the case of obligate carriers, the documentation must be submitted for the parent.
- Continuation requests: lab results or chart notes documenting a benefit from therapy.

Reference number(s)
5935-A

Coverage Criteria

Fabry Disease[1-3]

Authorization of 12 months may be granted for treatment of Fabry disease when the diagnosis of Fabry disease was confirmed by enzyme assay demonstrating a deficiency of alpha-galactosidase enzyme activity or by genetic testing, or the member is a symptomatic obligate carrier.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication enumerated in Section III.
- The member is receiving benefit from therapy (e.g., reduction in plasma globotriaosylceramide [Gb3] or Gb3 inclusions, improvement and/or stabilization in renal function, pain reduction).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Elfabrio.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document.
- Fabry disease revisited: Management and treatment recommendations for adult patients.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Elfabrio are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

The diagnosis of Fabry disease can be confirmed using several methods. According to Biegstraaten et al, a definite diagnosis of Fabry disease is made when the patient has a GLA mutation, deficiency of alpha-enzyme activity in leukocytes and one of the following: one or more characteristic sign(s) of Fabry disease (Fabry neuropathic pain, cornea verticillata or clustered angiokeratoma), an increase in plasma (lyso)Gb3, or a family member with a definite Fabry disease diagnosis carrying the same GLA mutation.

Additionally, Ortiz et al report a larger group of patients have later-onset phenotypes and varying levels of residual alpha-galactosidase enzyme activity. Severe clinical manifestations have been reported in at least 43% of obligate carrier women. Enzyme replacement therapy should be considered in these cases if there is laboratory, histological, or imaging evidence of injury to the kidney, heart or central nervous system regardless of the alpha-galactosidase enzyme activity.

References

1. Elfabrio [package insert]. Cary, NC: Chiesi USA, Inc.; May 2023.
2. Biegstraaten M, Arngrimsson R, Barbey F, et al. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document. Orphanet J Rare Dis. 2015; 1036.
3. Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: Management and treatment recommendations for adult patients. Mol Genet Metab. 2018;123(4):416-427.

Reference number(s)
6121-A

Standard Medicare Part B Management Elrexfio

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Elrexfio	elranatamab-bcmm

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Elrexfio is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Multiple Myeloma

Authorization of 12 months may be granted for treatment of relapsed or refractory multiple myeloma in members who have received at least 4 prior therapies, including at least one drug from each of the following categories:

- Anti-CD38 monoclonal antibody (e.g., daratumumab, isatuximab)
- Proteasome inhibitor (e.g., bortezomib, ixazomib, carfilzomib)

- Immunomodulatory agent (e.g., lenalidomide, pomalidomide, thalidomide)

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat an indication listed in the coverage criteria
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Elrexfio.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Elrexfio are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Elrexfio [package insert]. New York, NY: Pfizer Inc.; August 2023.

Reference number(s)
4739-A

Standard Medicare Part B Management Empaveli

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Empaveli	pegcetacoplan

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Empaveli is indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- For initial requests: Flow cytometry used to show results of glycosylphosphatidylinositol-anchored proteins (GPI-APs) deficiency.
- For continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

Coverage Criteria

Paroxysmal Nocturnal Hemoglobinuria

Authorization of 6 months may be granted for treatment of paroxysmal nocturnal hemoglobinuria (PNH) when all of the following criteria are met:

- The diagnosis of PNH was confirmed by detecting a deficiency of glycosylphosphatidylinositol-anchored proteins (GPI-APs) (e.g., at least 5% PNH cells, at least 51% of GPI-AP deficient poly-morphonuclear cells).
- Flow cytometry is used to demonstrate GPI-APs deficiency.
- Member has and exhibits clinical manifestations of disease (e.g., LDH > 1.5 ULN, thrombosis, renal dysfunction, pulmonary hypertension, dysphagia).
- The requested medication will not be used in combination with another complement inhibitor (e.g., Fabhalta, Piasky, Soliris, Ultomiris) for the treatment of PNH (for eculizumab and ravulizumab transition to Empaveli is allowed).

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Paroxysmal Nocturnal Hemoglobinuria

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy (e.g., improvement in hemoglobin levels, normalization of lactate dehydrogenase [LDH] levels).
- The requested medication will not be used in combination with another complement inhibitor (e.g., Fabhalta, Piasky, Soliris, Ultomiris) for the treatment of PNH.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Empaveli.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Management of paroxysmal nocturnal hemoglobinuria in the era of complement inhibitory therapy.

- Guidelines for the Diagnosis and Monitoring of Paroxysmal Nocturnal Hemoglobinuria and Related Disorders by Flow Cytometry.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Empaveli are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using percentage of PNH cells or percentage of GPI-AP deficiency poly-morphonuclear cells can be found in the guidelines for diagnosis of PNH (Borowitz et al and Preis et al). Flow cytometry is the gold standard for assessing the percentage of GPI-AP deficient poly-morphonuclear cells. Classic PNH is defined as greater than 50% of GPI-AP deficient PMNs. It is also possible to diagnose PNH by assessing the percentage of PNH cells. Most clinical trials for the complement inhibitors required at least 10% PNH cells, but the trials associated with Ultomiris only required 5% PNH cells. Therefore, the baseline requirement for all complement inhibitor programs will be at least 5%.

Currently there are no treatment guidelines or literature supporting the concomitant use of complement inhibitors (e.g., Fabhalta, Piasky, Soliris, Ultomiris) for the treatment of PNH.

References

1. Empaveli [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc.; February 2024.
2. Parker CJ. Management of paroxysmal nocturnal hemoglobinuria in the era of complement inhibitory therapy. Hematology. 2011; 21-29.
3. Borowitz MJ, Craig F, DiGiuseppe JA, et al. Guidelines for the Diagnosis and Monitoring of Paroxysmal Nocturnal Hemoglobinuria and Related Disorders by Flow Cytometry. Cytometry B Clin Cytom. 2010: 78: 211-230.
4. Preis M, Lowrey CH. Laboratory tests for paroxysmal nocturnal hemoglobinuria (PNH). Am J Hematol. 2014;89(3):339-341.
5. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. Hematology Am Soc Hematol Educ Program. 2016;2016(1):208-216.
6. Dezern AE, Borowitz MJ. ICCS/ESCCA consensus guidelines to detect GPI-deficient cells in paroxysmal nocturnal hemoglobinuria (PNH) and related disorders part 1 - clinical utility. Cytometry B Clin Cytom. 2018 Jan;94(1):16-22.

Reference number(s)
2666-A

Standard Medicare Part B Management
Entyvio IV

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name	Dosage Form
Entyvio	vedolizumab	intravenous (IV)

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met, the member has no exclusions to the prescribed therapy, and the drug or biological is usually not self-administered. The criteria outlined in this policy is only applicable to drugs not usually self-administered and are furnished incident to a physician's service. Requests for drugs on a region's self-administered drug list are not covered. Members enrolled in Medicare Part D may seek coverage under their Medicare Part D plan.

FDA-Approved Indications

- Adult patients with moderately to severely active ulcerative colitis (UC)
- Adult patients with moderately to severely active Crohn's disease (CD)

Compendial Uses

Immune checkpoint inhibitor-related toxicity

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Ulcerative colitis (UC) and Crohn's disease (CD)

For continuation requests: Chart notes or medical record documentation supporting positive clinical response to therapy or remission.

Immune Checkpoint Inhibitor-Related Toxicity

Chart notes, medical record documentation, or claims history supporting previous medications tried (if applicable), including response to therapy. If therapy is not advisable, documentation of clinical reason to avoid therapy.

Coverage Criteria

Ulcerative colitis (UC)

Authorization of 12 months may be granted for treatment of moderately to severely active ulcerative colitis.

Crohn's disease (CD)

Authorization of 12 months may be granted for treatment of moderately to severely active Crohn's disease.

Immune Checkpoint Inhibitor-Related Toxicity

Authorization of 6 months may be granted for treatment of immune checkpoint inhibitor-related toxicity when the the member has had an inadequate response, intolerance, or contraindication to systemic corticosteroids or infliximab.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Immune Checkpoint Inhibitor-Related Toxicity

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

All other indications

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Entyvio.
- Entyvio is being used to treat an indication listed in the coverage criteria section.
- The member is receiving benefit from therapy.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Entyvio.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Management of Immunotherapy-Related Toxicities
- An evidence-based systematic review on medical therapies for inflammatory bowel disease.
- American College of Gastroenterology (ACG) Clinical Guideline: Management of Crohn's Disease in Adults
- American Gastroenterological Association (AGA) Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis
- AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Entyvio are covered in addition to immune checkpoint inhibitor-related toxicity.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the continuation of therapy criteria for Crohn's disease can be found in the American College of Gastroenterology guidelines for the management of Crohn's disease (CD) and a review article by Talley et al.

The American College of Gastroenterology lists mucosal healing as determined by endoscopy as a goal of therapy. Mucosal healing is defined as an absence of ulceration and endoscopic scoring systems have been developed to quantify degree of ulceration and inflammation in patients with CD within the reach of the colonoscope. There are a limited number of studies that have examined the long-term impact of mucosal healing on the clinical course of disease. In patients with early-stage CD, complete mucosal healing after 2 years of therapy predicts sustained steroid-free, clinical remission 3 and 4 years out from initiation of treatment. Other clinical outcomes associated with mucosal healing in CD have been decreased surgery and hospitalizations. The simple endoscopic score for Crohn's disease (SES-CD) scoring system has been used prospectively to assess mucosal healing in patients treated with anti-tumor necrosis factor (anti-TNF) therapy as well as with anti-TNF/thiopurines combination therapy, demonstrating that changes can be measured; furthermore, there is a strong correlation between improvement in the SES-CD (mucosal) healing and clinical remission.

Better clinical outcomes such as decreased hospitalizations, surgery, and steroid use is associated with improved findings on CTE and MRE in patients with small bowel Crohn's disease.

Improvement in the symptoms of CD is also a goal of therapy. The most common symptom of Crohn's disease is chronic diarrhea, but some patients may not experience this symptom. Abdominal pain, often localized to the right lower quadrant of the abdomen and worsened postprandially, is common. Improvement in these symptoms as well as fatigue, weight loss, anemia, and recurrent fistulas is considered sufficient evidence to continue with therapy.

Support for the continuation of therapy for ulcerative colitis can be found in the American Gastroenterological Association guidelines for the management of moderate to severe ulcerative colitis. The Truelove and Witts criteria for classifying the severity of UC include the number of stools per day, the presence of blood in the stool, hemoglobin, colonic features on radiograph and other clinical signs such as abdominal tenderness and distention. Improvement in any of these factors while on Entyvio therapy is sufficient to continue using the requested medication.

Additionally, the American College of Gastroenterology indicates an elevation in C-reactive protein and erythrocyte sedimentation rate are indicators of active UC. The guidelines go on to indicate the goal of treatment is to achieve mucosal healing (defined as resolution of inflammatory changes (Mayo endoscopic subscore 0 or 1) to increase the likelihood of sustained steroid-free remission and prevent hospitalizations and surgery). Fecal calprotectin can be used as a surrogate for endoscopy when endoscopy is not feasible or available to assess for mucosal healing. If the patient's condition appears to be improving based on either of these factors, it is then considered acceptable to continue using the requested medication.

Support for using Entyvio for immune checkpoint inhibitor-related toxicities can be found in the National Comprehensive Cancer Network's guideline for management of immunotherapy-related toxicities. The NCCN Guideline supports the use of Entyvio for the management of mild (G1) diarrhea or colitis if persistent or progressive symptoms and positive lactoferrin/calprotectin. Entyvio can also be used for the management of immunotherapy-related moderate (G2) and strongly consider for severe (G3-4) diarrhea or colitis.

References

1. Entyvio [package insert]. Lexington, MA: Takeda Pharmaceuticals U.S.A., Inc.; September 2023.
2. Talley NJ, Abreu MT, Achkar J, et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. Am J Gastroenterol. 2011;106(Suppl 1):S2-S25.
3. Lichtenstein GR, Loftus Jr EV, Isaacs KI, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2018;113:481-517.
4. Rubin DT, Ananthakrishnan AN, et al. 2019 ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019;114:384-413.
5. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed January 4, 2024.
6. NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®). Management of Immunotherapy-Related Toxicities. Version 1.2022. Available at: www.nccn.org. Accessed January 4, 2024.
7. Schneider BJ, Naidoo J, Santomasso BD, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Guideline Update. J Clin Oncol. 2021; 39(36):4073-4126.
8. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. Gastroenterology. 2020; 158:1450-1461.

9. 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: 2496- 2508.
10. Self-Administered Drug Exclusion List: and Biologicals Excluded from Coverage- Medical Policy Article (A52527) Version RX. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.
11. Self-Administered Drug Exclusion List: (A52571). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.
12. Self-Administered Drug Exclusion List: (A53032). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.
13. Self-Administered Drug Exclusion List: (A53033). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.
14. Self-Administered Drug Exclusion List: Medical Policy Article (A53021). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.
15. Self-Administered Drug Exclusion List: (SAD List) (A52800). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.
16. Self-Administered Drug Exclusion List: (A53127). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.
17. Self-Administered Drug Exclusion List: (A53066). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.
18. Self-Administered Drug Exclusion List: Medical Policy Article (A53022). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.

Reference number(s)
6003-A

Standard Medicare Part B Management Epkinly

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Epkinly	epcoritamab- bysp

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

- Epkinly is indicated for the treatment of adult patients with relapsed or refractory diffuse large b-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B–cell lymphoma (HGBL), after two or more lines of systemic therapy.
- Epkinly is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Compendial Uses[2]

B-Cell Lymphomas:

- Diffuse Large B-Cell Lymphomas
- High Grade B-Cell Lymphomas
- Histologic Transformation of Indolent Lymphomas to Diffuse Large B-Cell Lymphoma
- Human Immunodeficiency Virus (HIV)- Related B-Cell Lymphomas
    - HIV-related diffuse large B-cell lymphoma
    - Primary effusion lymphoma
    - Human Herpes Virus Type 8 (HHV8)-positive diffuse large B-cell lymphoma, not otherwise specified
- Monomorphic Post-Transplant Lymphoproliferative Disorders

- Follicular Lymphoma

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

B-Cell Lymphomas[1-2]

Authorization of 12 months may be granted as a single agent for treatment of B-cell lymphoma after at least 2 prior lines of systemic therapy when the member has partial response, no response, progressive, relapsed or refractory disease with any of the following subtypes:

- Diffuse Large B-Cell Lymphoma (DLBCL)
- High Grade B- Cell Lymphoma
- Histologic Transformation of Indolent Lymphoma to DLBCL
- HIV-Related B- Cell Lymphoma including HIV-related DLBCL, primary effusion lymphoma, and HHV8-positive DLBCL, not otherwise specified
- Monomorphic Post-Transplant Lymphoproliferative Disorder
- Follicular Lymphoma

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat an indication in the coverage criteria section
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Epkinly.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)

  - Lexi-Drugs
  - Clinical Pharmacology
- NCCN Guideline: B-cell lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Epkinly are covered in addition to the following:

- Diffuse Large B-Cell Lymphomas
- High-grade B-Cell Lymphomas
- Histologic Transformation of Indolent Lymphomas to Diffuse Large B-Cell Lymphoma
- Human Immunodeficiency Virus (HIV)- Related B-Cell Lymphomas
  - HIV-related diffuse large B-cell lymphoma
  - Primary effusion lymphoma
  - Human Herpes Virus Type 8 (HHV8)-positive diffuse large B-cell lymphoma, not otherwise specified
- Monomorphic Post-Transplant Lymphoproliferative Disorders
- Follicular Lymphoma

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Epkinly to treat HIV-related B-cell lymphomas, follicular lymphoma and monomorphic post-transplant lymphoproliferative disorders can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Epkinly to treat partial response, no response, or progressive diffuse large B-cell lymphoma, high-grade B-cell lymphoma, and histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma in addition to the FDA-approved indications can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

References

1. Epkinly [package insert]. Plainsboro, NJ: Genmab US, Inc.; June 2024.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed May 9, 2024.

Reference number(s)
4820-A

Standard Medicare Part B Management Epoprostenol Injection Products

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name	Dosage Form
Flolan	epoprostenol	injection
Veletri	epoprostenol	injection
epoprostenol injection (all other brands)	epoprostenol	injection

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Flolan/Veletri/epoprostenol is indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group I) to improve exercise capacity. Studies establishing effectiveness included predominantly patients with New York Heart Association (NYHA) Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

Compendial Uses

- Angina pectoris
- Peripheral vascular disease (e.g., Raynaud's disease, thrombotic angiopathy)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Reference number(s)
4820-A

Coverage Criteria

Pulmonary Hypertension (PH)

Indefinite authorization may be granted for treatment of pulmonary hypertension when ALL of the following criteria are met:

- The pulmonary hypertension is not secondary to pulmonary venous hypertension (e.g., left-sided atrial or ventricular disease, left-sided valvular heart disease, etc.) or disorders of the respiratory system (e.g., chronic obstructive pulmonary disease, interstitial lung disease, obstructive sleep apnea, or other sleep disordered breathing, alveolar hypoventilation disorders, etc.).
- The member has primary pulmonary hypertension or pulmonary hypertension, which is secondary to one of the following conditions: connective tissue disease, thromboembolic disease of the pulmonary arteries, human immunodeficiency virus (HIV) infection, cirrhosis, diet drugs, congenital left to right shunts, etc. If these conditions are present, then all of the following criteria must be met:
    - The pulmonary hypertension has progressed despite maximal medical and/or surgical treatment of the identified condition.
    - The mean pulmonary artery pressure is greater than 25 mmHg at rest or greater than 30 mmHg with exertion.
    - The member has significant symptoms from the pulmonary hypertension (i.e., severe dyspnea on exertion, and either fatigability, angina, or syncope).
    - Treatment with oral calcium channel blocking agents has been tried and failed or has been considered and ruled out.

Angina Pectoris

Authorization of 3 months may be granted for treatment of angina pectoris.

Peripheral Vascular Disease (e.g., Raynaud’s disease, thrombotic angiopathy)

Authorization of 12 months may be granted for treatment of peripheral vascular disease (e.g., Raynaud’s disease, thrombotic angiopathy).

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication through a paid pharmacy or medical benefit.

Pulmonary Hypertension (PH)

Authorization for members who are requesting authorization for continuation of therapy must meet all requirements in the coverage criteria section.

Angina Pectoris

Authorization for 3 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat angina pectoris.
- The member is receiving benefit from therapy. Benefit is defined as either:
    - Disease stability
    - Disease improvement

Peripheral Vascular Disease (e.g., Raynaud's disease, thrombotic angiopathy)

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat peripheral vascular disease (e.g., Raynaud's disease, thrombotic angiopathy).
- The member is receiving benefit from therapy. Benefit is defined as either:
    - Disease stability
    - Disease improvement

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Flolan, Veletri, and generic epoprostenol.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- External Infusion Pumps Local Coverage Determination (L33794)

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Flolan, Veletri, and generic epoprostenol are covered in addition to the following:

- Angina pectoris
- Peripheral vascular disease (e.g., Raynaud's disease, thrombotic angiopathy)

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information and the External Infusion Pump Local Coverage Determination (L33794).

Support for using Flolan, Veletri, and generic epoprostenol to treat angina pectoris can be found in studies cited in Micromedex. Epoprostenol infusions have been relatively ineffective in patients with exertional angina and unstable angina. In Prinzmetal angina, limited studies suggest lack of beneficial effects in most patients.

Support for using epoprostenol for Prinzmetal angina (also known as variant angina) can be found in a small study by Chierchia et al (1982). The study evaluated the effects of intravenous (IV) epoprostenol (PGI2) in nine patients with variant angina and six normal volunteers. In normal subjects, PGI2 (2.5, 5, 10, and 20 nanograms/kg/min) had significant antiplatelet effects, caused a dose-dependent decrease in both systolic and diastolic arterial pressure and a decrease in pulmonary resistance. Heart rate increased in a dose-dependent manner, but no consistent effects on myocardial contractility (evaluated by ultrasound) were observed. Side effects were negligible and readily reversible. Although producing obvious antiplatelet and vasodilatory effects, PGI2 did not affect the number, severity and duration of spontaneous ischemic episodes due to coronary vasospasm in five patients and ergonovine-induced spasm in three. However, the number of ischemic episodes was consistently reduced in one patient during four consecutive periods of PGI2 infusion alternated with placebo. A severe, prolonged ischemic episode with ST elevation and pain was consistently observed in this patient every time PGI2 was discontinued. In the appropriate environment, PGI2 can be administered safely to patients with ischemic heart disease. Occasionally, PGI2 may result in a complete disappearance of ischemic episodes due to coronary vasospasm, but usually it is ineffective. These conflicting results could be related to different etiologies of coronary spasm.

Support for using Flolan, Veletri, and generic epoprostenol to treat peripheral vascular disease can be found in small studies. Belch et al. (1983) conducted a study of two groups of outpatients with Raynaud’s syndrome. The patients were randomly allocated to receive at weekly intervals for three weeks either a 5 h intravenous infusion of buffer or epoprostenol (prostacyclin, PGI2) in buffer (7.5 ng/kg/min after the first hour). PGI2 reduced the frequency and duration of ischemic attacks (both p less than 0.01). Hand temperature measurements with a thermocouple were significantly improved at 1 week; 6 weeks after the last infusion hand temperatures had returned to baseline. There was a corresponding loss of clinical response 8-10 weeks after the last infusion.

Additionally, Bellucci et al. (1986) studied infused prostacyclin (PGI2) given IV (7.5 ng/kg/min) three times at weekly intervals in 8 patients with Raynaud's phenomenon (RP). In 4 patients, improvement was long-term, more than 90 days after the last infusion (good responders); in 3 patients, improvement was mild, less than 15 days, and in one patient no improvement was observed (poor responders). Clinical response was always accompanied by improvement, although less prolonged, of capillary appearance and/or function, as judged by microscopy and/or hemodynamic tests (pulse volume index; radial artery blood flow). Lastly, increased catabolism of PGI2 seemed to be excluded in poor responders, since no statistical difference in PGI2 metabolism could be observed between the two groups..

References

1. Flolan [package insert]. Durham, NC: GlaxoSmithKline; October 2023
2. Veletri [package insert]. Titusville, NJ: Actelion Pharmaceuticals US, Inc.; July 2022.
3. Epoprostenol [package insert]. Titusville, NJ: GlaxoSmithKline; October 2023.
4. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/ (cited: 04/10/2024).
5. Chierchia S, Patrono C, Crea F, et al. Effects of intravenous prostacyclin in variant angina. Circulation. 1982;65(3):470-477.

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8. External Infusion Pumps (L33794) Version R30. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed April 10, 2024.
9. External Infusion Pumps - Policy Article (A52507) Version R33. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed April 10, 2024.

Reference number(s)
2920-A

Standard Medicare Part B Management Evenity

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Evenity	romosozumab-aqqg

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Evenity 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.

Limitations of Use

Limit duration of use to 12 monthly doses. If osteoporosis therapy remains warranted, continued therapy with an anti-resorptive agent should be considered.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in the coverage criteria section should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Postmenopausal osteoporosis treatment

Authorization of a total of 12 months may be granted for treatment of postmenopausal osteoporosis in members who are at high risk for fracture.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for a total of 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Evenity.
- Evenity is being used to treat an indication listed in the coverage criteria section.
- The member is receiving benefit from therapy. Benefit is defined as:
  - Disease stability, or
  - Disease improvement
- The member has not yet received 12 months of therapy with Evenity.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Evenity.
- The available compendium
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)
  - Lexi-Drugs
  - Clinical Pharmacology
- Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis
- Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Guideline Update

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Evenity are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the use of Evenity in postmenopausal women with osteoporosis can be found in the guidelines from the American Association of Clinical Endocrinologists and American College of Endocrinology. Evenity, in addition to abaloparatide, denosumab, teriparatide and zoledronate, should be considered for patients unable to use oral therapy and as initial therapy for patients at very high fracture risk. Treatment with Evenity should be limited to one year and treatment followed with a drug intended for long-term use (bisphosphonate, denosumab).

Support for the use of Evenity in postmenopausal women with osteoporosis can be found in the Endocrine Society guideline "Pharmacological Management of Osteoporosis in Postmenopausal Women". The guideline recommends

Evenity therapy in postmenopausal women with osteoporosis at very high risk of fracture, such as those with severe osteoporosis (i.e., low T-score < −2.5 and fractures) or multiple vertebral fractures. The guideline recommends treatment for up to 1 year for the reduction of vertebral, hip, and nonvertebral fractures. The recommended dosage is 210 mg monthly by subcutaneous injection for 12 months. Women at high risk of cardiovascular disease and stroke should not be considered for Evenity pending further studies on cardiovascular risk associated with this treatment. High risk includes prior myocardial infarction or stroke. In postmenopausal women with osteoporosis who have completed a course of Evenity, the guidelines recommend treatment with antiresorptive osteoporosis therapies to maintain bone mineral density gains and reduce fracture risk.

References

1. Evenity [package insert]. Thousand Oaks, CA: Amgen; April 2024.
2. Shoback D, Rosen CJ, Black DM, Cheung AM, Murad MH, Eastell R. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society guideline update. J Clin Endocrinol Metab. 2020;105(3):587-594.
3. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update. Endocr Pract. 2020;26(suppl 1):1-46.

Reference number(s)
4233-A

Standard Medicare Part B Management Exondys 51

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Exondys 51	eteplirsen

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Exondys 51 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.

This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with Exondys 51. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- Initial requests: laboratory confirmation of Duchenne muscular dystrophy (DMD) diagnosis with a DMD gene mutation that is amenable to exon 51 skipping (refer to examples in Appendix).
- Continuation of therapy requests: documentation (e.g., chart notes) of response to therapy.

Reference number(s)
4233-A

Coverage Criteria

Duchenne Muscular Dystrophy

Authorization of 6 months may be granted for treatment of DMD when all of the following criteria are met:

- Genetic testing was conducted to confirm the diagnosis of DMD and to identify the specific type of DMD gene mutation.
- The DMD gene mutation is amenable to exon 51 skipping (refer to examples in Appendix).
- Treatment with Exondys 51 is initiated before the age of 14.
- Member is able to achieve an average distance of at least 180 meters while walking independently over 6 minutes.
- Member will not exceed a dose of 30 mg/kg once weekly.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Exondys 51.
- Exondys 51 is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy as evidenced by remaining ambulatory (e.g., able to walk with or without assistance, not wheelchair dependent).
- The member will not exceed a dose of 30 mg/kg once weekly.

Appendix

Examples of DMD gene mutations (exon deletions) amenable to exon 51 skipping (not an all-inclusive list):

- Deletion of exon 50
- Deletion of exon 52
- Deletion of exons 45-50
- Deletion of exons 47-50
- Deletion of exons 48-50
- Deletion of exons 49-50

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Exondys 51.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Exondys 51 are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Exondys 51 [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc.; January 2022.
2. Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. Ann Neurol. 2013;74(5):637-47.
3. Cirak S, Arechavala-Gomeza V, Guglieri M, et al. Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. Lancet. 2011;378(9791):595-605.
4. Mendell JR, Goemans N, Lowes LP, et al; Eteplirsen Study Group and Telethon Foundation DMD Italian Network. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. Ann Neurol. 2016;79(2):257-271.
5. Randeree L, Eslick GD. Eteplirsen for paediatric patients with Duchenne muscular dystrophy: A pooled-analysis. J Clin Neurosci. 2018;49:1-6.

Reference number(s)
2507-A

Standard Medicare Part B Management
Eylea-Eylea HD

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Eylea	aflibercept
Eylea HD	aflibercept
Ahzantive	aflibercept-mrbb
Enzeevu	aflibercept-abzv
Opuviz	aflibercept-yszy
Pavblu	aflibercept-ayyh
Yesafili	aflibercept-jbvf

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Eyela

Eylea is indicated for the treatment of:

- Neovascular (wet) age-related macular degeneration
- Macular edema following retinal vein occlusion
- Diabetic macular edema
- Diabetic retinopathy
- Retinopathy of Prematurity

Eyela HD

Eylea HD is indicated for the treatment of:

- Diabetic macular edema
- Diabetic retinopathy
- Neovascular (wet) age-related macular degeneration

Ahzantive, Opuviz, Pavblu, Yesafili

Ahzantive, Opuviz, Pavblu and Yesafili are indicated for the treatment of:

- Diabetic macular edema
- Diabetic retinopathy
- Neovascular (wet) age-related macular degeneration
- Macular edema following retinal vein occlusion

Enzeevu

Enzeevu is indicated for the treatment of:

- Neovascular (wet) age-related macular degeneration

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Diabetic Macular Edema

Authorization of 12 months may be granted for treatment of diabetic macular edema.

Diabetic Retinopathy

Authorization of 12 months may be granted for treatment of diabetic retinopathy.

Neovascular (Wet) Age-Related Macular Degeneration

Authorization of 12 months may be granted for treatment of neovascular (wet) age-related macular degeneration.

Macular Edema Following Retinal Vein Occlusion (Eylea and Biosimilars Only)

Authorization of 12 months may be granted for treatment of macular edema following retinal vein occlusion.

Retinopathy of Prematurity (Eylea and Biosimilars Only)

Authorization of 12 months may be granted for treatment of retinopathy of prematurity.

Reference number(s)
2507-A

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when ALL of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member demonstrated a positive clinical response to therapy (e.g., improvement or maintenance in best corrected visual acuity [BCVA] or vision field, or a reduction in the rate of vision decline or the risk of more severe vision loss).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Eylea, Eylea HD, Ahzantive, Enzeevu, Opuviz, Pavblu and Yesafili.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Diabetic Retinopathy.
- American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Age-Related Macular Degeneration.
- American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Retinal Vein Occlusions.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Eylea, Eylea HD, Ahzantive, Enzeevu, Opuviz, Pavblu and Yesafili.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer’s prescribing information.

References

1. Eylea [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; December 2023.
2. Eylea HD [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; December 2023.
3. American Academy of Ophthalmology Retinal/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.
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5. American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Retinal Vein Occlusions. San Francisco, CA: American Academy of Ophthalmology; 2019. Available at: https://www.aao.org/preferred-practice-pattern/retinal-vein-occlusions-ppp.
6. Opuviz [package insert]. Cambridge, MA: Biogen MA Inc.; May 2024.
7. Yesafili [package insert]. Cambrdige, MA: Biocon Biologics Inc.; May 2024.
8. Ahzantive [package insert]. Martinsried/Planegg, Germany: Formycon AG; June 2024.
9. Enzeevu [package insert]. Princeton, NJ: Sandoz Inc.; August 2024.
10. Pavblu [package insert]. Thousand Oaks, CA: Amgen, Inc.; August 2024.

Reference number(s)
4848-A

Standard Medicare Part B Management Profilnine

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Profilnine	factor IX complex [human]

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Hemophilia B

Compendial Uses[2,3]

- Bleeding due to low levels of liver-dependent coagulation factors
- Factor II deficiency
- Factor X deficiency
- Anticoagulation reversal

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Reference number(s)
4848-A

Coverage Criteria

Hemophilia B[1]

Authorization of 12 months may be granted for treatment of hemophilia B.

Bleeding due to low levels of liver-dependent coagulation factors[2]

Authorization of 12 months may be granted for treatment of bleeding due to low levels of liver-dependent coagulation factors.

Factor II deficiency[3]

Authorization of 12 months may be granted for treatment of factor II deficiency.

Factor X deficiency[2,3]

Authorization of 12 months may be granted for treatment of factor X deficiency.

Anticoagulation reversal[2]

Authorization of 1 month may be granted for anticoagulation reversal.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Anticoagulation Reversal

All members (including new members) requesting authorization for continuation of therapy must meet all requirements in the coverage criteria.

All Other Indications

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication listed in the coverage criteria section.
- The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

Reference number(s)
4848-A

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Profilnine.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Profilnine are covered in addition to the following:

- Bleeding due to low levels of liver-dependent coagulation factors
- Factor II deficiency
- Factor X deficiency
- Anticoagulation reversal

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Profilnine to treat bleeding due to low levels of liver-dependent coagulation factors can be found in a study of 30 patients by Gazzard and colleagues. Factor IX was at least as effective as fresh frozen plasma in the treatment of clotting factor deficiency secondary to severe liver disease. In a comparison of the two agents in 30 patients with chronic liver disease, all patients had prothrombin times that were prolonged 4 seconds or more and were to undergo percutaneous needle liver biopsy. The first 15 patients were given 600 mL fresh frozen plasma over 30 minutes, followed by 300 mL 6 hours later. The second 15 patients were given 20 mL of factor IX complex containing 2000 units of factors II, IX, and X. Vital signs and signs of bleeding were monitored for 24 hours post-biopsy; packed cell volume and coagulation studies were performed. Although there was no evidence of bleeding in any patient, only 3 of 15 patients receiving fresh frozen plasma had a normal prothrombin time after biopsy, and in 7 of the 15 patients receiving factor IX, the prothrombin time was within normal limits 30 minutes after receiving the dose. Serum levels of clotting factors increased to above 10% of normal in all 30 patients, and were still increased 24 hours post-dosing. No thrombotic sequelae were reported.

Support for using Profilnine to treat factor II deficiency can be found in the guideline posted by the National Bleeding Disorders Foundation. Profilnine is a human plasma-derived prothrombin complex concentrate recommended for use in patients with factor II deficiency.

Support for using Profilnine to treat factor X deficiency can be found in a case report by Kouides and Kulzer. An 18-year-old male with severe factor X deficiency (level less than 1%) successfully used home-infusion prophylactic treatment with factor IX (Profilnine(R)) to overcome epistaxis and joint bleeding. Prior to initiation of the prophylactic regimen, the patient was treated on demand from 3 to 14 times a year. Nose bleeds were most common, followed by joint bleeds and hematomas (the result of trauma). His factor IX protocol was 30 units/kg twice a week at least 3 days apart. If breakthrough bleeding occurred, he was to infuse another dose. He was instructed not to infuse more than 2 doses in 24 hours or to receive infusions on more than 3 consecutive days. During the initial 12 months of prophylactic therapy, no breakthrough bleeding occurred. During an additional 11 months of therapy, he reported one bleeding episode that was the result of trauma. His quality of life improved after starting this protocol. He had no absences from school due to bleeding; he was able to participate in recreational basketball and track. No thrombotic events occurred. A trough level measured at 48 hours after factor IX infusion showed a factor X level of 30% (minimum hemostatic level 10% to 20%). Additionally, support can be found in the guideline posted by the National Bleeding Disorders Foundation. Profilnine is a human plasma-derived prothrombin complex concentrate recommended for use in patients with factor X deficiency.

Support for using Profilnine to treat drug toxicity due to anticoagulant can be found in a retrospective chart review by Safaoui et al. A retrospective chart review revealed that Factor IX complex in combination with traditional therapy achieved rapid reversal of warfarin-induced coagulopathy in patients with intracranial hemorrhage (n=28). Adult patients (mean age 78.2 years (yr); range, 55 to 94 yr; 50% male) were divided into 1 of 2 groups based on the time from presentation to administration of Factor IX complex, 60 minutes or less (group 1) or more than 60 minutes (group 2). All patients received Factor IX complex 2000 units. Patients with an INR greater than 3 at 10 minutes after Factor IX complex infusion received a repeat dose. Vitamin K 10 mg IV or subQ was administered to 82% (23 of 28) of patients and 96% (27 of 28) of patients received fresh frozen plasma. The mean INR at presentation for group 1 was 5.8 +/- 8.6, which significantly reduced to 2.2 +/- 0.76 (p=0.005) after treatment. Similarly, the mean INR at presentation for group 2 was 4.7 +/- 3.2, which significantly reduced to 1.8 +/- 0.73 (p=0.001) after treatment. Of 11 patients with an INR obtained within 30 minutes of Factor IX complex infusion, the mean time to INR correction was 13.5 minutes (min). For all patients, the mean time to INR correction was 116 min. At 24 hours, reversal of warfarin-induced coagulopathy remained significant 1.8 +/- 0.87 (p=0.012) and 1.2 +/- 0.28 (p=0.001) in group 1 and 2, respectively. No early thrombotic or allergic events were reported. Fatalities occurred in 10 patients designated as do not resuscitate.

Additionally, a retrospective chart review by Siddiq and colleagues found factor IX complex concentrate in combination with fresh frozen plasma and vitamin K (n=10) may be a more effective alternative than fresh frozen plasma (FFP) and vitamin K alone (n=9) for rapid reversal of warfarin-induced coagulopathy in patients with intracranial hemorrhage. Consecutive patients received either Factor IX complex concentrate 25 units/kg (INR less than 4) or 50 units/kg (INR greater than 4) IV push over 2 to 5 minutes in combination with vitamin K 10 mg IV infusion over 30 minutes and FFP 10 to 15 mL/kg (age 67.2 +/- 18.51 years (yr); 50% male) or FFP and vitamin K alone (76.89 +/- 18.5 yr; 56% male). INR was monitored upon presentation and approximately every 3 hours (hr) thereafter until a target INR of 1.4 or less was met. The mean INR at presentation was 2.44 +/- 1.48 for the Factor IX complex concentrate group and 1.84 +/- 0.31 for the FFP-vitamin K alone group. Both treatments significantly reduced INR to target level. The mean INR was reduced to 1.34 +/- 0.07 (p less than 0.005) in the Factor IX complex concentrate group and 1.34 +/-0.08 (p less than 0.05) in the FFP-vitamin K alone group. However, 80% of patients (8 of 10) met the target INR within 3 to 4 hr of treatment initiation in the Factor IX complex concentrate group compared with 33% (3 of 9) in the FFP-vitamin K alone group (p=0.012). The mean time required to correct INR was significantly less in the Factor IX complex concentrate group 4.25 +/- 2.12 hr compared with the FFP-vitamin K alone group 8.52 +/- 5.6 hr (p less than 0.05). No treatment complications were observed.

References

1. Profilnine [package insert]. Los Angeles, CA: Grifols Biologicals LLC; June 2023.
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3. National Hemophilia Foundation. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised October 2024. MASAC Document #290. https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed December 5, 2024.
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Reference number(s)
4852-A

Standard Medicare Part B Management Factor IX products

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Rebinyn	coagulation factor IX [recombinant], glycoPEGylated
Idelvion	coagulation factor IX [recombinant], albumin fusion protein
Alprolix	coagulation factor IX [recombinant], Fc fusion protein
Benefix	coagulation factor IX [recombinant]
Ixinity	coagulation factor IX [recombinant]
Rixubis	coagulation factor IX [recombinant]
Alphanine SD	coagulation factor IX [human]

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1-7]

Hemophilia B

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Reference number(s)
4852-A

Coverage Criteria

Hemophilia B[1-9]

Authorization of 12 months may be granted for treatment of hemophilia B.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for the factor IX products (Rebinyn, Idelvion, Alprolix, BeneFIX, Ixinity, Rixubis, AlphaNine SD).
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for the factor IX products are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Alprolix [package insert]. Waltham, MA: Bioverativ Therapeutics Inc.; May 2023.
2. BeneFIX [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals LLC.; November 2022.
3. Ixinity [package insert]. Chicago, IL: Medexus Pharma, Inc.; March 2024.
4. Rixubis [package insert]. Lexington, MA: Takeda Pharmaceuticals U.S.A., Inc.; March 2023.
5. AlphaNine SD [package insert]. Los Angeles, CA: Grifols Biologicals LLC; November 2022.
6. Idelvion [package insert]. Kankakee, IL: CSL Behring LLC; June 2023.
7. Rebinyn [package insert]. DK-2880 Bagsvaerd, Denmark: Novo Nordisk A/S; August 2022.
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Reference number(s)
4932-A

Standard Medicare Part B Management Factor VIII Concentrates

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Advate	antihemophilic factor [recombinant]
Adynovate	antihemophilic factor [recombinant], PEGylated
Alphanate	antihemophilic factor/von Willebrand factor complex [human]
Altuviiio	antihemophilic factor [recombinant], Fc-VWF-XTEN fusion protein-ehtl
Afstyla	antihemophilic factor [recombinant], single chain
Eloctate	antihemophilic factor [recombinant], Fc fusion protein
Esperoct	antihemophilic factor [recombinant], Glycopegylated-exei
Hemofil M	antihemophilic factor [human] monoclonal antibody purified
Humate-P	antihemophilic factor/von Willebrand factor complex [human]
Jivi	antihemophilic factor [recombinant], PEGylated-aucl
Koate	antihemophilic factor [human]
Kogenate FS	antihemophilic factor [recombinant]
Kovaltry	antihemophilic factor [recombinant]
Novoeight	antihemophilic factor [recombinant]
Nuwiq	antihemophilic factor [recombinant]
Recombinate	antihemophilic factor [recombinant]
Xyntha	antihemophilic factor [recombinant]

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Table: Factor VIII Concentrates and Covered Uses[1-19,20-24,34,35]

Recombinant Factor VIII Concentrates

Brand	Generic	FDA-Approved Indication(s)	Compendial Indication(s)
Advate	antihemophilic factor [recombinant]	Hemophilia A	Acquired Hemophilia A
Afstyla	antihemophilic factor [recombinant], single chain	Hemophilia A	None
Kogenate FS	antihemophilic factor [recombinant]	Hemophilia A	Acquired Hemophilia A
Kovaltry	antihemophilic factor [recombinant]	Hemophilia A	None
Novoeight	antihemophilic factor [recombinant]	Hemophilia A	Acquired Hemophilia A
Nuwiq	antihemophilic factor [recombinant]	Hemophilia A	None
Recombinate	antihemophilic factor [recombinant]	Hemophilia A	Acquired Hemophilia A
Xyntha	antihemophilic factor [recombinant]	Hemophilia A	Acquired Hemophilia A

Extended Half-life Recombinant Factor VIII Concentrates

Brand	Generic	FDA-Approved Indication(s)	Compendial Indication(s)
Adynovate	antihemophilic factor [recombinant], PEGylated	Hemophilia A	None
Altuviiio	antihemophilic factor [recombinant], Fc-VWF-XTEN fusion protein-ehtl	Hemophilia A	None
Eloctate	antihemophilic factor [recombinant], Fc fusion protein	Hemophilia A	None
Jivi	antihemophilic factor [recombinant], PEGylated-aucl	Hemophilia A	None

Brand	Generic	FDA-Approved Indication(s)	Compendial Indication(s)
Esperoct	antihemophilic factor [recombinant], Glycopegylated-exei	Hemophilia A	None

Human Plasma-Derived Factor VIII Concentrate

Brand	Generic	FDA-Approved Indication(s)	Compendial Indication(s)
Hemofil M	antihemophilic factor [human] monoclonal antibody purified	Hemophilia A	Acquired Hemophilia A

Human Plasma-Derived Factor VIII Concentrates That Contain Von Willebrand Factor

Brand	Generic	FDA-Approved Indication(s)	Compendial Indication(s)
Alphanate	antihemophilic factor/von Willebrand factor complex [human]	Hemophilia A, von Willebrand Disease	Acquired Hemophilia A, Acquired von Willebrand Syndrome
Humate-P	antihemophilic factor/von Willebrand factor complex [human]	Hemophilia A, von Willebrand Disease	Acquired Hemophilia A, Acquired von Willebrand Syndrome
Koate	antihemophilic factor [human]	Hemophilia A	Acquired Hemophilia A, von Willebrand Disease

Coverage Criteria

Hemophilia A[1-19,24,25,32,34,35]

Authorization of 12 months of Advate, Adynovate, Afstyla, Alphanate, Altuviiio, Eloctate, Esperoct, Hemofil M, Humate-P, Koate, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, or Xyntha may be granted for treatment of hemophilia A when either of the following criteria is met:

- Member has mild disease (see Appendix A) and has had an insufficient response to desmopressin or a documented clinical reason for not using desmopressin (see Appendix B).
- Member has moderate or severe disease (see Appendix A).

Authorization of 12 months of Jivi may be granted for treatment of hemophilia A when BOTH of the following criteria are met:

- Member has previously received treatment for hemophilia A with a factor VIII product.
- Member is ≥ 12 years of age.

Von Willebrand Disease (VWD)[20,21,23,24]

Authorization of 12 months of Alphanate, Humate-P, or Koate may be granted for treatment of VWD when any of the following criteria is met:

- Member has type 1, 2A, 2M, or 2N VWD and has had an insufficient response to desmopressin or a documented clinical reason for not using desmopressin (see Appendix B).
- Member has type 2B or type 3 VWD.

Acquired Hemophilia A[20,27-29]

Authorization of 12 months of Advate, Alphanate, Hemofil M, Humate-P, Koate, Kogenate FS, Novoeight, Recombinate, or Xyntha may be granted for treatment of acquired hemophilia A.

Acquired von Willebrand Syndrome[21-23]

Authorization of 12 months of Alphanate or Humate-P may be granted for treatment of acquired von Willebrand syndrome.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication listed in the coverage criteria section.
- The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

Appendix

Appendix A: Classification of Hemophilia by Clotting Factor Level (% Activity) and Bleeding Episodes[24,30]

Factor assay levels are required to determine the diagnosis and are of value in monitoring treatment response.

Severity	**Clotting Factor Level % activity**	**Bleeding Episodes**
Severe	<1%	Spontaneous bleeding episodes, predominantly into joints and muscles Severe bleeding with trauma, injury or surgery
Moderate	1% to 5%	Occasional spontaneous bleeding episodes Severe bleeding with trauma, injury or surgery

Severity	Clotting Factor Level % activity	Bleeding Episodes
Mild	6% to 40%	Severe bleeding with serious injury, trauma or surgery

Appendix B: Clinical Reasons For Not Utilizing Desmopressin in Patients with Hemophilia A and Type 1, 2A, 2M and 2N VWD[20,25,31,32]

- Age < 2 years
- Pregnancy
- Fluid/electrolyte imbalance
- High risk for cardiovascular or cerebrovascular disease (especially the elderly)
- Predisposition to thrombus formation
- Trauma requiring surgery
- Life-threatening bleed
- Contraindication or intolerance to desmopressin
- Severe type 1 von Willebrand disease
- Stimate Nasal Spray is unavailable due to backorder/shortage issues (where applicable)

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for the factor VIII agents listed in products referenced by this document section.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- The diagnosis, evaluation, and management of von Willebrand disease. Bethesda, MD: US Dept of Health and Human Services, National Institutes of Health; 2007.
- Current diagnostic and therapeutic approaches to patients with acquired von Willebrand syndrome: a 2013 update.
- WFH Guidelines for the Management of Hemophilia, 3rd edition.
- MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System.
- MASAC recommendations regarding the treatment of von Willebrand disease.
- Acquired hemophilia. World Federation of Hemophilia.
- International recommendations on the diagnosis and treatment of acquired hemophilia A.
- Acquired haemophilia A: a 2013 update.
- National Hemophilia Foundation. Hemophilia A (Factor VIII Deficiency).
- Desmopressin (DDAVP) in the management of patients with congenital bleeding disorders.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for the factor VIII agents listed in section I are covered in addition to the following:

- Acquired hemophilia A for Advate, Alphanate, Hemofil M, Humate-P, Koate, Kogenate FS, Novoeight, Recombinate, Xyntha
- Acquired von Willebrand syndrome for Alphanate and Humate-P
- Von Willebrand disease for Koate

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Advate, Adynovate, Afstyla, Alphanate, Altuviiio, Eloctate, Esperoct, Hemofil M, Humate-P, Koate, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate and Xyntha to treat mild hemophilia A can be found in the WFH Guidelines for the Management of Hemophilia. Mild disease is defined as having a clotting factor level of 6 to 40% of normal. The patient generally experiences severe bleeding with major trauma or surgery. It is rare these patients will bleed spontaneously. Desmopressin may be the treatment of choice for patients with mild hemophilia A when factor VIII can be raised to an appropriate therapeutic level because it avoids the expense and potential hazards of using clotting factor concentrates. Desmopressin is not appropriate in all situations. Patients under 2 years of age, pregnant patients, patients with electrolytes or fluid imbalance, patients at high risk for cerebrovascular disease, predisposition to thrombus formation, patients who experienced trauma severe enough to require surgery, and patients experiencing a life-threatening bleed are not ideal candidates for desmopressin therapy.

Support for using Advate, Adynovate, Afstyla, Alphanate, Altuviiio, Eloctate, Esperoct, Hemofil M, Humate-P, Koate, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate and Xyntha to treat moderate to severe hemophilia A can be found in the WFH Guidelines for the Management of Hemophilia. Patients with moderate to severe hemophilia A should be started on prophylaxis with factor VIII or a non-factor therapy like Hemlibra to prevent a recurring life-threatening bleed. Desmopressin is not appropriate in these patients.

Support for using Alphanate, Humate-P, and Koate to treat von Willebrand syndrome can be found in the National Institutes of Health publication called the "Diagnosis, Evaluation, and Management of von Willebrand Disease". Humate-P and Alphanate are approved by the FDA to treat von Willebrand syndrome. Koate has been used off-label for this use as well. Regarding the use of desmopressin, Type 2B and type 3 VWD does not respond consistently to desmopressin therapy and therefore desmopressin is not considered clinically useful in these patients.

Support for using Advate, Kogenate FS, Novoeight, Recombinate, and Xyntha to treat acquired hemophilia A can be found in the AHFS-DI database maintained by the American Society of Health System Pharmacists. Antihemophilic factor (recombinant) has been used in the management of bleeding episodes in some patients with acquired hemophilia A who have low levels of inhibitors. Although antihemophilic factor therapy may be effective in some patients with low levels of acquired antihemophilic factor inhibitors when given in high doses current evidence indicates that bypassing agents are substantially more effective in achieving hemostatic control and are considered the treatment of choice in patients with this condition.

Support for using Advate, Alphanate, Hemofil M, Humate-P, Koate, Kogenate FS, Novoeight, Recombinate, and Xyntha to treat acquired hemophilia A can be found in the international recommendations on the diagnosis and treatment of acquired hemophilia A (Tiede et al, 2020). Human (plasma-derived or recombinant) factor VIII is recommended if

recombinant factor VIIa, activated prothrombin complex concentrate and recombinant porcine factor VIII is unavailable, and the inhibitor titer is low.

Support for using Alphanate and Humate-P to treat acquired von Willebrand syndrome can be found in the National Institutes of Health publication called the “Diagnosis, Evaluation, and Management of von Willebrand Disease”. The guideline indicates DDAVP and VWF/FVIII concentrates are first line therapy. If a patient has an inadequate response to DDAVP and VWF/FVIII concentrates, intravenous immunoglobulin given alone was effective in controlling bleeding and raising VWF:RCo activity.

References

1. Advate [package insert]. Lexington, MA: Takeda Pharmaceuticals U.S.A., Inc.; March 2023.
2. Jivi [package insert]. Whippany, NJ: Bayer HealthCare LLC; August 2018.
3. Kogenate FS [package insert]. Whippany, NJ: Bayer HealthCare LLC; May 2016.
4. Kogenate FS with BIO-SET [package insert]. Whippany, NJ: Bayer HealthCare LLC; May 2016.
5. Kogenate FS with Vial Adapter [package insert]. Whippany, NJ: Bayer HealthCare LLC; December 2019.
6. Kovaltry [package insert]. Whippany, NJ: Bayer Healthcare LLC; December 2022.
7. Novoeight [package insert]. Plainsboro, NJ: Novo Nordisk Inc., July 2020.
8. Nuwiq [package insert]. Paramus, NJ: Octapharma USA, Inc., June 2021.
9. Recombinate with 5 mL Sterile Water for Injection using BAXAJECT II [package insert]. Lexington, MA: Takeda Pharmaceuticals U.S.A., Inc.; March 2023.
10. Xyntha [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals LLC.; July 2022.
11. Xyntha Solufuse [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals LLC.; July 2022.
12. Adynovate [package insert]. Lexington, MA: Takeda Pharmaceuticals U.S.A., Inc.; August 2023.
13. Afstyla [package insert]. Kankakee, IL: CSL Behring LLC.; June 2023.
14. Eloctate [package insert]. Waltham, MA: Bioverativ Therapeutics Inc.; May 2023.
15. Hemofil M [package insert]. Lexington, MA: Takeda Pharmaceuticals U.S.A., Inc.; March 2023.
16. Alphanate [package insert]. Los Angeles, CA: Grifols Biologicals LLC.; November 2022.
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https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed December 9, 2024.
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29. Franchini M, Mannucci PM. Acquired haemophilia A: a 2013 update. Thromb Haemost. 2013;110(6):1114-20.
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35. Altuviiio [package insert]. Waltham, MA: Bioverativ Therapeutics Inc.; September 2024.

Reference number(s)
2419-A

Standard Medicare Part B Management Fasenra

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Fasenra	benralizumab

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Maintenance Treatment of Severe, Eosinophilic Asthma

Fasenra is indicated for the add-on maintenance treatment of adult and pediatric patients aged 6 years and older with severe asthma, and with an eosinophilic phenotype.

Limitations of Use:

- Not for relief of acute bronchospasm or status asthmaticus

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Fasenra is indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Asthma

- For initial requests:
  - Chart notes or medical record documentation showing baseline blood eosinophil count, or dependance on inhaled corticosteroids, if applicable.
  - Chart notes, medical record documentation, or claims history supporting previous medications tried including drug, dose, frequency and duration.
- For continuation requests: Chart notes or medical record documentation supporting improvement in asthma control.

EGPA

- For initial requests:
  - Chart notes or medical record documentation showing pretreatment blood eosinophil count.
  - Chart notes, medical record documentation, or claims history supporting previous medications tried including drug, dose, frequency, and duration. If therapy is not advisable, documentation of clinical reason to avoid therapy.
- For continuation requests: Chart notes or medical record documentation supporting positive clinical response.

Coverage Criteria

Eosinophilic Asthma

Authorization of 12 months may be granted for treatment of eosinophilic asthma when all of the following criteria are met:

- Member is 6 years of age or older.
- Member has a baseline (pre-treatment with a biologic indicated for asthma) blood eosinophil count of at least 150 cells per microliter.
- Member has a history of severe asthma despite current treatment with both of the following medications at optimized doses, unless the member has a clinical reason to avoid these therapies:
  - Inhaled corticosteroid
  - Additional controller (i.e., long-acting beta2-agonist, long-acting muscarinic antagonist, leukotriene modifier, or sustained-release theophylline).
- Member will not use the requested medication concomitantly with other biologics indicated for asthma (e.g., Cinqair, Dupixent, Nucala, Tezspire, Xolair).

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Authorization of 12 months may be granted for treatment of EGPA when all of the following criteria are met:

- Member is 18 years of age or older.

- Member has a history or the presence of an eosinophil count of more than 1000 cells per microliter or a blood eosinophil level of greater than 10%.
- Member is currently taking oral corticosteroids, unless contraindicated or not tolerated.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication.

Eosinophilic Asthma

Authorization for 12 months may be granted for continuation of treatment of eosinophilic asthma when all of the following criteria are met:

- Member is 6 years of age or older.
- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication listed in the coverage criteria section.
- The member is receiving benefit from therapy as defined by reduction in the frequency and/or severity of symptoms and exacerbations.
- Member will not use the requested medication concomitantly with other biologics indicated for asthma (e.g., Cinqair, Dupixent, Nucala, Tezspire, Xolair).

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Authorization of 12 months may be granted for continuation of treatment of EGPA when all of the following criteria are met:

- Member is 18 years of age or older.
- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication listed in coverage criteria section.
- The member is receiving benefit from therapy as defined by reduction in the frequency and/or severity of symptoms and exacerbations.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Fasenra.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

- Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2023 update.
- Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Fasenra are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Fasenra to treat severe asthma can be found in the Global Initiative for Asthma (GINA) guidelines. For adults and adolescents 12 years of age and older, anti-IL5 receptor antagonist can be a drug used when either medium dose maintenance inhaled corticosteroids with formoterol or medium to high dose maintenance inhaled corticosteroids with long-acting beta2-agonists are not controlling the patient's asthma.

References

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Reference number(s)
4800-A

Specialty Guideline Management
FEIBA

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
FEIBA	anti-inhibitor coagulant complex [human]

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indication[1]

Hemophilia A and hemophilia B with inhibitors.

Compendial Use[2-5]

Acquired hemophilia A

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Hemophilia A with Inhibitors[1,3,6-8]

Authorization of 12 months may be granted for treatment of hemophilia A with inhibitors (see Appendix) when the inhibitor titer is ≥ 5 Bethesda units per milliliter (BU/mL) or if the member has a history of an inhibitor titer ≥ 5 BU.

Hemophilia B with Inhibitors[1,3,6-8]

Authorization of 12 months may be granted for treatment of hemophilia B with inhibitors (see Appendix) when the inhibitor titer is ≥ 5 Bethesda units per milliliter (BU/mL) or if the member has a history of an inhibitor titer ≥ 5 BU.

Acquired Hemophilia A[2-5]

Authorization of 12 months may be granted for treatment of acquired hemophilia A.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

Appendix

Appendix: Inhibitors - Bethesda Units (BU)[7,9]

The presence of inhibitors is confirmed by a specific blood test called the Bethesda inhibitor assay.

- High-titer inhibitors:
  - ≥ 5 BU/mL
  - Inhibitors act strongly and quickly neutralize factor
- Low-titer inhibitors:
  - < 5 BU/mL
  - Inhibitors act weakly and slowly neutralize factor

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for FEIBA.
- The available compendium
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)
  - Lexi-Drugs

    - Clinical Pharmacology
- International recommendations on the diagnosis and treatment of acquired hemophilia A.
- Acquired haemophilia A: a 2013 update.
- MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System.
- World Federation of Hemophilia (WFH) Guidelines for the Management of Hemophilia, 3rd edition.
- MASAC Recommendations Regarding Prophylaxis with Bypassing Agents in Patients with Hemophilia and High Titer Inhibitors.
- National Coverage Determination: Anti-Inhibitor Coagulant Complex (AICC).

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for FEIBA are covered in addition to acquired hemophilia A.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using FEIBA to treat acquired hemophilia A can be found in several guidelines.

The World Federation of Hemophilia supports using activated prothrombin complex concentrate (such as FEIBA) to treat bleeding episodes.

The International Recommendations on the Diagnosis and Treatment of Acquired Hemophilia A recommends recombinant activated factor VII (NovoSeven) and activated prothrombin concentrate complex. The guideline does not recommend one drug over another for the treatment for acute bleeds.

Treatment of hemophilia in patients with factor VIII inhibitor antibodies is covered according to the conditions outlined in National Coverage Determination Manual section Anti-Inhibitor Coagulant Complex (110.3).

References

1. FEIBA [package insert]. Lexington, MA: Takeda Pharmaceuticals U.S.A., Inc.; March 2024.
2. AHFS DI (Adult and Pediatric) [database online]. Hudson, OH: Lexi-Comp, Inc.; https://online.lexi.com/lco/action/doc/retrieve/docid/essential_ashp/988283 [available with subscription]. Accessed December 2, 2024.
3. Acquired hemophilia. World Federation of Hemophilia. http://www1.wfh.org/publications/files/pdf-1186.pdf. Accessed December 2, 2024.
4. Tiede A, Collins P, Knoebl P, et al. International recommendations on the diagnosis and treatment of acquired hemophilia A. Haematologica. 2020;105(7):1791-1801. doi:10.3324/haematol.2019.230771.
5. Franchini M, Mannucci PM. Acquired haemophilia A: a 2013 update. Thromb Haemost. 2013;110(6):1114-20.
6. National Hemophilia Foundation. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised October 2024. MASAC Document #290. https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed December 2, 2024.

7. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020;26 Suppl 6:1-158. doi:10.1111/hae.14046.
8. National Hemophilia Foundation. MASAC Recommendations Regarding Prophylaxis with Bypassing Agents in Patients with Hemophilia and High Titer Inhibitors. MASAC Document #220. https://www.hemophilia.org/sites/default/files/document/files/masac220.pdf. Accessed December 2, 2024.
9. Kruse-Jarres, R, Kempton CL, Baudo, F, et al. Acquired hemophilia A: Updated review of evidence and treatment guidance. Am J Hematol. 2017;92:695-705.
10. National Coverage Determination (NCD) for Anti-Inhibitor Coagulant Complex (AICC) (110.3 – Version 1). https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=150&ncdver=1&bc=0 Accessed December 2, 2024.

Reference number(s)
4235-A

Standard Medicare Part B Management Givlaari

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Givlaari	givosiran

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Givlaari is indicated for the treatment of adults with acute hepatic porphyria (AHP).

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

For initial requests: Elevated porphobilinogen (PBG) in the urine confirmed by a PBG quantitative random urine test, or an elevated porphyrin level (plasma or fecal).

Reference number(s)
4235-A

Coverage Criteria

Acute Hepatic Porphyria

Authorization of 12 months may be granted for treatment of acute hepatic porphyria when all of the following criteria are met:

- The member is actively symptomatic (e.g., porphyria attacks requiring hospitalization, urgent healthcare visits, or intravenous hemin administration), or the member has experienced 4 or more porphyria attacks per year.
- The member has an elevated urine porphobilinogen (PBG), or an elevated porphyrin level (plasma or fecal).

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication enumerated in coverage criteria section.
- The member is receiving benefit from therapy (e.g., reduction in porphyria attacks that required hospitalizations, urgent healthcare visit, or intravenous hemin administration).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Givlaari.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Givlaari are covered.

Reference number(s)
4235-A

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information and the ENVISION trial cited in the prescribing information.

References

1. Givlaari [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; April 2024.

Reference number(s)
4798-A

Specialty Guideline Management
Hemlibra

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Hemlibra	emicizumab-kxwh

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

Hemlibra is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

For continuation requests: Chart notes documenting benefit from therapy (e.g., reduced frequency or severity of bleeds).

Reference number(s)
4798-A

Coverage Criteria

Hemophilia A (congenital factor VIII deficiency)[1-3]

Authorization of 12 months may be granted for treatment of hemophilia A (congenital factor VIII deficiency) when all of the following criteria is met:

- Member must be using the requested medication for routine prophylaxis to prevent or reduce the frequency of bleeding episodes.
- Member meets one of the following criteria:
  - Member has mild disease (See Appendix A) and has had an insufficient response to desmopressin or a documented clinical reason for not using desmopressin (See Appendix B).
  - Member has moderate or severe disease (See Appendix A).
- Member will not use the requested medication in combination with Alhemo or Hympavzi.
- Member has not previously received treatment with a gene therapy product (e.g., Roctavian) for the treatment of hemophilia A.
- Prophylactic use of factor VIII products (e.g., Advate, Adynovate, Eloctate) will be discontinued after the first week of starting therapy with the requested medication.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).
- The member is not using the requested medication in combination with factor VIII products (e.g., Advate, Adynovate, Eloctate, etc.) for prophylactic use.

Dosage and Administration

For initial and continuation requests, dosing does not exceed the following:

- Induction: 3 mg/kg subcutaneously once weekly for the first 4 weeks.
- Maintenance: 1.5 mg/kg once weekly, or 3 mg/kg once every 2 weeks, or 6 mg/kg once every 4 weeks.

Appendix

Appendix A: Classification of Hemophilia by Clotting Factor Level (% Activity) and Bleeding Episodes[2,4]

Factor assay levels are required to determine the diagnosis and are of value in monitoring treatment response.

Severity	Clotting Factor Level % activity	Bleeding Episodes
Severe	<1%	Spontaneous bleeding episodes, predominantly into joints and muscles Severe bleeding with trauma, injury or surgery
Moderate	1% to 5%	Occasional spontaneous bleeding episodes Severe bleeding with trauma, injury or surgery
Mild	6% to 40%	Severe bleeding with serious injury, trauma or surgery

Appendix B: Clinical Reasons For Not Utilizing Desmopressin in Patients with Hemophilia A[3,5,6]

- Age < 2 years
- Pregnancy
- Fluid/electrolyte imbalance
- High risk for cardiovascular or cerebrovascular disease (especially the elderly)
- Predisposition to thrombus formation
- Trauma requiring surgery
- Life-threatening bleed
- Contraindication or intolerance to desmopressin
- Stimate Nasal Spray is unavailable due to backorder/shortage issues (where applicable)

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Hemlibra.
- The available compendium
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)
  - Lexi-Drugs
  - Clinical Pharmacology

- World Federation of Hemophilia (WFH) Guidelines for the Management of Hemophilia, 3rd edition
- National Hemophilia Foundation (NHF) Medical and Scientific Advisor Council (MASAC) Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Hemlibra are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Hemlibra to treat mild hemophilia A can be found in the WFH Guidelines for the Management of Hemophilia. Mild disease is defined as having a clotting factor level of 6 to 40% of normal. The patient generally experiences severe bleeding with major trauma or surgery. It is rare these patients will bleed spontaneously. Desmopressin may be the treatment of choice for patients with mild hemophilia A when factor VIII can be raised to an appropriate therapeutic level because it avoids the expense and potential hazards of using clotting factor concentrates. Desmopressin is not appropriate in all situations. Patients under 2 years of age, pregnant patients, patients with electrolytes or fluid imbalance, patients at high risk for cerebrovascular disease, predisposition to thrombus formation, patients who experienced trauma severe enough to require surgery, and patients experiencing a life-threatening bleed are not ideal candidates for desmopressin therapy.

Support for using Hemlibra to treat moderate to severe hemophilia A can be found in the WFH Guidelines for the Management of Hemophilia. Patients with moderate to severe hemophilia A should be started on prophylaxis with factor VIII or a non-factor therapy like Hemlibra to prevent a recurring life-threatening bleed. Desmopressin is not appropriate in these patients.

Currently there are no treatment guidelines or literature supporting the concomitant use of Hemlibra with Hympavzi or Alhemo or use after having received prior gene therapy for hemophilia A.

References

1. Hemlibra [package insert]. South San Francisco, CA: Genentech, Inc.; January 2024.
2. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020;26 Suppl 6:1-158. doi:10.1111/hae.14046.
3. National Hemophilia Foundation. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised October 2024. MASAC Document #290. https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed December 9, 2024.
4. National Hemophilia Foundation. Hemophilia A (Factor VIII Deficiency). Available at: http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx?menuid=180&contentid=45&rptname=bleeding. Accessed December 9, 2024.
5. AHFS DI (Adult and Pediatric) [database online]. Hudson, OH: Lexi-Comp, Inc.; http://online.lexi.com/lco/action/index/dataset/complete_ashp [available with subscription]. Accessed December 9, 2024.

6. Leissinger C, Carcao M, Gill JC, et al. Desmopressin (DDAVP) in the management of patients with congenital bleeding disorders. Haemophilia. 2014;20:158-167.

Reference number(s)
2474-A

Standard Medicare Part B Management Herceptin and Trastuzumab Biosimilars

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Herceptin	trastuzumab
Kanjinti	trastuzumab-anns
Ogivri	trastuzumab-dkst
Trazimera	trastuzumab-qyyp
Herzuma	trastuzumab-pkrb
Ontruzant	trastuzumab-dttb
Hercessi	Trastuzumab-strf

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Adjuvant breast cancer

Adjuvant treatment of human epidermal growth factor receptor 2 (HER2)-overexpressing node positive or node negative (estrogen receptor (ER)/progesterone receptor (PR) negative or with one high risk feature) breast cancer

- As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- As part of a treatment regimen with docetaxel and carboplatin
- As a single agent following multi-modality anthracycline based therapy

Metastatic breast cancer

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease

Metastatic gastric cancer

In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease

Compendial Uses

- HER2-positive breast cancer:
  - Neoadjuvant therapy
  - Treatment of recurrent, advanced unresectable, or stage IV (M1) disease
  - Treatment for no response to preoperative systemic therapy
- HER2-negative breast cancer treatment of stage IV (M1) disease
- Intra-cerebrospinal fluid (CSF) treatment of leptomeningeal metastases (malignant meningitis) from HER2-positive breast cancer
- HER2-positive esophageal and esophagogastric junction cancer
- HER2- positive uterine serous carcinoma and carcinosarcoma
- HER2-positive salivary gland tumors
- HER2-amplified and RAS and BRAF wild-type colorectal cancer
- HER2-positive biliary tract cancers
- HER2-positive non-small cell lung cancer
- Prostate cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- Human epidermal growth factor receptor 2 (HER2) status, where applicable
- RAS mutation status, where applicable
- BRAF mutation status, where applicable

Reference number(s)
2474-A

Coverage Criteria

Breast cancer

- Authorization of 12 months may be granted for neoadjuvant treatment of HER2-positive breast cancer as part of a complete treatment regimen.
- Authorization of 12 months may be granted for adjuvant treatment of HER2-positive breast cancer.
- Authorization of 12 months may be granted for treatment of HER2-positive breast cancer with no response to preoperative systemic therapy, recurrent, advanced, unresectable, or metastatic (including brain metastases) disease.
- Authorization of 12 months may be granted for intra-CSF treatment of leptomeningeal metastases (malignant meningitis) from HER2-positive breast cancer.
- Authorization of 12 months may be granted for treatment of stage IV HER2-negative breast cancer when used in combination with neratinib and fulvestrant.

Esophageal, gastric, or esophagogastric junction cancer

Authorization of 12 months may be granted for treatment or palliative therapy of HER2-positive esophageal, gastric, or esophagogastric junction cancer in combination with chemotherapy cancer.

Uterine serous carcinoma or carcinosarcoma

Authorization of 12 months may be granted for treatment of HER2-positive stage III-IV, metastatic or recurrent uterine serous carcinoma or carcinosarcoma in combination with carboplatin and paclitaxel and continued as a single agent for maintenance therapy.

Salivary gland tumors

Authorization of 12 months may be granted for treatment of recurrent, unresectable, or metastatic HER2-positive salivary gland tumors when used as a single agent or in combination with docetaxel or pertuzumab.

Colorectal cancer

Authorization of 12 months may be granted for treatment of unresectable, inoperable, advanced, or metastatic colorectal cancer, including appendiceal adenocarcinoma and anal adenocarcinoma, when all of the following criteria are met:

- Member has HER2-positive/amplified disease
- The disease is negative (wild-type) for RAS (KRAS and NRAS) and BRAF mutations
- The requested medication will be used in combination with tucatinib, pertuzumab, or lapatinib
- Member has received prior therapy for the disease or is not appropriate for intensive therapy

Biliary tract cancers

Authorization of 12 months may be granted for subsequent treatment of unresectable, resected gross residual, or metastatic HER2-positive biliary tract cancers (including intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer) when used in combination with pertuzumab or tucatinib.

Non-small cell lung cancer

Authorization of 12 months may be granted for treatment of HER2-positive non-small cell lung cancer.

Prostate cancer

Authorization of 12 months may be granted for treatment of prostate cancer.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for all members (including new members) when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat a diagnosis or condition enumerated in the coverage criteria.
- For members requesting reauthorization for adjuvant or neoadjuvant treatment of breast cancer, the maximum treatment duration is 12 months.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Herceptin, Kanjinti, Ogivri, Trazimera, Herzuma, and Ontruzant.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Breast cancer

- NCCN Guideline: Gastric cancer
- NCCN Guideline: Esophageal and esophagogastric junction cancers
- NCCN Guideline: Central nervous system cancers
- NCCN Guideline: Biliary tract cancers
- NCCN Guideline: Colon cancer
- NCCN Guideline: Uterine neoplasms
- NCCN Guideline: Rectal cancer
- NCCN Guideline: Head and neck cancers

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Herceptin, Kanjinti, Ogivri, Trazimera, Herzuma and Ontruzant are covered in addition to the following:

- HER2-positive breast cancer:
  - Neoadjuvant therapy
  - Treatment of recurrent or advanced unresectable disease
  - Treatment for no response to preoperative systemic therapy
- HER2-negative breast cancer treatment of stage IV (M1) disease
- Intra-cerebrospinal fluid (CSF) treatment of leptomeningeal metastases (malignant meningitis) from HER2-positive breast cancer
- HER2-positive esophageal and esophagogastric junction cancer
- HER2- positive uterine serous carcinoma and carcinosarcoma
- HER2-positive salivary gland tumors
- HER2-amplified and RAS and BRAF wild-type colorectal cancer
- HER2-positive biliary tract cancers
- HER2-positive non-small cell lung cancer
- Prostate cancer

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for all indications other than non-small cell lung cancer and prostate cancer can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for non-small cell lung cancer and prostate cancer can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

References

1. Herceptin [package insert]. South San Francisco, CA: Genentech, Inc.;June 2024.

2. Kanjinti [package insert]. Thousand Oaks, CA: Amgen, Inc.; October 2022.
3. Ogivri [package insert]. Cambridge, MA: Biocon Biologics Inc.; July 2023.
4. Trazimera [package insert]. Cork, Ireland: Pfizer Ireland Pharmaceuticals; November 2020.
5. Herzuma [package insert]. Jersey City, NJ: Organon LLC; June 2021.
6. Ontruzant [package insert]. Incheon, Republic of Korea: Samsung Bioepis Co.; June 2021.
7. Hercessi [package insert]. Raleigh, NC: Accord BioPharma Inc.; April 2024.
8. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed August 27, 2024.
9. Micromedex Solutions [electronic version]. Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com. Accessed August 27, 2024.
10. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Anal Carcinoma. Version 1.2024. Accessed August 27, 2024. https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf
11. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Head and Neck Cancers. Version 4.2024. Accessed August 27, 2024. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf

Reference number(s)
4615-A

Standard Medicare Part B Management Herceptin Hylecta

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Herceptin Hylecta	trastuzumab and hyaluronidase-oysk

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Herceptin Hylecta is indicated for adjuvant treatment of adults with HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer:

- As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- As part of a treatment regimen with docetaxel and carboplatin
- As a single agent following multi-modality anthracycline based therapy

Herceptin Hylecta is indicated in adults:

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease

Compendial Uses

HER2-positive breast cancer: may be substituted for intravenous trastuzumab and used as a single agent or in combination with other systemic therapies.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions: Human epidermal growth factor receptor 2 (HER2) status.

Coverage Criteria

Breast Cancer

Authorization of up to 12 months may be granted for treatment of adjuvant treatment of HER2-positive breast cancer.

Authorization of 12 months may be granted for treatment of HER2-positive breast cancer with no response to preoperative systemic therapy, recurrent, unresectable, advanced, or metastatic (including brain metastases) disease.

Authorization of up to 12 months may be granted for neoadjuvant treatment of HER2-positive breast cancer as part of a complete treatment regimen.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Breast Cancer in the Adjuvant and Neoadjuvant Setting

Authorization of 12 months (up to 12 months total) may be granted for adjuvant or neoadjuvant treatment of breast cancer when all of the following criteria are met:

The member is currently receiving therapy with the requested medication

The member is receiving benefit from therapy. Benefit is defined as:

- No evidence of unacceptable toxicity while on the current regimen AND
- No evidence of disease progression while on the current regimen

Breast Cancer with No Response to Preoperative Therapy or in the Recurrent, Unresectable, Advanced, or Metastatic Setting

Authorization of 12 months may be granted when all of the following criteria are met:

The member is currently receiving therapy with the requested medication

The member is receiving benefit from therapy. Benefit is defined as:

- No evidence of unacceptable toxicity while on the current regimen AND
- No evidence of disease progression while on the current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Herceptin Hylecta.
- The available compendium
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)
  - Lexi-Drugs
  - Clinical Pharmacology
- NCCN Guideline: Breast cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Herceptin Hylecta are covered in addition to using Herceptin Hylecta as a substitute for intravenous trastuzumab for HER2-positive breast cancer.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Herceptin Hylecta as a substitute for intravenous trastuzumab to treat HER2-positive breast cancer can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen). Herceptin Hylecta may be used as a single agent or in combination with other systemic therapies. Do not substitute for or with ado-trastuzumab emtansine (Kadcyla) or fam-trastuzumab deruxtecan-nxki (Enhertu).

References

1. Herceptin Hylecta [package insert]. South San Francisco, CA: Genentech, Inc.; June 2024.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed August 27, 2024.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 4.2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed August 27, 2024.

Reference number(s)
2478-A

Standard Medicare Part B Management Hyaluronates

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Durolane	hyaluronic acid
Euflexxa	1% sodium hyaluronat
Gel-One	cross-linked hyaluronate
Gelsyn-3	sodium hyaluronate 0.84%
Genvisc 850	sodium hyaluronate
Hyalgan	sodium hyaluronate
Hymovis	high molecular weight viscoelastic hyaluronan
Monovisc	high molecular weight hyaluronan
Orthovisc	high molecular weight hyaluronan
Supartz FX	sodium hyaluronate
Synojoynt	1% sodium hyaluronate
Synvisc	hylan G-F 20
Synvisc One	hylan G-F 20
Triluron	sodium hyaluronate
Trivisc	sodium hyaluronate
Visco-3	sodium hyaluronate
1% sodium hyaluronate	1% sodium hyaluronate

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1-17]

Treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics (e.g., acetaminophen).

Compendial Uses[18,19]

- Treatment of pain of arthropathy of the shoulder
- Treatment of subacromial impingement
- Treatment of temporomandibular joint disorder

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Osteoarthritis of the Knee or Shoulder

Authorization of 12 months may be granted for treatment of osteoarthritis in the knee or shoulder.

Subacromial Impingement

Authorization of 3 months may be granted for treatment of subacromial impingement.

Temporomandibular Joint Disorder

Authorization of 3 months may be granted for treatment of temporomandibular joint disorder.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Osteoarthritis of the Knee or Shoulder

Authorization of 12 months for osteoarthritis of the knee or shoulder may be granted when ALL of the following criteria are met:

- The member has previously received therapy in the same joint with a hyaluronate product.
- The member meets either of the following:

- The member will receive the first injection of the retreatment course after at least 6 months from the last injection of the previous completed course and the medication has been effective for treating the diagnosis or condition.
- A different hyaluronate product is being requested due to an adverse event with the previous course.

All Other Indications

Authorization of 3 months may be granted for all other indications when ALL of the following criteria are met:

- The hyaluronate product is being used to treat an indication in the coverage criteria section.
- The medication has been effective for treating the diagnosis or condition.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for the above referenced hyaluronate products.
- The available compendium
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)
  - Lexi-Drugs
  - Clinical Pharmacology
- 2019 American College of Rheumatology/Arthritis Foundation Guidelines for the management of osteoarthritis of the hand, hip, and knee.
- Osteoarthritis Research Society International (OARSI) guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for the above referenced hyaluronate products are covered in addition to the following:

- Osteoarthritis of the shoulder
- Subacromial impingement
- Temporomandibular joint disorder

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for knee osteoarthritis can be found in the OARSI guidelines from 2019. Intra-articular corticosteroids and hyaluronan injections are conditionally recommended in individuals with knee osteoarthritis in all groups. Intra-articular hyaluronic acid may have beneficial effects on pain at and beyond 12 weeks of treatment. Hyaluronic acid injections may have a more favorable long-term safety profile compared to repeated intra-articular corticosteroid injections.

Conversely, the American College of Rheumatology and Arthritis Foundation Guideline states that intra-articular hyaluronic acid injections are conditionally recommended against in patients with knee osteoarthritis. In prior systematic reviews, apparent benefits of hyaluronic acid injections in OA have been reported. These reviews have not, however, taken into account the risk of bias of the individual primary studies. Our review showed that benefit was restricted to the studies with higher risk of bias: when limited to trials with low risk of bias, meta-analysis has shown that the effect size of hyaluronic acid injections compared to saline injections approaches zero. The finding that best evidence fails to establish a benefit, and that harm may be associated with these injections, motivated the recommendation against use of this treatment.

Many providers want the option of using hyaluronic acid injections when glucocorticoid injections or other interventions fail to adequately control local joint symptoms. In clinical practice, the choice to use hyaluronic acid injections in the knee OA patient who has had an inadequate response to nonpharmacologic therapies, topical and oral NSAIDs, and intraarticular steroids may be viewed more favorably than offering no intervention, particularly given the impact of the contextual effects of intraarticular hyaluronic acid injections. The conditional recommendation against is consistent with the use of hyaluronic acid injections, in the context of shared decision-making that recognizes the limited evidence of benefit of this treatment, when other alternatives have been exhausted or failed to provide satisfactory benefit.

Support for shoulder osteoarthritis can be found in a study where patients were administered weekly injection of 25 mg sodium hyaluronate (high molecular weight) into the glenoid cavity or subacromial bursa. The injections improved pain at rest, pain on motion, and pain on pressure in approximately 75% of 62 patients with periarthritis of the shoulder. A series of 5 injections was planned, and further injections were discontinued if pain was resolved. If not, weekly or biweekly injections continued. The mean treatment was 6 ampules injected over 8 weeks, but ranged from 1 to 27 injections given over 2 to 40 weeks. Final global improvement ratings showed 11% markedly improved, 40% moderately improved, 31% slightly improved, and 18% unchanged. None worsened. Among activities of daily living improved more than 60% were hair grooming, tying a sash behind the back, removing upper garments, or being able to touch the opposite shoulder. Range of motion improved in each measure, with the greatest change noted in the angle of abduction.

Support for subacromial impingement can be found in a randomized, single-blind, open-comparator clinical study (n=80). Hyaluronate 20 mg injected into the subacromial space once weekly for 3 weeks was associated with greater self-rated pain relief of subacromial impingement syndrome of the shoulder compared with a single dexamethasone injection, although improvement in functional scores and use of rescue medication were similar. Participants older than 40 years of age who had subacromial impingement syndrome without a rotator cuff tear and who had pain for 3 months or longer without improvement despite conservative treatment with physiotherapy and NSAIDs were randomized to hyaluronate sodium 20 mg subacromial injection once weekly for 3 weeks (n=38; mean age, 55.9 years) or a single subacromial injection of dexamethasone disodium phosphate 5 mg with 4 mL lidocaine 2% (n=42; mean age, 54.1 years). In both treatment arms, the 100-point visual analogue scale (VAS) score decreased significantly from baseline to week 12, from 58.6 to 24.6 in the hyaluronate group (p less than 0.0001) and from 57.2 to 36.9 in the dexamethasone group (p less than 0.0001). The hyaluronate group demonstrated a significantly greater decrease in the VAS score at 12 weeks compared with the dexamethasone group (p=0.018). Functional score from baseline to week 12, assessed by the American Shoulder and Elbow Surgeons (ASES) standardized shoulder assessment form, improved from 18.2 to 22.8 in the hyaluronate group (p=0.0023) and from 17.5 to 21.9 in the dexamethasone group (p=0.0002), although no significant difference was observed between the treatment groups at week 12. The use of acetaminophen for rescue pain relief was similar between the hyaluronate and dexamethasone groups (26 of 38 and 29 of 42, respectively). Adverse events were generally mild, with nasopharyngitis (hyaluronate, 15.38%; dexamethasone, 13.46%) and muscle pain (hyaluronate, 9.62%; dexamethasone, 3.85%) reported most frequently.

Support for temporomandibular joint disorder can be found in a study where patients were injected with sodium hyaluronate into the articular cavities with internal derangement of temporomandibular joints (TMJs). The procedure decreased friction so that, surgically, the articular disc could be retracted and, clinically, degree of mouth opening increased in some patients. After 63 patients were randomized into either a test group of 43 patients (45 TMJs, 29 with disc displacement with reduction and 16 without reduction) or a control group of 20 patients (24 TMJs, 17 with disc displacement with reduction and 7 without reduction), injections were made into the articular cavity. Test-group patients received 0.3 to 1 mL sodium hyaluronate 1% up to 3 times, either into the upper cavity only or into both upper and lower cavities, while control-group patients received 1 mL of lidocaine 2%. At follow-up visits relief of joint pain was evaluated as very good, good, or of no effect. Results were very good for 17 TMJs in the test group and 4 in the control group; good for 19 in the test group and 8 in the control group; and of no effect for 9 in the test group and 12 controls (chi(2)=6.6535, p less than 0.01). The difference between disc displacement with reduction and without reduction was not significant.

References

1. Durolane [package insert]. Durham, NC: Bioventus LLC; September 2017.
2. Euflexxa [package insert]. Parsippany, NJ: Ferring Pharmaceuticals, Inc.; July 2016.
3. Gel-One [package insert]. Warsaw, IN: Zimmer, Inc.; May 2011.
4. Gelsyn-3 [package insert]. Durham, NC: Bioventus LLC; December 2017.
5. GenVisc 850 [package insert]. Doylestown, PA: OrthogenRx, Inc.; November 2019.
6. Hyalgan [package insert]. Florham Park, NJ: Fidia Pharma USA Inc.; August 2017.
7. Hymovis [package insert]. Florham Park, NJ: Fidia Pharma USA Inc.; June 2021.
8. Monovisc [package insert]. Bedford, MA: Anika Therapeutics, Inc.; July 2020.
9. Orthovisc [package insert]. Bedford, MA: Anika Therapeutics, Inc.; November 2021.
10. Supartz FX [package insert]. Durham, NC: Bioventus LLC; April 2015.
11. Synojoynt [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; March 2019.
12. Synvisc [package insert]. Ridgefield, NJ: Genzyme Biosurgery; May 2023.
13. Synvisc One [package insert]. Ridgefield, NJ: Genzyme Biosurgery; May 2023.
14. Triluron [package insert]. Florham Park, NJ: Fidia Pharma USA Inc.: July 2019.
15. Trivisc [package insert]. Doylestown, PA: OrthogenRx, Inc.; December 2017.
16. Visco-3 [package insert]. Warsaw, IN: Zimmer; May 2017.
17. 1% Sodium Hyaluronate [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; March 2019.
18. Micromedex Solutions [database online]. Ann Arbor, MI: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed October 23, 2023.
19. Kolasinski SL, Tuhina N, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guidelines for the management of osteoarthritis of the hand, hip, and knee. Arthritis Rheumatol. 2020 Jan 6. doi: 10.1002/art.41142. [Epub ahead of print]
20. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage. 2019;27(11):1578-1589.
21. Itokazu M & Matsunaga T: Clinical evaluation of high-molecular-weight sodium hyaluronate for the treatment of patients with periarthritis of the shoulder. Clin Ther 1995; 17(5):946-955.
22. Kim YS, Park JY, Lee CS, et al: Does hyaluronate injection work in shoulder disease in early stage? A multicenter, randomized, single blind and open comparative clinical study. J Shoulder Elbow Surg 2012; 21(6):722-727.

23. Zhiyuan G, Qiuliang W, Yingxi Z, et al: Visco-supplementation therapy in internal derangement of temporomandibular joint. Chin Med J 1998; 111(7):656-659.

Reference number(s)
6722-A

Standard Medicare Part B Management
Hympavzi

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Hympavzi	marstacimab-hncq

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

Hympavzi is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with:

- Hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or
- Hemophilia B (congenital factor IX deficiency) without factor IX inhibitors.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

For initial requests: Chart notes, lab tests documenting all of the following (where applicable):
Hemophilia A (congenital factor VIII deficiency):

- Severe factor VIII deficiency (factor VIII level of <1%)
- Absence of factor VIII inhibitors (lab test results required)

Hemophilia B (congenital factor IX deficiency):

- Moderately severe to severe factor IX deficiency (factor IX level of ≤ 2%)
- Absence of Factor IX inhibitors (lab test results required)

For continuation requests: Chart notes documenting benefit from therapy (e.g., reduced frequency or severity of bleeds).

Coverage Criteria

Hemophilia A (congenital factor VIII deficiency)[1,2]

Authorization of 12 months may be granted for hemophilia A (congenital factor VIII deficiency) when all of the following criteria are met:

- Member is 12 years of age or older.
- Member is ≥ 35 kg.
- Member has severe factor VIII deficiency (defined as factor VIII level of <1%).
- Member has no detectable or documented history of factor VIII inhibitors.
- Member must be using the requested medication for routine prophylaxis to prevent or reduce the frequency of bleeding episodes.
- Member will not use the requested medication to treat breakthrough bleeding.
- Member will not use the requested medication in combination with Hemlibra.
- Member has not previously received treatment with a gene therapy product (e.g., Roctavian) for the treatment of hemophilia A.
- Prophylactic use of factor VIII products will be discontinued prior to starting therapy with the requested medication.

Hemophilia B (congenital factor IX deficiency)[1,2]

Authorization of 12 months may be granted for hemophilia B (congenital factor IX deficiency) when all of the following criteria are met:

- Member is 12 years of age or older.
- Member is ≥ 35 kg.
- Member has moderately severe to severe factor IX deficiency (defined as factor IX level of ≤ 2%).
- Member has no detectable or documented history of factor IX inhibitors.
- Member must be using the requested medication for routine prophylaxis to prevent or reduce the frequency of bleeding episodes.
- Member will not use the requested medication to treat breakthrough bleeding.
- Member has not previously received treatment with a gene therapy product (e.g., Hemgenix) for the treatment of hemophilia B.
- Prophylactic use of factor IX products will be discontinued prior to starting therapy with the requested medication.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- Member is experiencing benefit from therapy (e.g., reduced frequency or severity of bleeds).
- Member has no detectable or documented history of factor VIII or IX inhibitors.
- Member is not using the requested medication in combination with factor VIII products (e.g., Advate, Adynovate, Eloctate) or factor IX products (e.g., Alprolix, Ixinity, Rebinyn) for prophylactic use.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Hympavzi.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Hympavzi are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Currently there are no treatment guidelines or literature supporting the concomitant use of Hympavzi and Hemlibra.

References

1. Hympavzi [package insert]. New York, NY: Pfizer Inc.; October 2024.
2. Davide Matino, Suchitra Acharya, Andrew Palladino, Eunhee Hwang, Regina McDonald, Carrie Turich Taylor, John Teeter; Efficacy and Safety of the Anti-Tissue Factor Pathway Inhibitor Marstacimab in Participants with Severe Hemophilia without Inhibitors: Results from the Phase 3 Basis Trial. *Blood* 2023; 142 (Supplement 1): 285.

Reference number(s)
2479-A

Standard Medicare Part B Management
Ilaris

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Ilaris	canakinumab

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

- Cryopyrin-associated periodic syndromes (CAPS) in adults and children 4 years of age and older including: Familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS)
- Tumor necrosis factor receptor associated periodic syndrome (TRAPS) in adult and pediatric patients
- Hyperimmunoglobulin D syndrome (HIDS)/Mevalonate kinase deficiency (MKD) in adult and pediatric patients
- Familial Mediterranean Fever (FMF) in adult and pediatric patients
- Active Still's disease, including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older
- Symptomatic treatment of adult patients with gout flares in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Cryopyrin-Associated Periodic Syndromes (CAPS)[1]

Authorization of 12 months may be granted for treatment of cryopyrin-associated periodic syndromes (CAPS) including familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS).

Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)[1]

Authorization of 12 months may be granted for treatment of tumor necrosis factor receptor associated periodic syndrome (TRAPS).

Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD)[1]

Authorization of 12 months may be granted for treatment of hyperimmunoglobulin D syndrome (HIDS) or mevalonate kinase deficiency (MKD).

Familial Mediterranean Fever (FMF)[1]

Authorization of 12 months may be granted for treatment of familial Mediterranean Fever (FMF).

Systemic Juvenile Idiopathic Arthritis[1]

Authorization of 12 months may be granted for treatment of active systemic juvenile idiopathic arthritis.

Active Adult-Onset Still's Disease[1]

Authorization of 12 months may be granted for treatment of active adult-onset Still's disease.

Gout Flares[1,3]

Authorization of 12 months may be granted for the treatment of gout flares when the member has had an inadequate response, intolerance, or contraindication to non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Ilaris.
- Ilaris is being used to treat an indication in the coverage criteria section.

- The member is receiving benefit from therapy as evidenced by low disease activity or improvement in signs and symptoms of the condition.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Ilaris.
- The available compendium
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)
  - Lexi-Drugs
  - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Ilaris are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Ilaris [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; September 2023.

Reference number(s)
4697-A

Standard Medicare Part B Management
Ilumya

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Ilumya	tildrakizumab-asmn

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy

FDA-Approved Indications

Ilumya is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia

Documentation

The following documentation must be available, upon request, for all submissions:

For continuation requests: Chart notes or medical record documentation supporting benefit of therapy.

Reference number(s)
4697-A

Coverage Criteria

Plaque psoriasis[1-4]

Authorization of 12 months may be granted for the treatment of moderate to severe plaque psoriasis

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Ilumya
- Ilumya is being used to treat an indication enumerated in coverage criteria section
- The member is receiving benefit from therapy

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Ilumya.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 4: Guidelines of care for the management and treatment of psoriasis with traditional systemic agents.
- Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 6: Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions.
- Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics.
- Joint AAD-NPF guidelines of care for the management of psoriasis with systemic nonbiologic therapies

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Ilumya are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer’s prescribing information.

References

1. Ilumya [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; December 2022.
2. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 4: Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol. 2009;61(3):451-485.
3. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 6: Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. J Am Acad Dermatol. 2011;65(1):137-174.
4. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. J Am Acad Dermatol. 2019;80(4):1029-1072.
5. Menter A, Gelfand JM, Connor C, et al. Joint AAD-NPF guidelines of care for the management of psoriasis with systemic nonbiologic therapies. J Am Acad Dermatol. 2020;82(6):1445-1486.

Reference number(s)
6501-A

Standard Medicare Part B Management Imdelltra

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Imdelltra	tarlatamab-dlle

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Extensive Stage Small Cell Lung Cancer[1]

Authorization of 12 months may be granted for treatment of extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication listed in the coverage criteria.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on current regimen AND
    - No evidence of disease progression while on current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Imdelltra.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Imdelltra are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Imdelltra [package insert]. Thousand Oaks, CA: Amgen Inc.; May 2024.

Reference number(s)
5656-A

Standard Medicare Part B Management Imjudo

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Imjudo	tremelimumab-actl

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

- Imjudo is indicated in combination with durvalumab for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC).
- Imjudo is indicated in combination with durvalumab and platinum-based chemotherapy for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.

Compendial Uses

- Recurrent and advanced NSCLC
- Esophageal and esophagogastric junction cancer
- Gastric cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions where applicable:

- Documentation of the absence of EGFR exon 19 deletion and L858R mutations and ALK rearrangements (unless testing is not feasible due to insufficient tissue).
- Documentation of laboratory report confirming microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumor status, where applicable.

Coverage Criteria

Hepatocellular Carcinoma

Authorization of 1 month for a one-time single dose may be granted for treatment of hepatocellular carcinoma when all of the following criteria are met:

- The requested medication will be used in combination with durvalumab (Imfinzi)
- The disease is unresectable or metastatic
- The member is ineligible for transplant

NSCLC

Authorization of 6 months for a total of 5 doses may be granted for treatment of recurrent, advanced or metastatic non-small cell lung cancer when all of the following criteria are met:

- The requested medication will be used in combination with durvalumab (Imfinzi) and platinum-based chemotherapy
- The tumor is negative for EGFR exon 19 deletion and L858R mutations and ALK rearrangements.

Esophageal, Esophagogastric Junction and Gastric Cancer

Authorization of 1 month for a one-time single dose may be granted for treatment of esophageal, esophagogastric junction or gastric cancer when all of the following criteria are met:

- The requested medication will be used in combination with durvalumab (Imfinzi) for neoadjuvant treatment
- The tumor is microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR)
- The member is medically fit for surgery

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Imjudo.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs

    - Clinical Pharmacology
- NCCN Guideline: Non-small cell lung cancer
- NCCN Guideline: Hepatocellular carcinoma
- NCCN Guideline: Gastric cancer
- NCCN Guideline: Esophageal and esophagogastric junction cancers

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Imjudo to treat gastric cancer and esophageal and esophagogastric junction cancers can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

References

1. Imjudo [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; June 2023.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed July 1, 2024.
3. Pietrantonio, Filippo, Raimondi Alessandra, Lonardi Sara, et al. Infinity: A multicenter, single-arm, multi-cohort, phase II trial of tremelimumab and durvalumab as neoadjuvant treatment of patients with microsatellite instability-high (MSI) resectable gastric or gastroesophageal junction adenocarcinoma (GAC/GEJAC). Journal of Clinical Oncology. 2023; 4: 358.

Reference number(s)
1979-A

Standard Medicare Part B Management infliximab

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Remicade	infliximab
Avsola	infliximab-axxq
Inflectra	infliximab-dyyb
Renflexis	infliximab-abda
Zymfentra	infliximab-dyyb
infliximab (all brands)	infliximab

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication[1-6]

Infliximab/Avsola/Inflectra/Remicade/Renflexis

Crohn's Disease

- Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response to conventional therapy.
- Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing CD.

Pediatric Crohn's Disease

Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active CD who have had an inadequate response to conventional therapy.

Ulcerative Colitis

Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy.

Pediatric Ulcerative Colitis

Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active UC who have had an inadequate response to conventional therapy.

Rheumatoid Arthritis in Combination with Methotrexate

Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis (RA).

Ankylosing Spondylitis

Reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS).

Psoriatic Arthritis

Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in adult patients with psoriatic arthritis (PsA).

Plaque Psoriasis

Treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis (PsO) who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

Zymfentra

- Maintenance treatment of moderately to severely active ulcerative colitis in adults following treatment with an infliximab product administered intravenously.
- Maintenance treatment of moderately to severely active Crohn's disease in adults following treatment with an infliximab product administered intravenously.

Compendial Uses[7-45]

- Adult-onset Still's disease
- Arthritis in Crohn's disease
- Non-radiographic axial spondyloarthritis
- Behcet's disease
- Gastrointestinal tract transplantation organ rejection
- Giant cell arteritis
- Acute graft versus host disease
- Hidradenitis suppurativa
- Juvenile idiopathic arthritis
- Kawasaki disease
- Necrobiosis lipoidica diabeticorum
- Polyarteritis nodosa
- Pyoderma gangrenosum
- Rheumatoid arthritis as monotherapy

- Severe, refractory SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome
- Sarcoidosis
- Subcorneal pustular dermatosis
- Synovitis
- Takayasu's arteritis
- Uveitis
- Immune checkpoint inhibitor-related toxicity
- Multisystem inflammatory syndrome in children (MIS-C)

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Crohn's disease (CD), ulcerative colitis (UC), rheumatoid arthritis (RA), ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA), psoriatic arthritis (PsA), plaque psoriasis (PsO), adult-onset Still's disease (AOSD), hidradenitis suppurativa, juvenile idiopathic arthritis (JIA), uveitis, and immune checkpoint inhibitor-related inflammatory arthritis

For continuation requests: Chart notes or medical record documentation supporting benefit of therapy.

Coverage Criteria

Crohn's Disease (CD)[1-6]

Authorization of 12 months may be granted for treatment of moderately to severely active Crohn's disease.

Ulcerative Colitis (UC)[1-6]

Authorization of 12 months may be granted for treatment of moderately to severely active ulcerative colitis.

Rheumatoid Arthritis (RA) (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[1-6]

Authorization of 12 months may be granted for treatment of moderately to severely active rheumatoid arthritis.

Ankylosing Spondylitis (AS) and Non-Radiographic Axial Spondyloarthritis (nr-axSpA) (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[1-7,13]

Authorization of 12 months may be granted for treatment of active ankylosing spondylitis and active non-radiographic axial spondyloarthritis.

Psoriatic Arthritis (PsA) (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[1-6]

Authorization of 12 months may be granted for treatment of active psoriatic arthritis.

Plaque Psoriasis (PsO) (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[1-6]

Authorization of 12 months may be granted for treatment of plaque psoriasis.

Adult-Onset Still's Disease (AOSD) (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[7]

Authorization of 12 months may be granted for treatment of active adult-onset Still's disease.

Arthritis In Crohn's Disease (CD) (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[7]

Authorization of 12 months may be granted for treatment of arthritis in a member with Crohn's disease.

Behcet's Disease (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[7]

Authorization of 12 months may be granted for treatment of Behcet's disease.

Gastrointestinal Tract Transplantation Organ Rejection (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[7]

Authorization of 6 months may be granted for treatment of gastrointestinal tract transplantation organ rejection.

Giant Cell Arteritis (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[7]

Authorization of 3 months may be granted for treatment of giant cell arteritis.

Acute Graft Versus Host Disease (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[7,14]

Authorization of 12 months may be granted for treatment of acute graft versus host disease.

Hidradenitis Suppurativa (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[7,17]

Authorization of 12 months may be granted for treatment of hidradenitis suppurativa.

Juvenile Idiopathic Arthritis (JIA) (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[7,12,18,27]

Authorization of 12 months may be granted for treatment of active juvenile idiopathic arthritis.

Kawasaki Disease (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[7]

Authorization of 1 month may be granted for treatment of Kawasaki disease.

Necrobiosis Lipoidica Diabeticorum (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[7]

Authorization of 12 months may be granted for treatment of necrobiosis lipoidica diabeticorum.

Polyarteritis Nodosa (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[7]

Authorization of 12 months may be granted for treatment of polyarteritis nodosa.

Pyoderma Gangrenosum (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[7]

Authorization of 12 months may be granted for treatment of pyoderma gangrenosum.

SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome (Avsola/Inflectra/ infliximab/Remicade/Renflexis only)[7]

Authorization of 12 months may be granted for treatment of severe, refractory SAPHO syndrome.

Sarcoidosis (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[7]

Authorization of 12 months may be granted for treatment of sarcoidosis.

Subcorneal Pustular Dermatosis (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[7]

Authorization of 6 months may be granted for treatment of subcorneal pustular dermatosis.

Synovitis (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[7]

Authorization of 12 months may be granted for treatment of synovitis.

Takayasu's Arteritis (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[7]

Authorization of 12 months may be granted for treatment of Takayasu's arteritis.

Uveitis (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[7,20,28]

Authorization of 12 months may be granted for treatment of uveitis.

Immune Checkpoint Inhibitor-Related Inflammatory Arthritis (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[14]

Authorization of 12 months may be granted for treatment of moderate or severe immune checkpoint inhibitor-related inflammatory arthritis.

Immune Checkpoint Inhibitor-Related Toxicity (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[14]

Authorization of 6 months may be granted for treatment of immune checkpoint inhibitor-related toxicity.

Multisystem Inflammatory Syndrome in Children (MIS-C) (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[7]

Authorization of 1 month may be granted for treatment of multisystem inflammatory syndrome in children (MIS-C) post severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who have failed to respond to standard pharmacologic therapy.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Crohn's Disease (CD) and Ulcerative Colitis (UC)

Authorization for 12 months may be granted when both of the following criteria are met:

- The member is currently receiving therapy with Avsola, Inflectra, infliximab, Remicade, Renflexis, or Zymfentra.
- The member is receiving benefit from therapy.

Gastrointestinal Tract Transplantation Organ Rejection, Giant Cell Arteritis, Kawasaki Disease, Subcorneal Pustular Dermatosis, Immune Checkpoint Inhibitor-Related Toxicity, And Multisystem Inflammatory Syndrome In Children (MIS-C) (Avsola/Inflectra/infliximab/Remicade/Renflexis only)[14]

All members (including new members) requesting authorization for continuation of therapy must meet all requirements in the coverage criteria.

All Other Indications (Avsola/Inflectra/infliximab/Remicade/Renflexis only)

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Avsola, Inflectra, infliximab, Remicade, or Renflexis.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for infliximab, Remicade, and its biosimilars.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
- EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update.
- 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.
- EULAR recommendations on management of Behcet's syndrome.
- North American clinical management guidelines for hidradenitis suppurativa: A publication from the United States and Canadian Hidradenitis Suppurativa Foundations: Part II: Topical, intralesional, and systemic medical management.
- British Association of Dermatologists guidelines for the management of hidradenitis suppurativa (acne inversa) 2018.
- 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis.
- 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis.

- Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association.
- 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Polyarteritis Nodosa.
- Etiology and management of pyoderma gangrenosum: a comprehensive review.
- European Respiratory Society (ERS) clinical practice guidelines on treatment of sarcoidosis.
- Comparison of ultrasonographic assessment of synovitis and joint vascularity with radiographic evaluation in a randomized, placebo-controlled study of infliximab therapy in early rheumatoid arthritis.
- Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial.
- Recommendations of the Italian Society of Rheumatology for the treatment of the primary large-vessel vasculitis with biological agents.
- Efficacy and tolerance of infliximab in refractory Takayasu arteritis: French multicentre study.
- A review of systemic biologics and local immunosuppressive medications in uveitis.
- Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders.
- NCCN guideline: Hematopoietic cell transplantation.
- NCCN guideline: Management of immunotherapy-related toxicities.
- COVID-19 Treatment Guidelines Panel: Coronavirus disease 2019 (COVID-19) treatment guidelines.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for infliximab, Remicade, and its biosimilars (excluding Zymfentra) are covered in addition to the following:

- Adult-onset Still’s disease
- Arthritis in Crohn’s disease
- Non-radiographic axial spondyloarthritis
- Behçet’s disease
- Gastrointestinal tract transplantation organ rejection
- Giant cell arteritis
- Acute graft versus host disease
- Hidradenitis suppurativa
- Juvenile idiopathic arthritis
- Kawasaki disease
- Necrobiosis lipoidica diabeticorum
- Polyarteritis nodosa
- Pyoderma gangrenosum
- Sarcoidosis
- Subcorneal pustular dermatosis
- Synovitis
- Takayasu’s arteritis
- Uveitis
- Immune checkpoint inhibitor toxicity
- Multisystem inflammatory syndrome in children (MIS-C)

Explanation of Rationale

Support for FDA-approved indications (Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis) can be found in the manufacturer's prescribing information.

Support for using infliximab for non-radiographic axial spondyloarthritis can be found in the 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. The guidelines recommend that patients who still have active ankylosing spondylitis (AS) despite treatment with NSAIDs, tumor necrosis factor inhibitor (TNFi) such as infliximab are recommended but the guideline does not recommend any particular TNFi.

Support for using infliximab to treat adult-onset Still's disease can be found in two published case series. Kraetsch et al reported adult-onset Still disease (AOSD) appears to favorably respond to treatment with infliximab. In a small, pilot study, 6 patients diagnosed with AOSD (4 with early onset of disease, and 2 with disease durations of 3 and 5 years, respectively) received an initial course of intravenous infusions of infliximab 5 mg/kg, at 0, 2, and 6 weeks. Further treatment with infliximab was given at 6- to 8-week intervals, contingent upon patient response. At the time of study enrollment, all patients had massive polyarthralgia, 5 had polyarthritis, 5 had persistent fever, 5 had a characteristic rash, 5 had persistent leukocytosis, 4 had splenomegaly, and all 6 patients had elevations of erythrocyte sedimentation rate (ESR) and elevated serum concentrations of C-reactive protein. Hyperferritinemia was seen in 3 patients. All patients showed a beneficial response to treatment, with complete resolution of rash, fever, myalgias, and splenomegaly (the latter after 3 treatments); arthralgia/arthritis resolved in 5 of 6 patients. Normalization also occurred in serological markers of disease activity (CRP, ESR, and ferritin concentration) in all patients. Favorable effects of treatment were evident after the first course of treatment with infliximab and were sustained with continuing infliximab treatment at 6-to-8 week intervals, with treatment durations extending from 5 to 28 months. In the 2 patients with long-standing disease of 3- and 5-years duration, swollen joint counts declined from 30 to 3, and from 3 to 0 joints, respectively; tender joint count declined similarly, from 33 to 3 and from 7 to 2 joints, respectively. Infliximab was tolerated well; 1 patient showed a moderate infusion reaction during the second treatment yet was able to resume infliximab therapy after a brief discontinuation of the infusion.

Cavagna et al indicated that infliximab appeared to induce clinical remission in 3 patients with chronically active, treatment-refractory, adult Still Disease (ASD). Each patient had a disease history of between 4- and 7-years duration, during which time they exhibited relapsing or refractory disease despite treatment with NSAIDs, prednisone, methotrexate (n=3), and cyclosporine (n=1). Patients were given intravenous infusions of infliximab 3 mg/kg at weeks 0, 2, 6, and then once every 8 weeks. Infliximab was to be given once every 4 weeks from week 30 thereafter, and methotrexate was maintained throughout the duration of the study. All patients experienced rapid regression of ASD symptoms (arthralgia, cutaneous rash, fever, pharyngitis), accompanied by progressive reductions in serum concentrations of ferritin, C-reactive protein, and erythrocyte sedimentation rate. One patient developed a diffuse, urticarial rash shortly after the fifth infliximab infusion, necessitating withdrawal from therapy at week 22. The 2 remaining patients both experienced brief relapses on weeks 20 and 28; both rapidly regained a state of remission following repeat infusions of infliximab, and continued to receive infliximab beyond 30 weeks, without signs of relapse. These 2 patients also tolerated tapered reductions in prednisone dosing. Neither of the remaining patients showed development of anticardiolipin antibodies, anti-double stranded DNA, or antinuclear antibodies after prolonged treatment.

Support for using infliximab to treat arthritis in Crohn's disease can be found in a case series by Elman et al. Infliximab appeared to be effective in suppressing joint inflammation associated with arthritis secondary to Crohn disease. In a

series of case reports, patients with treatment-refractory, joint inflammation associated with long-standing Crohn disease (9 to 31 years duration; n=4) were given intravenous infliximab 5 mg/kg at 8 to 16-week intervals after the initial induction schedule. All patients had prolonged episodes of joint and back pain associated with periods of quiescence in their inflammatory bowel disease; 2 patients had "sausage-shaped" finger and toe swelling, and 3 patients presented with pain in the sacroiliac joint (SI-joint). No patient had radiographic abnormalities of the SI-joint. All patients had been receiving treatment with prednisone up to 40 mg per day, accompanied by 1 or more antiarthritic agents including azathioprine, methotrexate, minocycline, and sulfasalazine. Patients had favorable responses to infliximab, experiencing clinically meaningful reductions in joint pain and swelling, allowing for dose reductions or withdrawals of corticosteroid and antiarthritic agents. One patient discontinued infliximab therapy due to anorexia and insomnia.

Support for Behcet's disease can be found the European League Against Rheumatism (EULAR) recommendations on management of Behcet syndrome (BS). Hatemi and colleagues (2018) noted that several new therapeutic modalities with different mechanisms of action have been studied in patients with BS. These researchers updated the recommendations in the light of these new data under the auspices of EULAR Standing Committee for Clinical Affairs. The recommendations on the medical management of muco-cutaneous, joint, eye, vascular, neurological and GI involvement of BS were modified; 5 overarching principles and a new recommendation about the surgical management of vascular involvement were added. For BS with eye involvement, among the monoclonal anti-TNF antibodies, although there is more accumulated experience with IFX, ADA also appeared to be an effective alternative. Switching between these agents appeared to be possible in patients with primary or secondary unresponsiveness or AEs. Patients presenting with an initial or recurrent episode of acute sight-threatening uveitis should be treated with high-dose glucocorticoids, IFX or IFN-alpha. Intravitreal glucocorticoid injection is an option in patients with unilateral exacerbation as an adjunct to systemic treatment.

Support for using infliximab to treat gastrointestinal tract organ transplantation rejection can be found in two case reports by Pascher et al. In 2 case reports, infliximab was effective in the treatment of steroid and OKT3 (muromonab-CD3)-refractory moderate to severe acute cellular rejection in intestinal transplant recipients. Following either 5 or 10 days of treatment with OKT3 and enhanced baseline immunosuppressive therapy, acute cellular rejection persisted. Patients were then treated with 3 mg/kg IV infliximab; both patients received 4 infusions, 2 to 4 weeks apart. Improvement was observed within 1 week of the first infusion. Absence of clinical symptoms and histological signs of rejection persisted for at least 8 months for 1 patient and at least 10 months for the other.

Support for using infliximab to treat giant cell arteritis can be found in an open-label case study (Cantini et al). Administration of infliximab was effective in provoking remission in patients with active, steroid-dependent giant cell arteritis (GCA). In an open-label case study, 4 patients with long-standing GCA (disease duration ranging from 42 to 54 months) were unable to tolerate the tapering of their daily corticosteroid dose to less than 12.5 mg. They were given a 3-dose regimen of intravenous infliximab 3 mg/kg, at 0, 2, and 6 weeks, concurrent with reduction of their steroid dose to prednisone 5 mg per day. Three patients experienced a complete response to infliximab therapy, exhibiting both clinical and humeral evidence of remission (resolution of cranial and systemic symptoms, articular symptoms, visual symptoms, and normalization of erythrocyte sedimentation rate and serum concentration of C-reactive protein) after the second dose of infliximab. These responders remained in remission for up to 6 months after the third infliximab infusion, without requiring further treatment with corticosteroid. The fourth patient initially showed a partial response to the first infusion; however, she experienced clinical relapse at the time of her second infusion, causing her to withdraw from the study per the prospectively established protocol. Infliximab was well tolerated by all patients, and adverse events were neither reported nor observed.

Support for hidradenitis suppurativa can be found in the North American clinical management guidelines for hidradenitis suppurativa: A publication from the United States and Canadian Hidradenitis Suppurativa Foundations: Part II: Topical,

intralesional, and systemic medical management. The guideline indicates infliximab is recommended for moderate-to-severe disease. Dose ranging studies are needed to determine the optimal dosage for management.

Support for juvenile idiopathic arthritis can be found in the 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. Using infliximab in combination with a DMARD was a strong recommendation despite the low quality of evidence, primarily given more extensive experience with the need for combination therapy to reduce the risk of antidrug antibody formation.

Support for Kawasaki disease can be found in the following document produced by the American Heart Association: Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. A 2-center, randomized, double-blind, placebo-controlled trial of infliximab plus IVIG for intensification of initial treatment enrolled 196 subjects. The study was powered for the primary outcome measure of reducing IVIG resistance from 20% to 5%. Secondary outcome measures included reduction of inflammatory parameters and the change in coronary artery Z scores. Although the number of fever days was shortened and inflammatory parameters normalized more rapidly in the infliximab-treated subjects, the rates of IVIG resistance were identical between the 2 arms. A striking finding was the complete prevention of IVIG infusion reactions in children randomized to the infliximab arm compared with a 13% reaction rate in subjects who received placebo before their IVIG infusion. There was a significant decrease in Z score for the LAD in favor of infliximab. However, there was no difference in the rate of coronary artery aneurysms between the groups, although the study was inadequately powered for this end point. On the basis of current information, addition of infliximab to initial therapy with IVIG is safe but does not prevent recrudescent fever.

A phase I multicenter, randomized, open clinical trial of infliximab (5 mg/kg intravenously over 2 hours) versus a second infusion of IVIG (2 g/kg) was performed to determine the safety, tolerability, and pharmacokinetics of infliximab for rescue therapy for patients who had fever at least 36 hours after the end of the initial IVIG infusion. The study enrolled 24 subjects with IVIG-resistant KD and determined that infliximab was well tolerated in infants and children with KD and that the pharmacokinetics were similar to adults, with circulating levels of the monoclonal antibody detected out to 10 weeks. In the Japanese trial, 20 KD patients resistant to 2 consecutive IVIG infusions (2 g/kg each) were treated with infliximab (5 mg/kg), and an apparent clinical response was achieved in 18 (90%). The 2 unresponsive patients were treated with plasma exchange with resolution of their inflammation. The coronary artery abnormalities detected by echocardiogram all subsequently resolved. There were no adverse reactions attributed to infliximab among the study subjects.

A retrospective review of 2 centers that consistently administered either a second dose of IVIG or infliximab to IVIG-resistant patients suggested that patients receiving infliximab had shorter hospitalization and fewer days of fever, but coronary artery outcomes and adverse events were similar. On the basis of these retrospective data, infliximab can be considered as an alternative to a second infusion of IVIG for resistant patients.

Support for using infliximab to treat necrobiosis lipoidica diabeticorum can be found in a case report by Kolde et al. Infliximab was an effective treatment for refractory ulcerated necrobiosis lipoidica in a 33-year-old man with diabetes mellitus. The patient received once monthly infusions of infliximab (5 mg/kg) for 2 months. Following treatment with infliximab, clinical improvement was reported, including healing of ulcerations, fading of erythematous infiltration, flattening of the raised margin, and substantial reduction in pain. Improvement of the necrobiosis lipoidica was sustained after the cessation of infliximab. The only reported adverse event was the development of miliary tuberculosis after the second infusion, which was possibly drug-related due to the temporal association with infliximab treatment.

Support for polyarteritis nodosa can be found in the 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Polyarteritis Nodosa. The guidelines recommend use of tumor necrosis factor inhibitors (TNFi) instead of cyclophosphamide to prevent strokes in patients with clinical manifestations of deficiency of adenosine deaminase 2 (DADA2) associated with polyarteritis nodosa (PAN). In addition, a case report by Matusuo et al. describes a 64-year-old man with a diagnosis of PAN who continually relapsed following treatments of glucocorticoids, methotrexate, cyclophosphamide, rituximab, and tacrolimus. After the fifth relapse, infliximab 5 mg/kg was administered at 0, 2, and 6 weeks, followed by 400 mg every 8 weeks. Clinical symptoms and laboratory values improved dramatically within 3 months of starting infliximab and daily prednisolone dose was tapered to 10 mg.

Support for pyoderma gangrenosum (PG) can be found in a study by Ahronowitz et al. Infliximab, an anti-TNFα monoclonal antibody binding both soluble and membrane-bound TNFα, is the only biologic that has shown efficacy in classic PG in a randomized, double-blind, controlled trial (level I evidence). Thirty patients were given either infliximab 5 mg/kg or placebo. At 2 weeks, 6 of 13 patients in the infliximab group showed improvement in the severity and/or size of ulcers, versus only 1 of 17 in the placebo group. After 2 weeks, the 16 non-responders in the placebo group were switched to infliximab and by week 6, 20 of 29 patients treated with infliximab demonstrated improvement in their PG lesions, with 6 of 29 showing complete resolution. Further studies are needed to determine the efficacy of infliximab in idiopathic PG.

Support for sarcoidosis can be found in the practice guidelines from the European Respiratory Society. The practice guidelines recommend the addition of infliximab to improve and/or preserve forced vital capacity (FVC) and quality of life in patients with symptomatic pulmonary sarcoidosis believed to be at higher risk for future mortality or permanent disability from sarcoidosis who have been treated with glucocorticoids or other immunosuppressive agents and have continued disease. Additionally, the guideline recommends the addition of infliximab (compared to no additional treatment) for patients with cutaneous sarcoidosis who have been treated with glucocorticoids and/or other immunosuppressive agents and have continued cosmetically important active skin disease. In patients with neurosarcoidosis that have been treated with glucocorticoids and a second-line agent (methotrexate, azathioprine, mycophenolate mofetil) with continued disease, the guidelines suggest adding infliximab.

Support for using infliximab to treat subcorneal pustular dermatosis can be found in a case report by Voightlander et al. Infliximab was effective in producing remission in a 79-year-old woman with treatment-refractory subcorneal pustular dermatosis (Sneddon-Wilkinson disease). The patient presented with disease flare (progressive, widespread erythema and pustular eruptions on the legs, forearms, trunk, and abdomen) that was recalcitrant to treatment with acitretin and methylprednisolone. Intravenous infliximab 5 mg/kg was given as a 2-hour infusion. Within 24 hours of treatment, serum analysis revealed a rapid decline in the number of peripheral granulocytes, accompanied by a decline (to within normal limits) in concentration of C-reactive protein. Complete resolution of pustules occurred within 2 days of infusion, leaving a residual scaling of the affected skin. The patient was able to tolerate the withdrawal of methylprednisolone over 3 days. Disease flare occurred 12 days after the first dose of infliximab; a second infliximab infusion (5 mg/kg) was given, provoking a complete remission within a day of the second treatment. Other than a mild, corticosteroid-responsive relapse, the patient remained in complete remission for a minimum of 6 months while receiving a maintenance therapy regimen of acitretin.

Support for synovitis can be found in a randomized, double-blind, placebo-controlled trial (n=20), significant reductions from baseline in MRI-measured synovitis were seen at 14 weeks and 1 year with infliximab plus methotrexate therapy. Disease Modifying Antirheumatic Drug- or oral corticosteroid-I rheumatoid arthritis patients with recent symptom onset (less than 12 months) and with metacarpophalangeal joint involvement were randomized to methotrexate 7.5 mg once weekly plus infliximab 3 mg/kg or placebo infusion at 0, 2, 6, and then every 8 weeks. MRI-measured synovitis at week-14 (primary endpoint) and at week-54 (secondary endpoint) from baseline were compared between the infliximab and

placebo groups. At week 14, median total synovitis score was significantly lower in the infliximab group (5.5 to 3.4) as compared with the placebo arm (6.2 to 5.9) (p less than 0.05). After 54 weeks, median total synovitis score was significantly lower in the infliximab group (3.8) as compared with the placebo arm (6.6) (p less than 0.05). Adverse effects with infliximab included infusion reaction (n=1), elevated liver function enzyme (n=1), and cutaneous vasculitis (n=1).

Additionally, in a placebo-controlled trial (n=24), infliximab plus methotrexate showed a significant percent reduction in total synovial thickness from baseline at 18 weeks compared with methotrexate alone. Patients with early phase rheumatoid arthritis (less than 2 years mean duration) with a minimum of 2 swollen metacarpophalangeal joints despite methotrexate treatment were randomized to methotrexate (escalating dose) plus infliximab 5 mg/kg or placebo infusion at 0, 2, 6, and then every 8 weeks. After 18 weeks, high frequency ultrasonography showed a 50% median reduction in synovial thickness with the infliximab group as opposed to a 1.2% median increase in synovial thickness in the placebo group (p=0.014).

Support for Takayasu's arteritis can be found in the Recommendations of the Italian Society of Rheumatology for the treatment of the primary large-vessel vasculitis with biological agents. According to the recommendations, tumor necrosis factor alpha-inhibiting agents are recommended in patients with persistently active Takayasu Arteritis for 6 months or more, or with 2 or more flares or relapses despite glucocorticoid therapy; this is in addition to 1 or more immunosuppressive agent unless not tolerated or contraindicated.

In a 12-month, multicenter, retrospective study (n=15), infliximab therapy resulted in a response rate of 73% to 87% and significantly reduced corticosteroid use in patients with refractory Takayasu arteritis. Patients (median age, 41 years; range, 17 to 61 years) with Takayasu arteritis (median time from disease onset to infliximab therapy, 37 months; range, 6 to 365 months) that was refractory to other nonsteroid immunosuppressive agents or steroids received infliximab 3 mg/kg (n=5) or 5 mg/kg (n=10) IV every 4 to 8 weeks (median, every 6 weeks). Patients were concomitantly receiving steroids (n=14; median prednisone dose, 20 mg; range, 5 to 35 mg/day) and other nonsteroid immunosuppressive therapies (methotrexate, n=7; azathioprine, n=4) with doses that were not modified in the 3 months before infliximab initiation. After a median follow-up of 43 months (range, 4 to 71 months), overall response (including partial or good response; determined by physician in change and by the presence of clinical and biological activity) was achieved in 87% (n=13/15), 77% (n=10/13), and 73% (n=8/11), respectively, at 3, 6, and 12 months. The percentage of patients with disease activity was significantly decreased from 73% at baseline to 20% at 3 months (p less than 0.005), 31% at 6 months (p less than 0.05), and 27% at 12 months (p less than 0.05). The median prednisone dose also significantly decreased from 20 mg (range, 5 to 35 mg) at baseline to 15 mg (range, 5 to 20 mg) at 3 months (p less than 0.005), 7.5 mg (range, 5 to 18 mg) at 6 months (p less than 0.05), and 6 mg (range, 2.5 to 30 mg) at 12 months (p less than 0.05). Additionally, C-reactive protein was decreased from a median of 30 mg/L (range, 4 to 70 mg/L) at baseline to 5 mg/L (range, 0 to 57 mg/L) at 3 months (p less than 0.05) and 6 mg/L (range, 0 to 50 mg/L) at 6 months (p less than 0.05); however, there was no significant difference from baseline at month 12. Adverse events included acute infusion reactions in 2 patients that led to discontinuation of infliximab therapy.

In a single center retrospective study (n=25), partial or complete remission occurred in 18 of 21 patients who received infliximab therapy for the treatment of refractory Takayasu arteritis. Patients (mean age, 35 years; range, 15 to 64 years; median disease duration, 116 months; range, 39 to 344 months; concurrent nonsteroid immunosuppressive therapy, n=18) with Takayasu arteritis who could not achieve stable remission with the use of low-dose prednisone (less than 10 mg/day) and who had received at least 1 additional immunosuppressive agent received infliximab (n=21) or etanercept (n=9). Five patients who were initially treated with etanercept were switched to infliximab. After a median follow-up of 28 months (range, 2 to 84 months), infliximab therapy (median dose 5 mg/kg IV (range, 4 to 10 mg/kg) every 6 weeks (range, 4 to 8 weeks)) resulted in remission (primary endpoint) in 18 patients (complete remission, n=12; partial

remission, n=6). In patients who received either etanercept or infliximab, the median prednisone dose was 19 mg (range, 5 to 50 mg) prior to therapy compared with 0 mg (range, 0 to 30 mg) after therapy; 60% of patients were able to completely discontinue prednisone. Relapse occurred in 12 of the 18 patients who initially achieved remission with infliximab; 6 patients required an increase in the dose of infliximab, and steroid therapy was added in 4 patients. Adverse events that required discontinuation of infliximab therapy included abnormal liver function tests (n=1), primary histoplasmosis in a patient who traveled to an endemic region (n=1), and breast cancer (n=1).

Support for uveitis can be found In the Expert Panel Recommendation for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. A committee of the American Uveitis Society performed a systematic review of literature to generate guidelines for use of these agents in ocular inflammatory conditions. A systematic review of published studies was performed. Recommendations were generated using the Grading of Recommendations Assessment, Development, and Evaluation group criteria. Based on these studies, the expert panel recommends infliximab and adalimumab can be considered as potential second-line immunomodulatory agents for the treatment of severe ocular inflammatory conditions including posterior uveitis, panuveitis, severe uveitis associated with seronegative spondyloarthropathy, and scleritis in patients requiring immunomodulation in patients who have failed or who are not candidates for antimetabolite or calcineurin inhibitor immunomodulation. Infliximab and adalimumab can be considered in these patients in preference to etanercept, which seems to be associated with lower rates of treatment success.

Support for acute graft versus host disease (GVHD) can be found in the National Comprehensive Cancer Network's guideline for hematopoietic cell transplantation. The NCCN Guideline for hematopoietic cell transplantation supports the use of infliximab in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options. Therapy for steroid-refractory acute GVHD is often used in conjunction with the original immunosuppressive agent.

Support for using infliximab to manage immune checkpoint inhibitor-related toxicity can be found in the National Comprehensive Cancer Network's guideline for the management of immunotherapy-related toxicities. The NCCN Guideline for the management of immunotherapy-related toxicities supports the use of adding infliximab for the management of the following immunotherapy- related conditions:

- Myocarditis, as a further intervention if no improvement within 24 to 48 hours of starting high-dose methylprednisolone
- Mild (G1) diarrhea or colitis if persistent or progressive symptoms and positive lactoferrin/calprotectin
- Moderate (G2) and strongly consider for severe (G3-4) diarrhea or colitis
- Moderate or severe inflammatory arthritis as additional disease modifying antirheumatic drug (DMARD) therapy if no improvement after holding immunotherapy and treating with oral corticosteroids or if unable to taper corticosteroids, or no response to conventional synthetic DMARDs
- G1-4 uveitis that is refractory to high-dose systemic corticosteroids
- Moderate (G2) pneumonitis if no improvement after 48-72 hours of corticosteroids or severe (G3-4) pneumonitis if no improvement after 48 hours of methylprednisolone
- Stage 3 acute kidney injury/elevated serum creatinine if toxicity remains more than stage 2 after four to six weeks of corticosteroids or if creatinine increases during steroid taper (once off steroids)

Support for the use of infliximab to treat multisystem inflammatory syndrome in children (MIS-C) can be found in the COVID-19 Treatment Guidelines Panel: Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health (NIH). In pediatric patients hospitalized with multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 (COVID19), initial first line treatment is IV immune globulin with low to moderate dose glucocorticoids, such as methylprednisolone (recommendation rating, A; evidence rating, based on nonrandomized trials or observation

cohort studies) and should be used in most patients (level of consensus, moderate). The risks versus benefits of treating immunocompromised MIS-C patients with immunomodulatory agents should be evaluated on an individual basis.

If MIS-C is refractory (no improvement within 24 hours of IV immune globulin and steroid initiation), initiate intensification immunomodulatory therapy (recommendation rating, A; evidence rating, expert opinion) (level of consensus, moderate) with higher-dose glucocorticoids, anakinra, or infliximab (recommendation rating, B; evidence rating, based on nonrandomized trials or observation cohort studies) (level of consensus, moderate). Infliximab should not be used in patients with MIS-C and features of macrophage activation syndrome (MAS) (level of consensus, moderate).

Severe illness may warrant dual therapy with higher-dose glucocorticoids plus anakinra (recommendation rating, B; evidence rating, expert opinion), or higher-dose glucocorticoids plus infliximab (recommendation rating, B; evidence rating, expert opinion). Anakinra and infliximab should not be given in combination.

Infliximab can be considered in patients with contraindications to long-term use of glucocorticoids (level of consensus, moderate). The effects of infliximab likely persist for weeks, which may provide a steroid-sparing effect.

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Reference number(s)
6106-A

Standard Medicare Part B Management
Izervay

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Izervay	avancincaptad pegol

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

Izervay is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Chart notes or medical records confirming the diagnosis of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

Exclusions

Coverage will not be provided for the treatment of geographic atrophy (GA) secondary to a condition other than age-related macular degeneration (AMD) (such as Stargardt disease, cone rod dystrophy, toxic maculopathies).

Coverage Criteria

Geographic Atrophy (GA) Secondary to Age-related Macular Degeneration[1,2]

Authorization of 12 months may be granted for treatment of geographic atrophy secondary to age-related macular degeneration.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member demonstrated a positive clinical response to therapy (e.g., improvement or maintenance in best corrected visual acuity [BCVA] or vision field, or a reduction in the rate of vision decline or the risk of more severe vision loss).

Summary of Evidence

The contents of this criteria were created after examining the following resources:

- The prescribing information for Izervay.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Age-Related Macular Degeneration Preferred Practice Pattern 2019.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Izervay are covered.

Reference number(s)
6106-A

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

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Reference number(s)
6146-A

Standard Medicare Part B Management Jesduvroq

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Jesduvroq	daprodustat

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indication[1]

Jesduvroq is indicated for the treatment of anemia due to chronic kidney disease (CKD) in adults who have been receiving dialysis for at least four months.

Limitations of Use

- Jesduvroq has not been shown to improve quality of life, fatigue, or patient well-being.
- Jesduvroq is not indicated for use:
  - As a substitute for red blood cell transfusions in patients who require immediate correction of anemia.
  - For treatment of anemia of chronic kidney disease in patients who are not on dialysis.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Note: Requirements regarding pretreatment hemoglobin level exclude values due to a recent transfusion.

Anemia due to Chronic Kidney Disease (CKD)[1-2]

Authorization of 12 weeks may be granted for the treatment of anemia due to chronic kidney disease in adult members receiving dialysis for at least 4 months with a pretreatment hemoglobin of less than or equal to 11 grams per deciliter (g/dL).

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 weeks may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Jesduvroq.
- Jesduvroq is being used to treat anemia due to chronic kidney disease (CKD) in adult members receiving dialysis.[3]
- Jesduvroq has been effective for treating the diagnosis or condition.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Jesduvroq.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service-Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Jesduvroq are covered.

Explanation of Rationale

Support for FDA-approved indications (anemia due to chronic kidney disease) can be found in the manufacturer's prescribing information.

References

1. Jesduvroq [package insert]. Durham, NC: GlaxoSmithKline; August 2023.
2. Singh AK, Carroll K, Perkovic V, et al. Daprodustat for the Treatment of Anemia in Patients Undergoing Dialysis. N Engl J Med. 2021;385(25):2325-2335.

Reference number(s)
6559-A

Standard Medicare Part B Management Kisunla

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Kisunla	donanemab-azbt

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Kisunla is indicated for the treatment of Alzheimer's disease. Treatment with Kisunla should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in the clinical trials.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Initial Requests

- Medical records (e.g., chart notes) documenting the following:
  - Diagnosis of mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease.
- Presence of amyloid pathology documented by either of the following:

    - Baseline positron emission tomography (PET) scan
    - Lumbar puncture results
- Clinician and member participation in a CMS-approved Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease CED Study Registry via CMS-facilitated portal.

Continuation Requests

- Continued clinician and member participation in a CMS-approved Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease CED Study Registry via CMS-facilitated portal.

Prescriber Specialties

This medication must be prescribed by or in consultation with a physician and/or clinical team who is participating in a CMS-approved Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease CED Study Registry via CMS-facilitated portal.

Coverage Criteria

Alzheimer's Disease[1-4,7,A]

Authorization of 7 months may be granted for treatment of Alzheimer's disease (AD) when all of the following criteria are met:

- Member must have mild cognitive impairment due to AD or mild AD dementia.
- Member must meet one of the following criteria:
    - Have a positron emission tomography (PET) scan confirming the presence of amyloid pathology.
    - Have results from a lumbar puncture confirming at least one of the following detected in cerebrospinal fluid (CSF) as determined by the lab assay:
        - Presence of elevated phosphorylated tau (P-tau) protein and/or elevated total tau (T-tau) protein, and reduced beta-amyloid-42 (AB42)
        - Low AB42/AB40 ratio
        - Elevated P-Tau/AB42 ratio
        - Elevated T-Tau/AB42 ratio
- Member must currently be participating in a CMS-approved Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease CED Study Registry with an appropriate clinical team and follow-up care via CMS-facilitated portal.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Kisunla.
- Kisunla is being used to treat an indication listed in the coverage criteria section.
- The member continues to participate in a CMS-approved Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease CED Study Registry with an appropriate clinical team and follow-up care via CMS-facilitated portal.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Kisunla.
- The available compendium
  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)
  - Lexi-Drugs
- National Coverage Determination (NCD) for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Kisunla are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Using Kisunla to treat mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease (AD) dementia is covered according to the conditions outlined in National Coverage Determination Manual section 200.3- Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease. Monoclonal antibodies directed against amyloid that are approved by the FDA for the treatment of AD based upon evidence of efficacy from a direct measure of clinical benefit may be covered in CMS-approved prospective comparative studies. Study data for CMS-approved prospective comparative studies may be collected in a registry. The information collected on the portal include the following:

- Individuals' clinical diagnosis (mild cognitive impairment or mild Alzheimer's disease dementia).
- Whether the individual is taking any anticoagulation or antiplatelet drugs.
- Results of the individual's amyloid positron emission tomography (PET) scan, cerebrospinal fluid (CSF) test, or other amyloid test.
- Specific anti-amyloid monoclonal antibody being administered.
- Whether there is evidence of adverse events such as brain swelling or hemorrhage referred to as ARIA-E or ARIAH-H.
- Results of tests of cognition and overall function that were used to diagnose and treat the individual with mild cognitive impairment or mild Alzheimer's disease dementia.

Support for using a lumbar puncture to confirm amyloid pathology in cerebrospinal fluid can be found in an article published by Schindler et al. Decreases in cerebrospinal fluid (CSF) Aβ42 levels and increases in CSF total Tau (tTau) and phosphorylated Tau-181 (pTau) may be the earliest markers of AD brain pathology. The ratio of Aβ42 with another AD biomarker (e.g. tTau/Aβ42, pTau/Aβ42, or Aβ42/Aβ40) may provide the best correlation with amyloid PET measures.

References

1. Kisunla [package insert]. Indianapolis, IN: Eli Lilly and Company; July 2024.
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4. Schindler SE, Gray JD, Gordon BA, et al. Cerebrospinal fluid biomarkers measured by Elecsys assays compared to amyloid imaging. Alzheimers Dement. 2018;14(11):1460-1469.
5. Centers for Medicare and Medicaid Services. Fact Sheet. June 22, 2023. Accessed July 8, 2024. https://www.cms.gov/files/document/fact-sheet-june-2023.pdf
6. Elecsys Phospho-Tau (181P) CSF 2022-12.

Internal References

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Reference number(s)
5788-A

Standard Medicare Part B Management Lamzede

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Lamzede	velmanase alfa-tycv

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Lamzede is indicated for the treatment of non-central nervous system manifestations of alpha-mannosidosis in adult and pediatric patients.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- Initial requests: alpha-mannosidase enzyme assay or genetic testing results supporting the diagnosis.
- Continuation of therapy requests: documentation (e.g., chart notes, lab results) of a response to therapy (e.g., improvement in 3-minute stair climbing test [3MSCT] from baseline, improvement in 6-minute walking test [6MWT] from baseline, improvement in forced vital capacity [FVC, % predicted] from baseline, reduction in serum or urine oligosaccharide concentration from baseline).

Reference number(s)
5788-A

Coverage Criteria

Alpha-mannosidosis[1-3]

Authorization of 12 months may be granted for treatment of non-central nervous system manifestations of alpha-mannosidosis when the diagnosis is confirmed by either of the following:

- A documented deficiency of alpha-mannosidase activity on enzyme assay, or
- Genetic testing results documenting pathogenic variant(s) in the MAN2B1 gene.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy (e.g., improvement in 3-minute stair climbing test [3MSCT] from baseline, improvement in 6-minute walking test [6MWT] from baseline, improvement in forced vital capacity [FVC, % predicted] from baseline, reduction in serum or urine oligosaccharide concentration from baseline).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Lamzede.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Presentation of a diagnostic algorithm from an international working group.
- Alpha-Mannosidosis – Gene Reviews.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Lamzede are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for use of genetic testing to confirm a diagnosis of alpha-mannosidosis can be found in a consensus statement from an international working group of experts. In Molecular Genetics and Metabolism, the diagnostic algorithm indicates that screening for alpha-mannosidosis is done by urine (less frequently serum) analysis of mannose-rich oligosaccharides and is often the first assay in the diagnostic path. Direct demonstration of low activity of acid alpha-mannosidase in blood leukocytes or cultured skin fibroblasts is considered to be the most reliable and diagnostic next step. Genetic analysis of MAN2B1 gene should be used to confirm the enzymatic diagnosis and may be used for prenatal diagnosis and genetic counselling of family members, but it should not replace biochemical testing.

References

1. Lamzede [package insert]. Cary, NC: Chiesi USA Inc.; February 2023.
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Reference number(s)
5735-A

Standard Medicare Part B Management Leqembi

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Leqembi	lecanemab-irmb

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Leqembi is indicated for the treatment of Alzheimer's disease. 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.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Initial Requests:

- Medical records (e.g., chart notes) documenting the following:
  - Diagnosis of mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease.
- Presence of amyloid pathology documented by either of the following:

  - Baseline positron emission tomography (PET) scan
  - Lumbar puncture results
- Clinician and member participation in a CMS-approved Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease CED Study Registry via CMS-facilitated portal.

Continuation requests:

Continued clinician and member participation in a CMS-approved Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease CED Study Registry via CMS-facilitated portal.

Prescriber Specialties

This medication must be prescribed by or in consultation with a physician and/or clinical team who is participating in a CMS-approved Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease CED Study Registry via CMS-facilitated portal.

Coverage Criteria

Alzheimer's Disease

Authorization of 7 months may be granted for treatment of Alzheimer's disease (AD) when all of the following criteria are met:

- Member must have mild cognitive impairment due to AD or mild AD dementia.
- Member must meet one of the following criteria:
  - Have a positron emission tomography (PET) scan confirming the presence of amyloid pathology.
  - Have results from a lumbar puncture confirming at least one of the following detected in cerebrospinal fluid (CSF) as determined by the lab assay:
    - Presence of elevated phosphorylated tau (P-tau) protein and/or elevated total tau (T-tau) protein, and reduced beta-amyloid-42 (AB42)
    - Low AB42/AB40 ratio
    - Elevated P-Tau/AB42 ratio
    - Elevated T-Tau/AB42 ratio
- Member must currently be participating in a CMS-approved Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease CED Study Registry with an appropriate clinical team and follow-up care via CMS-facilitated portal.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Leqembi.
- Leqembi is being used to treat an indication listed in the coverage criteria section.
- The member continues to participate in a CMS-approved Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease CED Study Registry with an appropriate clinical team and follow-up care via CMS-facilitated portal.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Leqembi.
- The available compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
- National Coverage Determination (NCD) for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Leqembi are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Using Leqembi to treat mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease (AD) dementia is covered according to the conditions outlined in National Coverage Determination Manual section 200.3- Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease. Monoclonal antibodies directed against amyloid that are approved by the FDA for the treatment of AD based upon evidence of efficacy from a direct measure of clinical benefit may be covered in CMS-approved prospective comparative studies. Study data for CMS-approved prospective comparative studies may be collected in a registry. The information collected on the portal include the following:

- Individuals' clinical diagnosis (mild cognitive impairment or mild Alzheimer's disease dementia).
- Whether the individual is taking any anticoagulation or antiplatelet drugs.
- Results of the individual's amyloid positron emission tomography (PET) scan, cerebrospinal fluid (CSF) test, or other amyloid test.
- Specific anti-amyloid monoclonal antibody being administered.

- Whether there is evidence of adverse events such as brain swelling or hemorrhage referred to as ARIA-E or ARIAH-H.
- Results of tests of cognition and overall function that were used to diagnose and treat the individual with mild cognitive impairment or mild Alzheimer's disease dementia.

Support for using a lumbar puncture to confirm amyloid pathology in cerebrospinal fluid can be found in an article published by Schindler et al. Decreases in cerebrospinal fluid (CSF) Aβ42 levels and increases in CSF total Tau (tTau) and phosphorylated Tau-181 (pTau) may be the earliest markers of AD brain pathology. The ratio of Aβ42 with another AD biomarker (e.g. tTau/Aβ42, pTau/Aβ42, or Aβ42/Aβ40) may provide the best correlation with amyloid PET measures.

References

1. Leqembi [package insert]. Nutley, NJ: Eisai Inc.; July 2023.
2. National Coverage Determination (NCD) for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD) (200.3 – Version 1). https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=375&ncdver=1 Accessed May 1, 2024.
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4. Schindler SE, Gray JD, Gordon BA, et al. Cerebrospinal fluid biomarkers measured by Elecsys assays compared to amyloid imaging. Alzheimers Dement. 2018;14(11):1460-1469.
5. Centers for Medicare and Medicaid Services. Fact Sheet. June 22, 2023. Accessed May 1, 2024. https://www.cms.gov/files/document/fact-sheet-june-2023.pdf
6. Elecsys Phospho-Tau (181P) CSF 2022-12.

Reference number(s)
5120-A

Standard Medicare Part B Management
Leqvio

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Leqvio	inclisiran

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Leqvio 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).

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Initial requests:

- With clinical atherosclerotic cardiovascular disease (ASCVD): Chart notes confirming clinical ASCVD or ASCVD event(s) (if applicable) (see Appendix A).
- Without ASCVD: Untreated (before any lipid lowering therapy) LDL-C level.

Both initial and continuation requests:

- LDL-C level must be dated within six months preceding the authorization request.
- If member has contraindication or intolerance to statins, chart notes or medical documentation confirming the contraindication or intolerance (see Appendix B).

Coverage Criteria

Primary Hyperlipidemia Including Heterozygous Familial Hypercholesterolemia (HeFH)[1-6,12]

Authorization of 12 months may be granted for treatment of primary hyperlipidemia when one of the following criteria is met:

- Member meets all of the following criteria:
  - Member has a history of clinical ASCVD (see Appendix A).
  - Member meets either of the following criteria:
    - Member has a current LDL-C level ≥ 70 mg/dL.
    - Member has a current LDL-C level ≥ 55 mg/dL and has multiple ASCVD events (see Appendix A) or high-risk conditions (e.g., 65 years of age or older, familial hypercholesterolemia, diabetes, chronic kidney disease, history of congestive heart failure).
  - Member meets either of the following criteria:
    - Member has received at least three months of treatment with a high-intensity statin. If the member is unable to tolerate a high-intensity statin dose, a moderate-intensity statin dose may be used.
    - Member has a contraindication or intolerance to statin therapy (see Appendix B).
  - Member will continue to receive concomitant statin therapy if no contraindication or intolerance (see Appendix B).
- Member meets all of the following criteria:
  - Member had an untreated (before any lipid-lowering therapy) LDL-C level ≥ 190 mg/dL in the absence of a secondary cause.
  - Member has a current LDL-C level ≥ 100 mg/dL.
  - Member meets either of the following criteria:
    - Member has received at least three months of treatment with a high-intensity statin. If the member is unable to tolerate a high-intensity statin dose, a moderate-intensity statin dose may be used.
    - Member has a contraindication or intolerance to statin therapy (see Appendix B).
  - Member will continue to receive concomitant statin therapy if no contraindication or intolerance (see Appendix B).

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Leqvio.
- Leqvio is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy. Benefit is defined as achieved or maintained an LDL-C reduction (e.g., LDL-C is now at goal, robust lowering of LDL-C).
- Member will continue to receive concomitant statin therapy if no contraindication or intolerance (see Appendix B).

Appendix

Appendix A. Clinical ASCVD[5-7,10,11]

- Acute coronary syndromes
- Myocardial infarction
- Stable or unstable angina
- Coronary or other arterial revascularization procedure (e.g., percutaneous coronary intervention [PCI], coronary artery bypass graft [CABG] surgery)
- Stroke of presumed atherosclerotic origin
- Transient ischemic attack (TIA)
- Non-cardiac peripheral arterial disease (PAD) of presumed atherosclerotic origin (e.g., carotid artery stenosis, lower extremity PAD)
- Obstructive coronary artery disease (defined as ≥ 50% stenosis on cardiac computed tomography angiogram or catheterization)
- Coronary Artery Calcium (CAC) Score ≥ 300

Appendix B. Contraindications to Statin Therapy[6,8,9]

- Score of 7 or higher on the Statin-Associated Muscle Symptom Clinical Index (SAMS-CI) and failed statin rechallenge
- Presence of statin-associated muscle symptoms with elevation in creatine kinase (CK) level > 3 times upper limit of normal (ULN)
- Statin-associated elevation in creatine kinase (CK) level ≥ 10 times ULN
- Active liver disease, including unexplained persistent elevations in hepatic transaminase levels (e.g., alanine transaminase [ALT] level ≥ 3 times ULN)
- Pregnancy or planned pregnancy
- Breastfeeding

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Leqvio.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Diagnosis and Treatment of Heterozygous Familial Hypercholesterolemia from the American Heart Association.
- National Lipid Association recommendations for patient-centered management of dyslipidemia.
- 2018 AHA/ACC guideline on the management of blood cholesterol: report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.
- 2022 American College of Cardiology Expert Consensus Decision Pathway on the Role of Nonstatin therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk.
- 2024 Cardiovascular disease and risk management: standards of care in diabetes from American Diabetes Association.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Leqvio and are included.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

In 3 large randomized studies, inclisiran significantly reduced LDL-C compared with placebo in patients who were on maximally tolerated statin doses but still required LDL-C lowering.

Support for using Leqvio in patients with heterozygous familial hypercholesterolemia is found in the package insert and the ORION-9 trial. The ORION-9 randomized trial (N=482) compared inclisiran with placebo in adults with heterozygous familial hypercholesterolemia and elevated LDL-C despite maximally tolerated doses of statin therapy with or without ezetimibe; patients receiving a PCSK9 monoclonal antibody were excluded. Patients were administered Leqvio as a subcutaneous injection on days 1, 90, 270 and 450. Patients had an LDL-C of at least 100 mg/dL (2.6 mmol/L). Mean percent change in LDL-C from baseline at day 510 was significantly greater with inclisiran compared with placebo (-39.7% vs +8.2%; difference, -47.9 percentage points; 95% CI, -53.5 to -42.3); mean absolute change in LDL-C levels was -59 versus +9.9 mg/dL (-1.5 vs +0.3 mmol/L). The time-averaged percent change in LDL-C between day 90 and day 540 was also significantly greater with inclisiran (-38.1% vs +6.2%; difference, -44.3 percentage points; 95% CI, -48.5 to -40.1); mean absolute change was -56.9 vs +5.8 mg/dL (-1.5 vs +0.1 mmol/L). The percent change in PCSK9 level from baseline at day 510 was significantly greater with inclisiran versus placebo (-60.7% vs +17.7%); mean absolute change was -282.6 vs +54.5 mcg/L. Additional significant reductions in percent change from baseline at day 510 were reported for total cholesterol (-26.1% vs +6.8%), apolipoprotein B (-34% vs +2.9%), and non-HDL-C (-36.1% vs +7.5%). An LDL-C goal of less than 100 mg/dL was achieved by 65.3% versus 8.8% for inclisiran versus placebo and an LDL-C goal of less

than 70 mg/dL was achieved by 40.8% with inclisiran versus 1.3% with placebo. Among 432 patients who had genetic testing, 80.8% had single LDLR variant, 5.3% had APOB variants, and 8.6% had a variant in LDLR and either APOB or PCSK9. Patients with LDLR variants had the highest mean baseline LDL-C level (160.8 mg/dL [4.2 mmol/L]). There were significant differences in mean percent change in LDL-C with inclisiran versus placebo from baseline at day 510 in patients with LDLR pathogenic variants (n=231; difference, -46 percentage points), LDLR probably pathogenic variants (n=17; difference, -48.3 percentage points), LDLR variants of uncertain significance (n=8; difference, -42.3 percentage points), APOB variants (n=23; difference, -52.1 percentage points), 2 variants (n=37; difference, -41.2 percentage points), no variants (n=115; difference, -59.2 percentage points), and no genetic testing (n=50; difference, -46.8 percentage points). There were no significant differences between inclisiran and placebo in the incidence of adverse events (76.8% vs 71.7%), but serious adverse events were significantly less frequent with inclisiran (7.5% vs 13.8%). Injection site reactions were more frequent with inclisiran (17% vs 1.7%) but were mostly mild.

The ORION-10 randomized trial (N=1561) compared inclisiran with placebo in adults with atherosclerotic cardiovascular disease (ASCVD) and elevated LDL-C despite maximally tolerated doses of statin therapy with or without additional lipid-lowering therapy; patients receiving a PCSK9 monoclonal antibody were excluded. Patients had an LDL-C of at least 70 mg/dL (1.8 mmol/L). Inclisiran 284 mg was administered as a 1.5-mL subcutaneous injection on days 1, 90, 270, and 450. Mean percent change in LDL-C from baseline at day 510 was significantly greater with inclisiran compared with placebo (-51.3% vs +1%; difference, -52.3 percentage points; 95% CI, -55.7 to -48.8); mean absolute change was -56.2 versus -2.1 mg/dL (-1.45 vs -0.05 mmol/L). The time-adjusted percent change in LDL-C between day 90 and day 540 was also significantly greater with inclisiran (-51.3% vs +2.5%; difference, -53.8 percentage points; 95% CI, -56.2 to -51.3); mean absolute change was -53.7 vs -0.4 mg/dL (-1.39 vs -0.01 mmol/L). The percent change in PCSK9 levels from baseline at day 510 was significantly greater with inclisiran versus placebo (-69.8% vs +13.5%). Additional significant reductions in percent change from baseline at day 510 were reported for total cholesterol (-33.6% vs +0.4%), apolipoprotein B (-44.8% vs -1.7%), non-HDL-C (-47.4% vs -0.1%). LDL-C goals of less than 70 mg/dL and less than 100 mg/dL were achieved in 74.4% and 83.4% of inclisiran-treated patients compared with 15.3% and 49.6% of placebo-treated patients. There were no significant differences between inclisiran and placebo in the incidence of adverse events (73.5% vs 74.8%) or serious adverse events (22.4% vs 26.3%). Injection site reactions were more frequent with inclisiran (2.6% vs 0.9%) but were mostly mild.

The ORION-11 randomized trial (N=1617) compared inclisiran with placebo in adults with ASCVD (approximately 87.5%) or an ASCVD risk equivalent (type 2 diabetes, familial hypercholesterolemia, or 10-year risk of cardiovascular event of at least 20% on Framingham Risk Score). Patients had elevated LDL-C despite maximally tolerated doses of statin therapy with or without additional lipid-lowering therapy, and patients receiving a PCSK9 monoclonal antibody were excluded. Patients with ASCVD had an LDL-C of at least 70 mg/dL (1.8 mmol/L), and patients with an ASCVD risk equivalent had an LDL-C of at least 100 mg/dL (2.6 mmol/L). Inclisiran 284 mg was administered as a 1.5-mL subcutaneous injection on days 1, 90, 270, and 450. Mean percent change in LDL-C from baseline at day 510 was significantly greater with inclisiran compared with placebo (-45.8% vs +4%; difference, -49.9 percentage points; 95% CI, -53.1 to -46.6); mean absolute change was -50.9 versus +1 mg/dL (-1.32 vs +0.03 mmol/L). The time-adjusted percent change in LDL-C between day 90 and day 540 was also significantly greater with inclisiran (-45.8% vs +3.4%; difference, -49.2 percentage points; 95% CI, -51.6% to -46.8%); mean absolute change was -48.6 vs +0.3 mg/dL (-1.26 vs +0.01 mmol/L). The percent change in PCSK9 levels from baseline at day 510 was significantly greater with inclisiran versus placebo (-63.6% vs +15.6%). Additional significant reductions in percent change from baseline at day 510 were reported for total cholesterol (-28% vs +1.8%), apolipoprotein B (-38.2% vs +0.8%), and non-HDL-C (-41.2% vs +2.2%). LDL-C goals of less than 70 mg/dL and less than 100 mg/dL were achieved in 69.6% and 81.6% of inclisiran-treated patients compared with 12.9% and 52.7% of placebo-treated patients. There were no significant differences between inclisiran and placebo in the incidence of adverse events

(82.7% vs 81.5%) or serious adverse events (22.3% vs 22.5%). Injection site reactions were more frequent with inclisiran (4.7% vs 0.5%) but were mostly mild.

Support for the goal LDL-C to achieve with lipid-lowering therapy can be found in the expert consensus decision pathway on the role of nonstatin therapies published by the American College of Cardiology (ACC) and the standard of care in diabetes for cardiovascular disease (CVD) and risk management published by American Diabetes Association (ADA). According to ACC's report, patients with ASCVD are categoried into 2 groups: not at very high risk and at very high risk. LDL-C goal of ≤ 70 mg/dL is recommended for patients not at very high risk where ≤ 55 mg/dL is recommended for patients at very high risk. Very high-risk is defined as patients with a history of multiple ASCVD events or 1 major ASCVD event and multiple high-risk conditions. High-risk conditions defined by the report include: age 65 years or older, HeFH, history of prior coronary artery bypass surgery or percutaneous coronoary intervention outside of the makor ASCVD event(s), diabetes, hypertension, chronic kidney disease, current smoking, persistently elevated LDL-C despite on maximally tolerated statin therapy and ezetimibe, and history of congestive heart failure. In the CVD risk and management standards of care in diabetes from ADA, the ADA recommends LDL-C goal of < 55 mg/dL for patients with diabetes and ASCVD with a maximally tolerated statin, with the addition of ezetimibe or a PCSK9 inhibitor if this goal LDL-C is not achived. If patient is intolerant to statin therapy, PCSK9 inhibitor concomitant therapy with bempedoic acid or Leqvio as an alternative cholesterol-lowering therapy is recommended.

References

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Reference number(s)
4458-A

Standard Medicare Part B Management Leukine

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Leukine	sargramostim

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Acute Myeloid Leukemia Following Induction Chemotherapy

Leukine is indicated to shorten time to neutrophil recovery and to reduce the incidence of severe, life-threatening, or fatal infections following induction chemotherapy in adult patients 55 years and older with acute myeloid leukemia (AML).

Autologous Peripheral Blood Progenitor Cell Mobilization and Collection

Leukine is indicated 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 and Bone Marrow Transplantation

Leukine is indicated for acceleration of myeloid reconstitution following autologous peripheral blood progenitor cell (PBPC) or bone marrow transplantation in adult and pediatric patients 2 years of age and older with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) and Hodgkin's lymphoma (HL).

Allogeneic Bone Marrow Transplantation (BMT)

Leukine is indicated for the acceleration of myeloid reconstitution in adult and pediatric patients 2 years of age and older undergoing allogeneic BMT from human leukocyte antigens (HLA)-matched related donors.

Allogeneic or Autologous Bone Marrow Transplantation: Treatment of Delayed Neutrophil Recovery or Graft Failure

Leukine is indicated for the treatment of adult and pediatric patients 2 years and older who have undergone allogeneic or autologous BMT in whom neutrophil recovery is delayed or failed.

Acute Exposure to Myelosuppressive Doses of Radiation (H-ARS)

Leukine is indicated 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 [H-ARS]).

Compendial Uses

- Prophylaxis and treatment of chemotherapy-induced febrile neutropenia in non-myeloid malignancies
- Treatment of neutropenia and anemia in patients with myelodysplastic syndromes (MDS)
- Acute myeloid leukemia
- Agranulocytosis (non-chemotherapy drug induced)
- Aplastic anemia
- Neutropenia related to HIV/AIDS
- Stem cell transplantation-related indications
- Neuroblastoma
- Severe chronic neutropenia (congenital, cyclic, or idiopathic)
- Crohn's disease
- Malignant melanoma
- Pulmonary alveolar proteinosis
- Rhinocerebral mucormycosis
- Hepatitis B vaccination, response enhancement
- Metastatic renal cell carcinoma

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Primary Prophylaxis of Febrile Neutropenia

Documentation of the member's diagnosis and chemotherapeutic regimen.

Reference number(s)
4458-A

Coverage Criteria

Neutropenia in Cancer Patients Receiving Myelosuppressive Chemotherapy

Authorization of 6 months may be granted for prevention or treatment of febrile neutropenia when both of the following criteria are met:

- The member will not receive chemotherapy at the same time as they receive radiation therapy.
- One of the following criteria is met:
    - The requested medication will be used for primary prophylaxis or secondary prophylaxis of febrile neutropenia in members with solid tumors or non-myeloid malignancies.
    - The requested medication will be used for treatment of high-risk febrile neutropenia (FN) in members who have any of the following prognostic factors that are predictive of clinical deterioration:
        - Age greater than 65 years
        - Being hospitalized at the time of the development of fever
        - Sepsis syndrome
        - Invasive fungal infection
        - Pneumonia or other clinically documented infection
        - Prolonged (neutropenia expected to last greater than 10 days) or profound (absolute neutrophil count less than 0.1×10^9/L) neutropenia
        - Prior episodes of febrile neutropenia

Neuroblastoma

Authorization of 6 months may be granted for treatment of high-risk neuroblastoma when used with one of the following:

- Dinutuximab (Unituxin) and isotretinoin (13-cis-retinoic acid [RA])
- Temozolomide, irinotecan, and dinutuximab (Unituxin)
- Naxitamab-gqgk (Danyelza)

Malignant Melanoma

Authorization of 6 months may be granted for the treatment of malignant melanoma when used in either of the following settings:

- For metastatic melanoma in combination with temozolomide, interferon-alfa 2b, and interleukin-2.
- As adjuvant therapy in stage III or stage IV disease

Other Indications

Authorization of 6 months may be granted for members with any of the following indications:

- Myelodysplastic syndrome (anemia or neutropenia)
- Acute myeloid leukemia

- Agranulocytosis (non-chemotherapy drug induced)
- Aplastic anemia
- Neutropenia related to HIV/AIDS
- Stem cell transplantation-related indications
- Severe chronic neutropenia (congenital, cyclic, or idiopathic)
- Hematopoietic Syndrome of Acute Radiation Syndrome:
  Treatment for radiation-induced myelosuppression following a radiological/nuclear incident
- Moderately to severely active Crohn's disease
- Pulmonary alveolar proteinosis
- Rhinocerebral mucormycosis
- Hepatitis B vaccination response enhancement
- Renal cell carcinoma with pulmonary metastases when used with Interleukin-2 therapy

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 6 months may be granted for the treatment of renal cell carcinoma when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy. Benefit is defined as:
  - No evidence of unacceptable toxicity while on current regimen
  - No evidence of disease progression while on the current regimen.

Authorization of 6 months may be granted for the treatment of pulmonary alveolar proteinosis when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy.

For all other diagnoses, all members (including new members) requesting authorization for continuation of therapy must meet all requirements in the coverage criteria.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Leukine.
- The available compendium
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)
  - Lexi-Drugs

    - Clinical Pharmacology
- The prescribing information for Danyelza.
- NCCN Guideline: Hematopoietic growth factors
- NCCN Guideline: Acute myeloid leukemia
- NCCN Guideline: Neuroblastoma
- Recommendations for the use of white blood cell growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update.
- 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Leukine are covered in addition to the following:

- Prophylaxis and treatment of chemotherapy-induced febrile neutropenia in non-myeloid malignancies
- Treatment of neutropenia and anemia in patients with myelodysplastic syndromes (MDS)
- Acute myeloid leukemia
- Agranulocytosis (non-chemotherapy drug induced)
- Aplastic anemia
- Neutropenia related to HIV/AIDS
- Stem cell transplantation-related indications
- Neuroblastoma
- Severe chronic neutropenia (congenital, cyclic, or idiopathic)
- Crohn's disease
- Malignant melanoma
- Pulmonary alveolar proteinosis
- Rhinocerebral mucormycosis
- Hepatitis B vaccination, response enhancement
- Metastatic renal cell carcinoma

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Leukine prophylaxis and treatment of chemotherapy-induced febrile neutropenia in non-myeloid malignancies can be found in the National Comprehensive Cancer Network's guideline for Hematopoietic Growth Factors. The NCCN Guideline for Hematopoietic Growth Factors supports the use of Leukine for treatment of chemotherapy-induced febrile neutropenia in patients who have not received prophylactic granulocyte colony-stimulating factors but who have risk factors for an infection-associated complication.

Support for using Leukine to treat neutropenia and anemia in patients with MDS can be found in several studies listed in the American Hospital Formulary System Drug Information reference. Leukine has been used in an effort to increase leukocyte counts in some adults with myelodysplastic syndrome (MDS) classified as refractory anemia (RA), refractory anemia with excess blasts (RAEB), or refractory anemia with excess blasts in transformation (RAEB-T). While the drug has shown some promise for this use, further study is needed to evaluate the benefits and risks of biosynthetic GM-CSF therapy in patients with MDS, pending accumulation of such data, this use generally should be limited to protocol

conditions. MDS is a heterogeneous group of disorders and several factors (e.g., biologic characteristics of the leukemic clone, presence of an abnormal karyotype, or high initial leukemia burden) may result in considerable variation in response to sargramostim therapy. Use of sargramostim therapy in patients with MDS generally results in an increase in the absolute number of granulocytes and monocytes in most patients and an increase in the absolute number of eosinophils and lymphocytes in many patients. Although an increase in platelets and/or reticulocytes is evident in a few patients with MDS receiving sargramostim, platelet and reticulocyte counts are unaffected in most patients and the need for red blood cell transfusions generally is unchanged during therapy with the drug. Prolonged maintenance therapy with sargramostim appears necessary in patients with MDS since leukocyte counts return to pretreatment levels within 2–10 days after sargramostim is discontinued.Whether use of sargramostim in patients with MDS will alter (either increase or decrease) the rate of progression to AML or affect the usually fatal outcome of the disease is unclear and requires further study. The rate of progression to AML in untreated patients with MDS is approximately 10–20%, 40–50%, or 60–75% in those with RA, RAEB, or RAEB-T, respectively. There is concern, but no clear evidence indicated to date, that use of biosynthetic GM-CSFs may stimulate progression to AML in patients with MDS since in vitro evidence indicates that the drugs can stimulate the growth of myeloid leukemic blast cells and because an increase in the percentage of leukemic blasts in both bone marrow and peripheral blood has occurred in some patients with MDS receiving sargramostim. Although filgrastim (a biosynthetic G-CSF) also has been used in the treatment of MDS, the relative efficacy of these two hematologic growth factors has not been evaluated to date in controlled studies.

Support for using Leukine to treat acute myeloid leukemia can be found in the National Comprehensive Cancer Network's guideline for acute myeloid leukemia. The NCCN Guideline states there is no evidence for whether growth factors have a positive or negative impact on long-term outcome if used during consolidation. Growth factors may be considered as part of supportive care for postremission therapy. Growth factors are not routinely recommended in postremission therapy, except in life-threatening infections or when signs and symptoms of sepsis are present, and the leukemia is believed to be in remission.

Support for using Leukine to treat non-chemotherapy drug induced agranulocytosis can be found in a study by Rospond, Glowacki and Mailliard. Leukine has been used effectively in several patients to hasten recovery from sulfasalazine-associated agranulocytosis. A case report by Bjorkhom and colleagues found biosynthetic GM-CSFs can be used to treat methimazole-associated agranulocytosis in a patient with hyperthyroidism.

Support for using Leukine to treat aplastic anemia can be found several studies listed in the American Hospital Formulary Service Drug Information reference. Leukine has been used with some success in an effort to increase leukocyte counts in a limited number of adults and adolescents 15 years of age or older with moderate to severe aplastic anemia. Use of biosynthetic GM-CSFs such as Leukine in these patients resulted in an increase in ANCs that was sustained throughout the period of treatment and a transient increase in absolute eosinophil counts; most patients also had an increase in monocyte and lymphocyte counts. Erythrocyte and platelet counts and transfusion requirements generally were unaffected, although a few patients had increases in hemoglobin concentrations and/or platelet counts. Further study is needed to evaluate more fully use of sargramostim in aplastic anemia and to determine the optimum dosage and long-term safety and efficacy of the drug in these patients; pending accumulation of such data, this use generally should be limited to protocol conditions.

Support for using Leukine to treat neutropenia related to HIV/AIDS can be found several studies listed in the American Hospital Formulary Service Drug Information reference. Leukine has been used in patients with human immunodeficiency virus (HIV) infection in an effort to correct or minimize HIV-associated neutropenia and/or for the treatment of drug-induced neutropenia (e.g., neutropenia associated with use of zidovudine, interferon alfa, and/or cytotoxic chemotherapy) in HIV-infected patients. When used in patients with HIV infection, biosynthetic GM-CSFs effectively increase the number of neutrophils, monocytes, and eosinophils in most patients; however, the drugs appear

to have no consistent effect on the absolute number of lymphocytes nor on the ratio of helper/inducer ($CD4^+$, $T4^+$) to suppressor/cytotoxic ($CD8^+$, $T8^+$) T cells.

Support for using Leukine for stem cell transplantation-related indications can be found in the American Society of Clinical Oncology clinical practice guideline. The ASCO guideline supports using Leukine for mobilization and after transplantation of autologous PBPC and after autologous or allogenic bone marrow transplant. Leukine should be started on the day of the bone marrow transplant and continue until the absolute neutrophil count is greater than 1.5x10(9)/L for three consecutive days. Leukine should be discontinued early or the dose of Leukine should be reduced by 50% if the absolute neutrophil count increases to greater than 20x10(9)/L.

Support for using Leukine in combination with Danyelza to treat neuroblastoma can be found in the prescribing information for Danyelza. Danyelza is indicated, in combination with GM-CSF, for the treatment of pediatric patients 1 year of age and older and adult patients 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.

Support for using Leukine in combination with dinutuximab (Unituxin) and isotretinoin (13-cis-retinoic acid [RA]) or Leukine in combination with temozolomide, irinotecan, and dinutuximab (Unituxin) to treat high-risk neuroblastoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Leukine to treat severe chronic neutropenia (congenital, cyclic, or idiopathic) can be found in several studies listed in the American Hospital Formulary Service Drug Information reference. Sargramostim has been used with variable success in an effort to increase neutrophil counts in patients with various primary neutropenias, including congenital neutropenia, acquired idiopathic neutropenia, and glycogen storage disease type Ib. In addition, another biosynthetic GM-CSF, molgramostim, has been used with some success in patients with congenital neutropenia, cyclic neutropenia, acquired idiopathic neutropenia, or autoimmune neutropenia. While biosynthetic GM-CSFs may ameliorate the underlying neutropenia in certain patients with these conditions, this effect is unpredictable and not all patients with primary neutropenias respond to the drugs. Filgrastim (a biosynthetic G-CSF) has effectively increased neutrophil counts in some patients with severe congenital neutropenia, chronic idiopathic neutropenia, or cyclic neutropenia who did not respond to sargramostim therapy. In addition, it has been suggested that filgrastim may be more effective than sargramostim or other biosynthetic GM-CSFs in the treatment of primary neutropenia since filgrastim therapy results in more consistent increases in the neutrophil count and does not cause eosinophilia. In a study in children 1–19 years of age with severe congenital neutropenia (Kostmann syndrome), sargramostim therapy resulted in an increase in the absolute granulocyte count in all patients. However, an increase in the ANC occurred in only one patient; in most patients, the increase in granulocytes during sargramostim therapy resulted from an increase in eosinophils or monocytes rather than neutrophils. When sargramostim was used in a few patients with glycogen storage disease type Ib, neutrophil counts increased during therapy with the drug and there was a decrease in inflammatory bowel symptoms. Use of sargramostim in a patient with idiopathic neutropenia also resulted in an increase in the neutrophil count.

Support for using Leukine to treat Crohn's disease can be found in a study by Korzenik and colleagues. Korzenik et al conducted a multicenter, randomized, placebo-controlled trial of 124 patients with Crohn's disease that concluded Leukine improved clinical response and remission when compared to placebo; however, the primary study endpoint was not met. Patients with moderate to severe active Crohn disease (defined as a score of 220 to 475 on the Crohn Disease Activity Index (CDAI)) and no prior history of sargramostim or filgrastim use were eligible for enrollment. Thirty-five percent of patients who were on stable doses of antibiotics and/or aminosalicylates for at least 4 weeks were included

in the study; however, use of azathioprine, mercaptopurine, methotrexate, or oral or rectal glucocorticoids within 4 weeks or antitumor necrosis factor therapy within 12 weeks of study treatment was not permitted. Patients were randomized (2:1) to receive either sargramostim 6 micrograms/kilogram (mcg/kg) (n=81; median age, 36 years (yr); median CDAI score, 300) or placebo (n=43; median age, 41 yr; median CDAI score, 300) subcutaneously once daily for 56 days. Most patients in this study had previously received glucocorticoids (90%) and/or immunosuppressive medications (69%). At day 57, the primary endpoint of a clinical response defined as a CDAI score decrease of at least 70 points from baseline was not significantly different between the 2 study arms (sargramostim arm, 54%; placebo arm, 44%; p=0.28). However, significantly more patients treated with sargramostim compared to placebo achieved the predefined secondary endpoints of clinical response defined as a CDAI score decrease of at least 100 points from baseline (48% versus (vs) 26%; p=0.01), remission at day 57 (defined as a CDAI score of 150 or less) (40% vs 19%; p=0.01), and improved quality of life (defined as an increase in the Inflammatory Bowel Disease Questionnaire (IBDQ) score from baseline) (28 vs 16 points; p=0.04) at day 57. Additionally, the median CDAI score was significantly lower at day 57 in the sargramostim-treated patients than in the placebo-treated patients (184 vs 240; p=0.02). At 30 days following treatment, evaluable patients who received sargramostim (n=53) had higher clinical response and remission rates compared to patients who received placebo (n=30) (CDAI score decrease of at least 70, 48% vs 28%; p=0.03; CDAI score decrease of at least 100, 42% vs 21%; p=0.02; remission, 33% vs 14%, p=0.02). Adverse events which occurred significantly (p less than 0.001) more often in the sargramostim arm compared to the placebo arm were injection-site reactions (90% vs 12%) and bone pain (37% vs 7%). Serious adverse events possibly related to sargramostim therapy occurred in 3 patients and included migraine; anorexia, weakness and lethargy; and right-sided weakness consistent with a demyelinating event.

Support for using Leukine to treat malignant melanoma can be found in a study by Spitler et al. In an open-label, multicenter, phase II trial, granulocyte-macrophage colony-stimulating factor (GM-CSF) may be a useful adjuvant therapy to prolong survival in patients with stage III or IV malignant melanoma. Patients who were clinically disease-free as a result of surgical resection of nodal or metastatic disease (n=48) were administered multiple 28-day cycles of subcutaneous GM-CSF 125 micrograms/square meter once daily for 14 days followed by 14 days of rest. Median treatment duration was 11.5 cycles (range 2 to 49). The response of these patients was compared to historical controls matched for age, sex, and the number of positive nodes in stage III patients, and the presence of visceral or nonvisceral metastases and site of metastasis in stage IV patients. Overall median survival was significantly longer in patients who received GM-CSF as compared to the historical controls (37.5 months and 12.2 months; p less than 0.001) with 1-year survival rates of 89% and 45% (p less than 0.001) and 2-year survival rates of 64% and 15% (p less than 0.001), respectively. These rates remained significant when patients were stratified according to stage III or IV disease. Overall disease-free survival was also significantly prolonged in the GM-CSF group (p=0.03), although there was no difference between groups when stratified by stage of disease. Adverse events included transient myalgias, weakness, mild fatigue, rash, and mild erythema at injection siteSupport for using Leukine to treat pulmonary alveolar proteinosis can be found in a prospective, open-label study by Venkateshiah et al. Leukine therapy demonstrated good activity for the treatment of PAP. Patients (N=25; median age, 45 years; range, 21 to 57 years) with moderate disease were eligible for enrollment. Patients with a history of 2 or more lavages in the previous 4 months could also participate in the study at 3 months following their last whole-lung lavage (WLL) for a severe PAP exacerbation (n=21). Treatment consisted of Leukine 250 mcg/day subQ for the first month, 5 mcg/kg/day for the second month, and 9 mcg/kg/day for the third month. The Leukine dose could be increased to 12 mcg/kg/day at month 3, 15 mcg/kg/day at month 4, and 18 mcg/kg/day at month 5 if the patient was tolerating therapy but the response was suboptimal. When an adequate response was achieved, therapy could be continued for 3 to 12 months. At a mean follow-up of 39 +/- 17.3 months, 12 patients (48%) had an improvement in oxygenation with a 10 or greater mmHg decrease in the room air alveolar-arterial oxygen gradient (P(A-a)O2) (primary endpoint), with 8 patients not requiring WLL or home oxygen. Responders had significantly higher changes of PaO2, P(A-a)O2, diffusing capacity, total lung capacity, and 6-minute walk distance compared to patients who

did not respond to Leukine therapy. At 6 months, the responders also had significantly improved quality of life scores (assessed by the Short Form-36 questionnaire) from baseline compared to non-responders for all measures except bodily pain. Common adverse effects with Leukine therapy included injection-site reactions (redness (n=18), itching (n=11), swelling (n=12)), shortness of breath (n=10), and fatigue (n=7).

Support for using Leukine to treat rhinocerebral mucormycosis in a case series by Garcia-Diaz, Palau and Pankey. Three patients with non-neutropenic rhinocerebral zygomycosis were successfully treated with the addition of granulocyte-macrophage colony-stimulating factor (GM-CSF) to traditional surgical and medical treatment. A 51-year-old woman with diabetes and bronchial asthma requiring steroid therapy developed sinusitis with left- sided face pain, periorbital swelling, erythema, and blurred vision; her left pupil was dilated and unresponsive to light, and she had a black nasal discharge. She received amphotericin B and an intranasal ethmoidectomy and medial maxillectomy; cultures showed Rhizopus species. The disease worsened with extensive bony sequestrum of the left maxilla and palate which was treated surgically. GM-CSF was added (total 4500 mcg), and the patient recovered with no recurrence in 4 years of follow-up. A 65-year-old man with diabetes and asthmatic bronchitis requiring steroid therapy developed right-sided maxillary pain and was found to have osteomyelitis. Histopathology of the maxillary bone was compatible with zygomycosis. He received amphotericin B but the disease progressed requiring debridement and right medial maxillectomy. His creatinine level increased; he received amphotericin B lipid complex (ABLC) and GM-CSF (425 mcg/day SC) and recovered with no recurrence with 3 years of follow-up. A 52-year-old woman with diabetes in ketoacidosis developed right eye pain and was found to have pansinusitis. She underwent right ethmoidectomy and removal of mucous membranes from right ethmoid and maxillary sinuses. Histology was consistent with zygomycosis. She received ABLC and GM-CSF 250 mcg/day SC but developed osteomyelitis of the right orbit requiring inferior orbitotomy. Histology was again consistent with zygomycosis. Treatment with ABLC and GM-CSF (total 45,000 micrograms) was discontinued approximately 5 months later as the patient was asymptomatic and biopsy showed no fungal elements; there was no recurrence in 2 years of follow-up.

Support for using Leukine for response enhancement following hepatitis B vaccination can be found in a study by Anandh, Bastani and Ballal. In chronic hemodialysis patients, granulocyte-macrophage colony-stimulating factor (GM-CSF) as adjuvant therapy resulted in enhanced seroconversion after hepatitis B vaccinations. In a randomized study (n=28), patients who received GM-CSF 4-5 micrograms per kilogram (mcg/kg) 24 hours before the first dose of their initial series of 3 hepatitis B vaccinations (40 mcg each) had significantly higher antibody titers, and the seroconversion rate (5 of 6 patients) was higher than those randomized to receive vaccine alone (2 of 6). Another group of patients who had failed to seroconvert after their primary series were randomized to receive or not receive GM-CSF 24 hours before a booster dose of 40 mcg of vaccine. Significantly (p less than 0.02) more patients seroconverted after receiving GM-CSF before their booster (7 of 8) than those receiving booster alone (2 of 8) and antibody titers were significantly higher (p less than 0.05) in those who received GM-CSF. Side effects were few and minor. The GM-CSF product used in this study was not mentioned.

Support for using Leukine to treat metastatic renal cell carcinoma can be found in a study by Hotton et al. Treatment with a combination of interleukin-2 (IL-2) and granulocyte-macrophage colony-stimulating factor (GM-CSF) did not produce total tumor burden shrinkage of 50% or greater, or pulmonary metastases reduction of 50% or greater, in any of the 14 evaluable patients with renal cell carcinoma and pulmonary metastases in a phase Ib/II trial. Median survival had not been reached at time of publication; 6 of 16 patients died during approximately 14 months of follow-up. Six patients with prior nephrectomy and 10 patients without prior nephrectomy were enrolled. The study was discontinued when a 60-year-old woman with a history of polycythemia vera developed a grade 4 thrombocytopenia and multiple cerebral hemorrhages and died. Postmortem examination revealed acute multifocal cerebral venous thrombosis, hemorrhagic venous infarcts, subdural and subarachnoid hemorrhage, and thrombosis of the superior vena cava and renal veins. Other toxicities included transient lymphopenia, eosinophilia, and elevated prothrombin times in 2 patients

on warfarin therapy. Interleukin-2 was administered as a 96-hour continuous intravenous infusion on Days 1 through 4, days 8 through 11, and days 15 through 18 at a dose of 4.5 X 10(6) International Units/m(2) per day (27 of 31 total courses). GM-CSF was administered subcutaneously on days 8 through 19 at a dose of 1.25 mg/kg/day (12 of 31 courses) and 2.5 mg/kg/day (18 of 31 courses). There was a 14- to 19-day rest period between courses. The authors advise extreme caution with particular attention to early evidence of neurotoxicity in any further trials combining IL-2 and GM-CSF.

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Reference number(s)
4212-A

Standard Medicare Part B Management levoleucovorin-Fusilev-Khapzory

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name	Dosage Form
Fusilev	levoleucovorin	powder/solution
Khapzory	levoleucovorin	powder

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

- Levoleucovorin/Fusilev/Khapzory is indicated for rescue after high-dose methotrexate therapy in osteosarcoma.
- Levoleucovorin/Fusilev/Khapzory is indicated for diminishing the toxicity associated with overdosage of folic acid antagonists or impaired methotrexate elimination in adult and pediatric patients.
- Levoleucovorin/Fusilev/Khapzory is indicated for the treatment of adults with metastatic colorectal cancer in combination with fluorouracil.

Compendial Uses

- Rescue treatment after high-dose methotrexate therapy
- Combination with fluorouracil-based chemotherapy regimens

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Reference number(s)
4212-A

Coverage Criteria

Authorization of 12 months may be granted for any of the settings listed below when leucovorin is not an appropriate/available option at this time:

- Rescue treatment after high-dose methotrexate therapy
- Treatment of a folate antagonist overdose or impaired methotrexate elimination
- Combination therapy with fluorouracil-based chemotherapy regimens

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication listed in the coverage criteria section.
- Leucovorin is not an appropriate/available option at this time.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen and
    - No evidence of disease progression while on the current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Fusilev, Khapzory, and levoleucovorin.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Fusilev, Khapzory, and levoleucovorin are covered in addition to the following:

- Rescue treatment after high-dose methotrexate therapy
- Combination with fluorouracil-based chemotherapy regimens

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Fusilev, Khapzory, and levoleucovorin when leucovorin is not available can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

References

1. Fusilev [package insert]. East Windsor, NJ: Acrotech Biopharma LLC; November 2020.
2. Levoleucovorin injection [package insert]. Bridgewater, NJ:Amneal Pharmaceuticals LLC; April 2023.
3. Khapzory [package insert]. East Windsor, NJ: Acrotech Biopharma LLC; March 2024.
4. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed July 2, 2024.

Reference number(s)
6238-A

Standard Medicare Part B Management Loqtorzi

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Loqtorzi	toripalimab-tpzi

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

- Loqtorzi is indicated, in combination with cisplatin and gemcitabine, for first-line treatment of adults with metastatic or with recurrent locally advanced nasopharyngeal carcinoma (NPC).
- Loqtorzi is indicated, as a single agent, for the treatment of adults with recurrent unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy.

Compendial Uses[2]

Nasopharyngeal Carcinoma (NPC)

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Reference number(s)
6238-A

Coverage Criteria

Nasopharyngeal Carcinoma (NPC)[1,2]

Authorization of 12 months may be granted when either of the following criteria are met:

- The requested medication will be used in combination with cisplatin and gemcitabine for the treatment of unresectable, metastatic or recurrent locally advanced NPC.
- The requested medication will be used as a single agent for treatment of recurrent, unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months (for up to 24 months total when being used as first line therapy) may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat an indication listed in the coverage criteria section
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen, and
    - No evidence of disease progression while on the current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Loqtorzi.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Head and neck cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Loqtorzi are covered.

Reference number(s)
6238-A

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Loqtorzi [package insert]. Redwood City, CA: Coherus BioSciences, Inc; October 2023.
2. The NCCN Drugs & Biologics Compendium 2024 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed March 6, 2024.

Reference number(s)
2508-A

Standard Medicare Part B Management
Lucentis - Byooviz -Cimerli

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) OTC products are not included unless otherwise stated.

Brand Name	Generic Name
Lucentis	ranibizumab
Byooviz	ranibizumab-nuna
Cimerli	ranibizumab-eqrn

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1,3,4]

Lucentis, Byooviz and Cimerli are indicated for:

- Neovascular (wet) age-related macular degeneration
- Macular edema following retinal vein occlusion
- Myopic choroidal neovascularization

Lucentis and Cimerli are also indicated for:

- Diabetic macular edema
- Diabetic retinopathy

Compendial Uses[2]

Retinopathy of prematurity

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Reference number(s)
2508-A

Coverage Criteria

Neovascular (wet) age-related macular degeneration[1,3,4]

Authorization of 12 months may be granted for treatment of neovascular (wet) age-related macular degeneration.

Macular edema following retinal vein occlusion[1,3,4]

Authorization of 12 months may be granted for treatment of macular edema following retinal vein occlusion.

Diabetic macular edema[1,4]

Authorization of 12 months may be granted for the treatment of diabetic macular edema.

Diabetic retinopathy[1,4]

Authorization of 12 months may be granted for the treatment of diabetic retinopathy.

Myopic choroidal neovascularization[1,3,4]

Authorization of 12 months may be granted for the treatment of myopic choroidal neovascularization.

Retinopathy of prematurity[2]

Authorization of 12 months may be granted for the treatment of retinopathy of prematurity.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when ALL of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member demonstrated a positive clinical response to therapy (e.g., improvement or maintenance in best corrected visual acuity [BCVA] or vision field, or a reduction in the rate of vision decline or the risk of more severe vision loss).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Lucentis, Byooviz, and Cimerli
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Lucentis, Byooviz and Cimerli are covered in addition to retinopathy of prematurity.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for retinopathy of prematurity can be found in a retrospective single center study of 128 infants with Type 1 ROP and 18-month follow-up examinations found recurrence rates of 16.7% (1 of 6 patients) with intravitreal ranibizumab 0.25 mg and 8.3% (1 of 12 patients) with intravitreal bevacizumab 0.625 mg following initial regression within 48 hours in all patients who received either ranibizumab or bevacizumab. Recurrence was defined as recurrent plus or preplus disease or neovascularization, or progression of traction. In a third group of 36 patients who received LPC therapy, initial regression occurred in 1 to 2 weeks except in 5 patients who required retreatment with LPC at 10 days. Differences in the ranibizumab, bevacizumab, and LPC groups at baseline were found in birth weight (840, 841, and 1112 grams, respectively), number of patients with Stage 3 disease (16.7%, 16.7%, and 61.1%, respectively), APROP (83.3%, 83.3%, and 19.4%, respectively), and Zone II disease (66.7%, 83.3%, and 88.9%, respectively). A fourth group of 74 patients with spontaneously regressed ROP was included. The two patients who recurred after ranibizumab or bevacizumab therapy achieved successful regression following subsequent LPC therapy. Mean total vascularization time was significantly shorter with ranibizumab (61.8 weeks of PMA) compared with bevacizumab (73 weeks of PMA). Following LPC, one patient experienced exudative retinal detachment and nystagmus in both eyes and one patient had macular ectopia and nystagmus; no ocular complications were noted in other groups other than transient preretinal hemorrhages.

Ranibizumab compared with laser photocoagulation (LPC), did not demonstrate a significant difference for the primary outcome (composite of survival with no active retinopathy, no unfavorable structural outcomes, or need for a different treatment modality at 24 weeks; 80% vs 66%; OR, 2.19; 95% CI, 0.99 to 4.82) in the randomized RAINBOW trial in infants with retinopathy of prematurity (ROP; N=214). Included infants (median gestational age 26 weeks) had bilateral ROP zone I stage 1+, 2+, 3, or 3+, zone II stage 3+, or aggressive posterior ROP (AP-ROP). Infants with zone II stage 2+ were excluded. Treatment success (alive and without treatment switch and unfavorable structural outcome or active ROP at day 169) was not significantly different between groups; achieved in 80% with ranibizumab 0.2 mg, 75% with ranibizumab 0.1 mg, and 66% with laser therapy. In a post-hoc analysis accounting for potential confounders (gestational age, geographical region, and gender) the primary outcome was significant for ranibizumab 0.2 mg compared with laser (OR 2.32; 95% CI, 1.04 to 5.16). There was no significant between-group difference in the plasma vascular endothelial growth factor (VEGF) levels. There was 1 death associated with ranibizumab 0.1 mg or the procedure due to respiratory failure. Interventions included a single bilateral intravitreal dose of ranibizumab 0·2 mg, 0·1 mg, or laser therapy. The ranibizumab groups were permitted up to 2 additional treatments in each eye at a minimum of

28-day intervals and in the laser group supplementary treatment to skip lesions was allowed up to day 11. Additional treatments were needed in 31% with ranibizumab 0.2 mg , 31% with ranibizumab 0.1 mg, and 19% with laser therapy.

References

1. Lucentis [package insert]. South San Francisco, CA: Genentech, Inc.; February 2024.
2. Micromedex Solutions [database online]. Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com/. Accessed February 15, 2024.
3. Byooviz [package insert]. Cambridge, MA: Biogen, Inc.; October 2023.
4. Cimerli [package insert]. Redwood City, CA: Coherus BioSciences, Inc.; November 2022.
5. Kabatas EU, Kurtul BE, Altiaylik Ozer P, et al: Comparison of intravitreal bevacizumab, intravitreal ranibizumab and laser photocoagulation for treatment of type 1 retinopathy of prematurity in Turkish preterm children. Curr Eye Res 2017; 42(7):1054-1058.
6. Stahl A , Lepore D , Fielder A , et al: Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial. Lancet 2019; 394(10208):1551-1559.

Reference number(s)
5713-A

Standard Medicare Part B Management Lunsumio

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Lunsumio	mosunetuzumab-axgb

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Lunsumio is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy.

Compendial Use

Follicular Lymphoma

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Follicular Lymphoma

Authorization of 12 months may be granted for treatment of follicular lymphoma when both of the following criteria are met:

- The disease had a partial or no response to treatment or the disease is relapsed or progressive
- The member has tried at least 2 prior lines of systemic therapy

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat an indication listed in the coverage criteria section
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Lunsumio.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: B-cell lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Lunsumio are covered in addition to follicular lymphoma that did not respond to prior therapy, or partially responded to prior therapy.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Lunsumio to treat follicular lymphoma that did not respond to prior therapy or partially responded to prior therapy can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Reference number(s)
5713-A

References

1. Lunsumio [package insert]. South San Francisco, CA: Genentech, Inc.; December 2022.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed June 2, 2024.

Reference number(s)
2304-A

Standard Medicare Part B Management
Mylotarg

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Mylotarg	gemtuzumab ozogamicin

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Acute Myeloid Leukemia (AML)

- Newly diagnosed CD33-positive AML in adults and pediatric patients 1 month and older
- Relapsed or refractory CD33-positive AML in adults and pediatric patients 2 years and older

Compendial Uses[2]

Acute promyelocytic leukemia (APL)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

For AML and APL (initial requests): Testing or analysis confirming tumor is CD33-positive.

Reference number(s)
2304-A

Coverage Criteria

Acute Myeloid Leukemia (AML)/ Acute Promyelocytic Leukemia (APL)[1,2]

Authorization of 12 months may be granted for the treatment of AML/APL if the tumor is CD33-positve as confirmed by testing or analysis to identify the CD33 antigen.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all the following criteria are met:

- The member is currently receiving therapy with Mylotarg.
- Mylotarg is being used to treat an indication enumerated in the coverage criteria section
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen and
    - No evidence of disease progression while on the current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Mylotarg.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Acute myeloid leukemia

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Mylotarg are covered in addition to acute promyelocytic leukemia.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Mylotarg to treat acute promyelocytic leukemia can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

References

1. Mylotarg [package insert]. Philadelphia, PA: Pfizer; August 2021.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed January 5, 2024.

Reference number(s)
4237-A

Standard Medicare Part B Management Neulasta and biosimilars

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Neulasta	pegfilgrastim
Fulphila	pegfilgrastim-jmdb
Fylnetra	pegfilgrastim-pbbk
Nyvepria	pegfilgrastim- apgf
Stimufend	pegfilgrastim-fpgk
Udenyca	pegfilgrastim-cbqv
Ziextenzo	pegfilgrastim-bmez

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Neulasta

- Patients with Cancer Receiving Myelosuppressive Chemotherapy
  Neulasta 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.
- Hematopoietic Subsyndrome of Acute Radiation Syndrome
  Neulasta is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

Fulphila

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.

Udenyca

- 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.
- Hematopoietic Subsyndrome of Acute Radiation Syndrome
  Udenyca is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation.

Ziextenzo

- 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.
- Hematopoietic Subsyndrome of Acute Radiation Syndrome
  Ziextenzo is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation.

Nyvepria

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.

Fylnetra

Patients with Cancer Receiving Myelosuppressive Chemotherapy
Fylnetra 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.

Stimufend

- Patients with Cancer Receiving Myelosuppressive Chemotherapy
  Stimufend 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.
- Hematopoietic Subsyndrome of Acute Radiation Syndrome
  Stimufend is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation.

Compendial Uses

- Stem cell transplantation-related indications
- Prophylaxis for chemotherapy-induced febrile neutropenia in patients with solid tumors
- Hematopoietic Acute Radiation Syndrome

- Hairy cell leukemia, neutropenic fever

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Primary Prophylaxis of Febrile Neutropenia

Documentation of the member's diagnosis and chemotherapeutic regimen.

Coverage Criteria

Prevention of neutropenia in cancer patients receiving myelosuppressive chemotherapy

Authorization of 6 months may be granted for prevention of febrile neutropenia for members with solid tumors or non-myeloid malignancies when the requested medication will not be administered with weekly chemotherapy regimens and the member will not receive chemotherapy at the same time as they receive radiation therapy.

Other indications

Authorization of 6 months may be granted for members with any of the following indications:

- Stem cell transplantation-related indications
- Hematopoietic subsyndrome of acute radiation syndrome
- Hairy cell leukemia with neutropenic fever following chemotherapy

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must meet all requirements in the coverage criteria.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Neulasta, Fulphila, Fylnetra, Nyvepria, Stimufend, Udenyca, and Ziextenzo.

- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Hematopoietic growth factors
- NCCN Guideline: Hematopoietic cell transplantation
- NCCN Guideline: Hairy cell leukemia

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Neulasta and its biosimilars are covered in addition to the following:

- Stem cell transplantation-related indications
- Prophylaxis for chemotherapy-induced neutropenia in patients with solid tumors
- Hairy cell leukemia, neutropenic fever

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer’s prescribing information.

Support for using pegfilgrastim in mobilization of peripheral blood progenitor cells can be found in a study of patients with non-Hodgkin lymphoma by Russel et al. Patients with non-Hodgkin's lymphoma received one cycle of mobilizing chemotherapy (ifosfamide, carboplatin and etoposide, ICE). Twenty-four hours later they were randomized, double-blind, to receive a single dose of pegfilgrastim 6 mg or 12 mg, or filgrastim 5 mg/kg/day (until the end of leukapheresis). Following leukapheresis (collection phase), patients rested or received one or two 'salvage' cycles of ICE. High-dose BEAM chemotherapy was then given before peripheral blood progenitor cell transplantation. The primary end-point was the patients' mean yield of CD34(+) cells/kg during the collection phase. Ninety patients were randomized and received a study drug; 63% completed the collection phase. The patients' mean (95% CI) CD34(+) cell harvest per leukapheresis was 0.8 (0.5-1.4), 0.8 (0.5-1.6) and 1.2 (0.7-2.0)x10(6) cells/kg for the pegfilgrastim 6 mg, pegfilgrastim 12 mg and filgrastim groups, respectively. Twenty (69%), 17 (59%) and 23 (72%) patients in these three groups achieved the targeted minimum harvest (>/=2 x 10(6) cells/kg). The mean total harvests were 1.7, 1.4 and 2.2 x 10(6) cells/kg, respectively. Post-transplantation, the median days to absolute neutrophil count recovery (>/=0.5 x 10(9)/L) were 12, 11, and 11, respectively. Pegfilgrastim and filgrastim were generally well tolerated.

In a phase 2 study by Fruehauf et al, a single dose of pegfilgrastim 12 mg demonstrated favorable CD34+ cell yields when administered following myeloablative chemotherapy for the mobilization of peripheral blood progenitor cells (PBPC) in patients with multiple myeloma (MM). Patients aged 18 to 65 years (median age, 57 years; range, 40 to 65 years) with stage 2 or 3 MM who were candidates for an autologous transplant were eligible for study enrollment. Most patients had previously received induction therapy with VAD (vincristine, doxorubicin, dexamethasone). Following myeloablative chemotherapy with CAD (cyclophosphamide, doxorubicin, dexamethasone), patients received a single dose of subcutaneous pegfilgrastim 12 mg (n=26) on day 5, approximately 24 hours after chemotherapy completion. In patients with a CD34+ cell count of 20 x 10(6) cells/L or greater (at day 10 or greater), leukapheresis was started between days 15 to 20 and continued until a CD34+ cell count fell to 5 x 10(6)/L or less or a target CD34+ cell harvest of 7.5 x 10(6)/kg was achieved. In patients with a CD34+ cell count between 5 and 20 x 10(6) cells/L (at day 13 or greater) and a platelet count of 30 x 10(9)/L, leukapheresis was continued until the target harvest of 7.5 x 10(6)/kg was achieved. Additional

treatment with filgrastim 10 mcg/kg was given if the CD34+ cell count fell by greater than 25% per day starting from day 16 without reaching 20 x 10(6) cells/L. The transplant phase consisted of high-dose melphalan followed by PBPC transfusion. Patients were compared with historical control patients from the same center who received filgrastim (n=52; median age, 60 years; range, 31 to 70 years) matched (1:2) for prior therapy, disease stage, and induction therapy response before mobilization. A CD34+ cell target yield of 7.5 x 10(6) cells/kg or greater (primary endpoint) was achieved in 23 patients (88%; 95% confidence interval, 70% to 98%) who received pegfilgrastim and 41 patients (79%) who received filgrastim (median number of apheresis procedures to target CD34+ cell yield: pegfilgrastim, 2 (range, 1 to 4); filgrastim, 2 (range, 1 to 6)). Three patients who received pegfilgrastim required additional treatment with filgrastim to achieve the target CD34+ cell yield, and all 26 patients received a transplant. The median total CD34+ cell harvests were 9.7 X 10(6) cells/kg (range, 4.9 to 40.5 x 10(6) cells/kg) and 9.95 x 10(6) cells/kg (range, 2.6 to 99.9 X 10(6) cells/kg) for the pegfilgrastim and filgrastim groups, respectively; additionally, the median CD34+ cells per leukapheresis were 4.4 x 10(6) cells/kg (range, 0.9 to 40.5 x 10(6) cells/kg) and 3.4 x 10(6) cells/kg (range, 0.1 to 63.6 x 10(6) cells/kg), respectively. Hematologic recovery following transplant was similar in the pegfilgrastim and filgrastim groups for the median time to leucocyte count of 1 x 10(9)/L or greater (14 days (range, 10 to 21 days) and 14 days (range, 8 to 24 days), respectively) and median time to platelets of 20 x 10(9)/L or greater (11 days (range, 0 to 15 days) and 11 days (range, 0 to 16 days). Adverse events reported with pegfilgrastim use were grade 1 thoracic pain (n=1) and nausea (n=1).

Support for using pegfilgrastim in hematopoietic cell mobilization can be found in the National Comprehensive Cancer Network's guideline for hematopoietic cell transplantation. The NCCN Guideline for hematopoietic cell transplantation supports the use of pegfilgrastim as treatment for hematopoietic cell mobilization for autologous donors in combination with plerixafor.

Support for using pegfilgrastim for neutropenic fever in a patient being treated for hairy cell leukemia can be found in the National Comprehensive Cancer Network's guideline for hairy cell leukemia. The NCCN Guideline for hairy cell leukemia supports using neutrophil growth factors for patients with neutropenic fever following systemic therapy.

Support for hematopoietic acute radiation syndrome can be found in the National Comprehensive Cancer Network's guideline for hematopoietic growth factors in addition to the prescribing information for Neulasta. The NCCN Guideline for hematopoietic growth factors supports the use of pegfilgrastim in patients with radiation-induced myelosuppression following a radiologic/nuclear incident.

References

1. Neulasta [package insert]. Thousand Oaks, CA: Amgen Inc.; February 2021.
2. Fulphila [package insert]. Cambridge, MA: Biocon Biologics Inc.; June 2023.
3. Udenyca [package insert]. Redwood City, CA: Coherus BioSciences, Inc; December 2023.
4. Ziextenzo [package insert]. Princeton, NJ: Sandoz Inc.; February 2024.
5. Nyvepria [package insert]. Lake Forest, IL: Hospira, Inc.; March 2023.
6. Fylnetra [package insert]. Piscataway, NJ: Kashiv BioSciences, LLC; May 2022.
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Reference number(s)
4758-A

Standard Medicare Part B Management Neupogen and filgrastim biosimilars

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Neupogen	filgrastim
Granix	tbo-filgrastim
Nivestym	filgrastim-aafi
Releuko	filgrastim-ayow
Zarxio	filgrastim-sndz
Nypozi	filgrastim-txid

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Neupogen

Patients with Cancer Receiving Myelosuppressive Chemotherapy

Neupogen 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 significant incidence of severe neutropenia with fever.

Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

Neupogen is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).

Patients with Cancer Undergoing Bone Marrow Transplantation

Neupogen is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, (e.g., febrile neutropenia) in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation.

Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

Neupogen is indicated for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.

Patients with Severe Chronic Neutropenia

Neupogen is indicated for chronic administration to 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.

Patients Acutely Exposed to Myelosuppressive Doses of Radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

Neupogen is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).

Nivestym

Patients with Cancer Receiving Myelosuppressive Chemotherapy

Nivestym 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 significant incidence of severe neutropenia with fever.

Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

Nivestym is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).

Patients with Cancer Undergoing Bone Marrow Transplantation (BMT)

Nivestym is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, (e.g., febrile neutropenia) in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.

Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

Nivestym is indicated for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.

Patients with Severe Chronic Neutropenia

Nivestym is indicated for chronic administration to 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.

Granix

Granix is indicated to reduce the duration of severe neutropenia in adult and pediatric patients 1 month and older with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Zarxio

Patients with Cancer Receiving Myelosuppressive Chemotherapy

Zarxio 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 significant incidence of severe neutropenia with fever.

Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

Zarxio is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with acute myeloid leukemia (AML).

Patients with Cancer Undergoing Bone Marrow Transplantation

Zarxio is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, (e.g., febrile neutropenia) in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.

Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

Zarxio is indicated for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.

Patients with Severe Chronic Neutropenia

Zarxio is indicated for chronic administration to 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.

Releuko

Patients with Cancer Receiving Myelosuppressive Chemotherapy

Releuko 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 significant incidence of severe neutropenia with fever.

Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

Releuko is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).

Patients with Cancer Undergoing Bone Marrow Transplantation

Releuko is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, (e.g., febrile neutropenia), in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.

Patients with Severe Chronic Neutropenia

Releuko is indicated for chronic administration to 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.

Nypozi

Patients with Cancer Receiving Myelosuppressive Chemotherapy

Nypozi 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 significant incidence of severe neutropenia with fever.

Patients With Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

Nypozi is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).

Patients with Cancer Undergoing Bone Marrow Transplantation

Nypozi is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, (e.g., febrile neutropenia) in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation.

Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

Nypozi is indicated for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.

Patients With Severe Chronic Neutropenia

Nypozi is indicated for chronic administration to 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.

Patients Acutely Exposed to Myelosuppressive Doses of Radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

Nypozi is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation.

Compendial Uses

- Treatment of chemotherapy-induced febrile neutropenia
- Prophylaxis for chemotherapy-induced febrile neutropenia in patients with solid tumors
- Treatment of anemia and neutropenia in patients with myelodysplastic syndromes (MDS)
- Stem cell transplantation-related indications
- Agranulocytosis (non-chemotherapy drug induced)
- Aplastic anemia
- Neutropenia related to human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS)
- Neutropenia related to renal, heart or lung transplantation
- Acute myeloid leukemia

- Supportive care for neutropenic patients with CAR T-cell-related toxicities
- Hairy Cell Leukemia, neutropenic fever
- Chronic Myeloid Leukemia, treatment of persistent neutropenia due to tyrosine kinase inhibitor therapy
- Glycogen Storage Disease (GSD) Type 1
- Reducing the instance of neonatal sepsis in infants with preeclampsia-associated neutropenia
- Perioperative administration of filgrastim to patients with esophageal cancer undergoing esophagectomy reduced infectious complications following surgery
- Improving the neutrophil count in Shwachman syndrome

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions: For febrile neutropenia, submit member's diagnosis and chemotherapeutic regimen.

Coverage Criteria

Neutropenia In Cancer Patients Receiving Myelosuppressive Chemotherapy

Authorization of 6 months may be granted for prevention or treatment of febrile neutropenia when both of the following criteria are met:

- The member will not receive chemotherapy at the same time as they receive radiation therapy.
- One of the following criteria is met:
- The requested medication will be used for primary prophylaxis or secondary prophylaxis of febrile neutropenia in members with solid tumors or non-myeloid malignancies.
- The requested medication will be used for treatment of high-risk febrile neutropenia (FN) in members who have any of the following prognostic factors that are predictive of clinical deterioration:
- Age greater than 65 years
- Being hospitalized at the time of the development of fever
- Sepsis syndrome
- Invasive fungal infection
- Pneumonia or other clinically documented infection
- Prolonged (neutropenia expected to last greater than 10 days) or profound (absolute neutrophil count less than 0.1 x 109/L) neutropenia
- Prior episodes of febrile neutropenia

Other Indications

Authorization of 6 months may be granted for members with any of the following indications:

- Myelodysplastic syndrome (anemia or neutropenia)
- Stem cell transplantation-related indications (including applicable gene therapy protocols)
- Agranulocytosis (non-chemotherapy drug induced)
- Aplastic anemia
- Neutropenia related to HIV/AIDS
- Neutropenia related to renal, heart or lung transplantation
- Acute myeloid leukemia
- Severe chronic neutropenia (congenital, cyclic, or idiopathic)
- Hematopoietic Subsyndrome of Acute Radiation Syndrome
  Treatment for radiation-induced myelosuppression following a radiological/nuclear incident
- CAR T-cell-related toxicities
  Supportive care for neutropenic patients with CAR T-cell-related toxicities
- Hairy Cell Leukemia
  Members with hairy cell leukemia with neutropenic fever following chemotherapy
- Chronic Myeloid Leukemia
  Members with chronic myeloid leukemia (CML) for treatment of persistent neutropenia due to tyrosine kinase inhibitor therapy
- Glycogen Storage Disease (GSD) Type 1
  Individuals with GSD Type 1 for treatment of low neutrophil counts
- Reducing the instance of neonatal sepsis in infants with preeclampsia-associated neutropenia
- Perioperative administration of filgrastim to patients with esophageal cancer undergoing esophagectomy to reduce infectious complications following surgery
- Improving the neutrophil count in Shwachman syndrome

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 6 months may be granted for the treatment of chronic myeloid leukemia when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy. Benefit is defined as:
  - No evidence of unacceptable toxicity while on the current regimen
  - No evidence of disease progression while on the current regimen

For all other diagnoses, all members (including new members) requesting authorization for continuation of therapy must meet all requirements in the coverage criteria.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Neupogen, Granix, Nivestym, Nypozi, Releuko, and Zarxio.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Myelodysplastic syndromes
- NCCN Guideline: Hematopoietic growth factors
- NCCN Guideline: Hematopoietic cell transplantation
- NCCN Guideline: Management of immunotherapy-related toxicities
- NCCN Guideline: Acute myeloid leukemia
- NCCN Guideline: Hairy cell leukemia
- NCCN Guideline: Chronic myeloid leukemia
- Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics
- 2010 Update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumors.
- Recommendations for the use of white blood cell growth factors: American Society of Clinical Oncology Practice Guideline Update
- 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline
- 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Neupogen, Granix, Nivestym, Nypozi, Releuko, and Zarxio are covered in addition to the following:

- Treatment of chemotherapy-induced febrile neutropenia
- Prophylaxis for chemotherapy- induced febrile neutropenia in patients with solid tumors
- Treatment of anemia and neutropenia in patients with myelodysplastic syndromes (MDS)
- Stem cell transplantation-related indications
- Agranulocytosis (non-chemotherapy drug induced)
- Aplastic anemia
- Neutropenia related to human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS)
- Neutropenia related to renal, heart or lung transplantation
- Acute myeloid leukemia
- Supporting care for neutropenic patients with CAR T-cell-related toxicities
- Hairy cell leukemia, neutropenic fever
- Chronic myeloid leukemia, treatment of persistent neutropenia due to tyrosine kinase inhibitor therapy
- Glycogen storage disease type I
- Reducing the instance of neonatal sepsis in infants with preeclampsia-associated neutropenia

- Perioperative administration of filgrastim to patients with esophageal cancer undergoing esophagectomy reduced infectious complications following surgery
- Improving neutrophil count in Shwachman syndrome

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using filgrastim to treat anemia and neutropenia in patients with myelodysplastic syndromes can be found in the National Comprehensive Cancer Network's guideline for myelodysplastic syndromes. The NCCN Guideline for myelodysplastic syndromes supports the use of filgrastim as treatment of lower risk (IPSS-R very low, low, intermediate) disease associated with symptomatic anemia with no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts greater than or equal to 15% (or ring sideroblasts greater than or equal to 5% with an SF3B1 mutation), with serum erythropoietin less than or equal to 500 mU/mL in combination with an erythropoiesis-stimulating agent (ESA). The guideline also supports using filgrastim to treat lower risk disease as previously described following no response (despite adequate iron stores) or erythroid response followed by loss of response to an ESA alone.

Support for using filgrastim as prophylaxis against febrile neutropenia in patients receiving chemotherapy for solid tumors and non-myeloid malignancies can be found in the National Comprehensive Cancer Network's guideline for hematopoietic growth factors. The NCCN Guideline for hematopoietic growth factors supports the use of filgrastim as prophylaxis of chemotherapy-induced febrile neutropenia or other dose limiting neutropenic events in high-risk (greater than 20% overall risk of febrile neutropenia) in patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings.

The guideline also supports using filgrastim for prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in intermediate-risk (10% to 20% overall risk of febrile neutropenia) patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings who have one or more patient risk factors. Consider using filgrastim for prophylaxis of chemotherapy-induced febrile neutropenia or other dose-limiting neutropenic events in low-risk (<10% overall risk of febrile neutropenia) patients with solid tumors and non-myeloid malignancies receiving treatment in the curative/adjuvant or palliative settings who have 2 or more patient-related risk factors. Use of granulocyte colony-stimulating factors in this setting is based on clinical judgment.

Support for using filgrastim as treatment of chemotherapy-induced febrile neutropenia can be found in the National Comprehensive Cancer Network's guideline for hematopoietic growth factors. The NCCN Guideline for hematopoietic growth factors supports the use of filgrastim in patients who have been receiving prophylactic filgrastim. Consider in patients who have not received prophylactic granulocyte colony-stimulating factors but who have risk factors for an infection-associated complication.

Support for using filgrastim in hematopoietic stem cell transplantation can be found in the National Comprehensive Cancer Network's guideline for hematopoietic stem cell transplantation. The NCCN Guideline supports the use of filgrastim as treatment for hematopoietic cell mobilization for autologous donors in combination with any of the following: plerixafor, in combination with cyclophosphamide with or without plerixafor, as a single agent, or in combination with disease-specific chemotherapy with or without plerixafor. Filgrastim can also be used as treatment for hematopoietic cell mobilization for allogenic donors as a single agent. Finally, filgrastim can be used as additional therapy for insufficient collection of stem cells in combination with plerixafor following treatment with filgrastim alone or filgrastim and disease-specific chemotherapy.

Support for using filgrastim in the management of CAR T-cell-related toxicities can be found in the National Comprehensive Cancer Network's guideline for Management of Immunotherapy-related toxicities. Filgrastim can be considered as supportive care for neutropenic patients.

Support for using filgrastim in patients with acute myeloid leukemia can be found in the National Comprehensive Cancer Network's guideline for acute myeloid leukemia. The NCCN Guideline supports the use of filgrastim for treatment induction in patients who are candidates for intensive induction therapy with favorable-risk AML (CBF-AML, NPM1-mutated/FLT3 wild-type AML, in-frame bZIP mutation in CEBPA) in combination with fludarabine, high-dose cytarabine, and idarubicin plus gemtuzumab ozogamicin. Filgrastim can also be used for treatment induction in patients as part of an alternative non-anthracycline-containing regimen (eg, FLAG) who are candidates for intensive induction therapy who exceed anthracycline dose or have cardiac issues but are still able to receive aggressive therapy. It is appropriate to use filgrastim as a component of repeating the initial successful induction regimen if late relapse (≥12 months since induction regimen). Filgrastim can be used for relapsed/refractory disease in combination with cladribine and cytarabine, with or without mitoxantrone or idarubicin. Finally, filgrastim can be used for relapsed/refractory disease in combination with fludarabine and cytarabine, with or without idarubicin.

Support for using filgrastim in hairy cell leukemia can be found in the National Comprehensive Cancer Network's guideline for hairy cell leukemia. The NCCN Guideline indicates that neutrophil growth factors, such as filgrastim, are indicated for patients with neutropenic fever following systemic therapy.

Support for using filgrastim in chronic myeloid leukemia can be found in the National Comprehensive Cancer Network's guideline for chronic myeloid leukemia. The NCCN Guideline for chronic myeloid leukemia supports the use of granulocyte colony stimulating factors to overcome imatinib-induced neutropenia in patients with persistent neutropenia.

Support for using filgrastim to treat aplastic anemia is supported by two studies. In a series of 17 Japanese adults with severe aplastic anemia, an immunosuppressive regimen with concomitant granulocyte colony-stimulating factor (G-CSF) induced a good response in 82%. Dosing consisted of intravenous (IV) methylprednisolone 20 milligrams/kilogram/day (mg/kg/day) on days 1 to 3 with decreasing doses of 10 mg/kg/day to 2.5 mg/kg/day for days 4 to 6, anti-lymphocyte globulin or anti-thymocyte globulin 30 mg/kg/day for 5 days, oral cyclosporine 5 mg/kg/day initially then adjusted to maintain trough levels at 200 to 250 nanograms/milliliter, and subcutaneous G-CSF 250 micrograms/day. Good response was defined as meeting at least two of the following criteria: absolute reticulocyte, neutrophil, and platelet counts above 60,000/microliter, 1000/microliter and 50,000/microliter, respectively, or hemoglobin increase of greater than 2 grams/deciliter without transfusion. The median time to reach this endpoint in responders was 3 months. Three of 17 individuals died, including two non-responders and one responder who later developed paroxysmal nocturnal hemoglobinuria (PNH). Three other instances of PNH and one case of myelodysplastic syndrome ensued. Of 14 survivors (5.7 to 63.1 months of follow-up), only three did not require maintenance immunosuppression with or without G-CSF, or bone marrow transplant (Matsuo et al).

In a randomized trial of 69 children with moderate to severe acquired aplastic anemia, the addition of granulocyte colony-stimulating factor (G-CSF) to a multi-drug immunosuppressive regimen did not improve efficacy. 50 subjects classified as having very severe aplastic anemia (VSAA) (platelet, reticulocyte and neutrophil counts less than 20,000/microliter (mcL), 20,000/mcL and 200/mcL, respectively) were uniformly treated with a G-CSF-containing regimen. The overall trilineage response rates in the very severe aplastic anemia (VSAA), G-CSF +, and G-CSF - groups were not statistically significant at 3 months (47%, 39%, and 53%), 6 months (71%, 55%, and 77%), and 12 months (73%, 60%, and 73%), respectively. The 3 groups did not differ significantly with respect to survival, infectious complications, relapse rates, new cytogenetic abnormalities, or clonal disease evolution. Subjects received intravenous (IV) horse anti-thymocyte globulin (Lymphoglobuline(R)) 1.5 vials/10 kilograms (kg)/day infused over 12 hours for 5 days,

methylprednisolone 2 milligrams (mg)/kg/day IV on days 1 to 7, then 1 mg/kg/day orally on days 8 to 14 and tapered to end on day 30, oral cyclosporine 6 mg/kg/day adjusted to maintain whole blood trough levels of 100 to 200 nanograms/milliliter on days 1 to 180, oral danazol 5 mg/kg/day on days 1 to 180, with (G-CSF +; n=35) or without (G-CSF -; n=34) IV or subcutaneous G-CSF 400 micrograms/square meter days 1-90. G-CSF administration was changed to thrice weekly once the absolute neutrophil count reached 5x10(9) per liter. Drug treatment was well tolerated with drug-related toxicity similar among the G-CSF + and G-CSF - groups. The authors recommend against initial adjunctive G-CSF except in VSAA (Kojima et al).

Support for using filgrastim to treat neutropenia related to renal, heart or lung transplantation can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using filgrastim for glycogen storage disease type I can be found in a guideline published by the American College of Medical Genetics and Genomics. Neutropenia and recurrent infections are a common manifestation of glycogen storage disease type 1. Administration of granulocyte colony stimulating factors like filgrastim increases blood neutrophil counts to normal or above normal levels. Neutropenic patients with GSD Ib should be treated with G-CSF, particularly if there is already a history and pattern of fever, infections, or enterocolitis. The lowest effective G-CSF dose should be used to avoid worsening of splenomegaly, hypersplenism, hepatomegaly, and bone pain. G-CSF should be administered subcutaneously starting at 0.5–1.0 µg per kilogram per day given daily or every other day. The G-CSF dose should be increased stepwise at approximately 2-week intervals until the target ANC of more than 500 to up to 1.0×10^9 /l is reached. This dose then should be maintained, adjusting for subsequent increases in the patient's weight with growth and development. Blood count with manual differential should be monitored several times per year. Bone marrow examinations are not recommended unless there is an unexpected change in the patient's other blood counts.

Support for using filgrastim to reduce neonatal sepsis in infants with preeclampsia-associated neutropenia can be found in a study by Kocherlakota et al. Filgrastim was found to be beneficial in increasing the absolute neutrophil count (ANC) and reducing the incidence of neonatal sepsis in infants with preeclampsia-associated neutropenia. In an unblinded study, patients (n=28) were assigned to conventional treatment or treatment with filgrastim (5 or 10 micrograms/kilogram (mcg/kg)/day). The ANC had doubled in 24 hours in the 10 mcg/kg group and no change was seen in the 5 mcg/kg group or conventional treatment group. In the filgrastim group, 13% were diagnosed with sepsis, whereas 54% in the conventional treatment group were.

Support for using filgrastim to reduce infectious complications following esophagectomy can be found in a small study by Schafer et al. When compared to patients in a historical control group (n=77), filgrastim administration to patients with esophageal cancer undergoing esophagectomy (n=20) resulted in a significant reduction in the infection rate during the 10 days following surgery. Patients in the study group were given filgrastim 300 micrograms/day (mcg/day) subcutaneously to 480 mcg/day depending on body weight starting 2 days before surgery and discontinued on day 7 following surgery. Ten days following surgery, no complications had occurred in the study group; however, 29.9% of patients (n=23) in the control developed infections (p=0.008). For postoperative days 11 and up, the significant difference in infection between the two groups was not maintained.

Support for using filgrastim to improve neutrophil count in Shwachman syndrome can be found in a case report by Adachi et al. Filgrastim has successfully treated a 1.5-year-old male with Shwachman syndrome. Improvement in the neutrophil count (from 552/microliter (mcL) to 45,300/mcL) occurred following 7 days of filgrastim therapy (100 micrograms/square meter).

Support for using filgrastim to treat neutropenia caused by HIV can be found in guidelines issued by the U.S. Public Health Service (USPHS). Administration of granulocyte-macrophage (GM-CSF) may be considered for patients with human immunodeficiency virus (HIV) infection to reverse neutropenia. This use, however, would not be routinely indicated. The recommended dosage is 5 to 10 micrograms/square meter/day given subcutaneously for 2 to 4 weeks.

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Reference number(s)
6597-A

Standard Medicare Part B Management Niktimvo

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Niktimvo	axatilimab-csfr

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Niktimvo is indicated for the treatment of chronic graft-versus-host disease (cGVHD) after failure of at least two prior lines of systemic therapy in adult and pediatric patients weighing at least 40 kg.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Chronic graft-versus-host disease (cGVHD)[1]

Authorization of 12 months may be granted for treatment of cGVHD when all of the following criteria are met:

- The member has failed at least two prior lines of systemic therapy AND
- The member weighs at least 40 kg.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Niktimvo
- Niktimvo is being used to treat an indication listed in the coverage criteria section
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen and
    - No evidence of disease progression while on the current regimen.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Niktimvo.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Niktimvo [package insert]. Wilmington, DE: Incyte Corporation; August 2024.

Reference number(s)
4799-A

Standard Medicare Part B Management Novoseven RT

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Novoseven RT	coagulation factor VIIa [recombinant]

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

- Hemophilia A or hemophilia B with inhibitors
- Congenital factor VII deficiency
- Glanzmann's thrombasthenia
- Acquired hemophilia

Compendial Uses[2-6,12-13]

- Acquired von Willebrand syndrome
- Inhibitors to factor XI
- Drug action reversal, anticoagulation
- Postoperative hemorrhage, cardiac surgery

All other indications will be assessed on an individual basis.Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Reference number(s)
4799-A

Coverage Criteria

Congenital Factor VII Deficiency[1,8]

Authorization of 12 months may be granted for treatment of congenital factor VII deficiency.

Hemophilia A with Inhibitors[1,7,8]

Authorization of 12 months may be granted for treatment of hemophilia A with inhibitors (see Appendix) when the inhibitor titer is ≥ 5 Bethesda units per milliliter (BU/mL) or the member has a history of an inhibitor titer ≥ 5 BU.

Hemophilia B with Inhibitors[1,7,8]

Authorization of 12 months may be granted for treatment of hemophilia B with inhibitors (see Appendix) when the inhibitor titer is ≥ 5 Bethesda units per milliliter (BU/mL) or the member has a history of an inhibitor titer ≥ 5 BU.

Glanzmann's Thrombasthenia[1,9-11]

Authorization of 12 months may be granted for treatment of Glanzmann's thrombasthenia.

Acquired Hemophilia[1]

Authorization of 12 months may be granted for treatment of acquired hemophilia.

Acquired von Willebrand Syndrome[2-4]

Authorization of 12 months may be granted for treatment of acquired von Willebrand syndrome when other therapies failed to control the member's condition (e.g., desmopressin or factor VIII/von Willebrand factor).

Inhibitors to Factor XI[5-6,12]

Authorization of 12 months may be granted for treatment of inhibitors to factor XI.

Anticoagulation Reversal[13]

Authorization of 1 month may be granted for emergency reversal of anticoagulation.

Postoperative Hemorrhage following Cardiac Surgery[13]

Authorization of 1 month may be granted for treatment of postoperative hemorrhage following cardiac surgery.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Anticoagulation Reversal

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

Postoperative Hemorrhage following Cardiac Surgery

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

All Other Indications

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

Appendix/Appendices

Appendix: Inhibitors - Bethesda Units (BU)[7]

The presence of inhibitors is confirmed by a specific blood test called the Bethesda inhibitor assay.

- High-titer inhibitors:
  - ≥ 5 BU/mL
  - Inhibitors act strongly and quickly neutralize factor
- Low-titer inhibitors:
  - < 5 BU/mL
  - Inhibitors act weakly and slowly neutralize factor

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Novoseven RT.
- The available compendium
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium

  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)
  - Lexi-Drugs
  - Clinical Pharmacology
- WFH Guidelines for the Management of Hemophilia, 3rd edition.
- MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System.
- World Federation of Hemophilia. Platelet function disorders.
- Use of recombinant activated factor VII in patients with Glanzmann's thrombasthenia: a review of the literature.
- Congenital factor XI deficiency: an update.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Novoseven RT are covered in addition to the following:

- Acquired von Willebrand syndrome
- Inhibitors to factor XI
- Drug action reversal, anticoagulation
- Postoperative hemorrhage, cardiac surgery

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using NovosevenRT to treat acquired von Willebrand syndrome can be found in a study by Tiede et al. Use of recombinant factor VIIa has been reported in AVWS and in von Willebrand disease patients, particularly those who develop alloantibodies against VWF. It is usually administered with a dose of 90 µg/kg (range, 40-150 µg/kg) and for a median of 3 doses (range, 1-54 doses). Treatment is usually effective with responses reported in 96% of patients. Adverse events appear to be uncommon; myocardial infarction was reported in one patient with type 2A von Willebrand disease. The rate of thromboembolic complications is low in hemophilia patients receiving recombinant factor VIIa, but it is currently unknown whether this is holds for patients with AVWS or von Willebrand disease. Caution should be exerted, particularly in elderly patients and those at risk of thromboembolism.

Support for using Novoseven RT to treat inhibitors to factor XI can be found in several articles.

Duga and Salomon state the treatment of factor XI deficiency is difficult because factors influencing bleeding risks are still unknown. The use of lower doses of recombinant activated factor VII in comparison with the doses commonly applied in hemophilia A or B seems promising also when assessed in vitro by thrombin generation test.

Individuals with severe factor XI deficiency who have developed a factor XI inhibitor may not have an increase in factor XI with factor XI replacement products and may require treatment with a bypassing agent such as recombinant activated factor VII (recombinant factor VIIa; rFVIIa). In their review, Roberts et al (2004) state recombinant VIIa has also been used to treat patients with factor XI deficiency either with or without inhibitors to factor XI. Doses of 90 to 120 µg/kg every 2 to 3 hours until bleeding ceases have been found to be effective in this condition, but the optimal dose has not been clearly defined. Some investigators now consider rfVIIa to be the treatment of choice in factor XI deficiency and for inhibitors to factor XI (Roberts 2004).

Support for using Novoseven RT to reverse the effects of anticoagulants can be found in a study by Ingerslev, Vanek and Culic. Activated recombinant factor VII (rFVIIa) was beneficial for patients requiring emergency anticoagulation reversal in a database review of an international, internet-based registry (n=18). Patients who received rFVIIa as rescue treatment for bleeding during or after a surgical or invasive procedure, who had verifiable results and provider consent were included. The anticoagulants utilized, which required reversal included low-molecular-weight heparin (n=6), unfractionated heparin (n=8), coumarin (n=3) and warfarin (n=1). All but 1 patient received a single dose of rFVIIa. The median dose was 87.35 micrograms/kilogram (mcg/kg) (range, 20 to 106 mcg/kg). The primary outcome was cessation of hemorrhage. Cessation of hemorrhage was achieved in 10 patients. A marked reduction in hemorrhage occurred in 5 patients and a considerable slowing of hemorrhage occurred in 3 patients. Neither the severity of initial bleeding nor the dose of rFVIIa seemed to influence efficacy. The need for blood products (packed red blood cells, whole, blood, fresh frozen plasma, cryoprecipitate or platelets) or fluid therapy (crystalloids or colloids) from 24 hours before to 24 hours after treatment significantly improved (p less than 0.001 and p less than 0.05, respectively). No adverse effects were reported and rFVIIa was considered well tolerated. Of the 18 patients, 14 had reported final outcomes: 8 were discharged, 1 stayed in the ICU, and 5 fatalities occurred but were not attributed to rFVIIa.

Ilyas and colleagues completed a retrospective, cohort-controlled database review of elderly patients with intracranial hemorrhage (n=54). Elderly patients treated with warfarin, who presented with a new or developing intracranial bleed and an international normalized ratio (INR) greater than 1.4 received rFVIIa 10 to 100 micrograms/kilogram (mcg/kg) (n=24; age 76.5 +/- 11 years (yr); 50% male). Demographics of the historical controls was similar (n=30; age 76.4 +/- 12.4 yr; 63% male). Patients treated with rFVIIa rapidly achieved INR reduction to 1.3 or less compared with historical controls, 2.4 +/- 1.5 hours (hr) vs 13.7 +/- 15.6 hr, respectively, and INR remained corrected for an average of 12.2 +/- 8.8 hr. Patients treated with rFVIIa required noticeably less plasma for hemostasis compared with historical controls 4 +/- 3 units vs 7.7 +/- 4.4 units, respectively. A dose-response effect in duration of INR correction was observed: 3 hr INR correction with rFVIIa 1.2 milligrams (mg), 13 hr INR correction with 2.4 to 4.8 mg, and 17 hr INR correction for doses greater than 4.8 mg. Most patients received vitamin K 10 mg IV within the first 12 hours of treatment. One patient experienced a myocardial infarction that was temporally related to rFVIIa administration but fully recovered. A study limitation is the retrospective study design.

Support for using Novoseven RT to treat postoperative hemorrhage after cardiac surgery can be found in a meta-analysis by Ponschab et al. In a meta-analysis of 6 clinical trials (2 randomized, 3 propensity matched, and 1 case matched) (n=470), using recombinant activated factor VII (rFVIIa) (18 mcg/kg to 70 mcg/kg given in repeatable doses, and 90 mcg/kg given as a single dose) in post-cardiac surgery patients did not significantly reduce the rate of surgical reexploration (13% vs 42% in the rFVIIa and control groups, respectively) (odds ratio (OR) 0.27; 95% confidence interval (CI) 0.04 to 1.9; p=0.19), and was associated with an increased rate of stroke (4.7% vs 0.9% in the rFVIIa and control groups, respectively) (OR 3.69; 95% CI 1.1 to 12.38; p=0.03). Incidence in overall perioperative vascular events (myocardial infarction, stroke, and DVT) (7.5% vs 5.6% in the rFVIIa and control groups, respectively) (OR 1.84; 95% CI 0.82 to 4.09; p=0.14), and mortality (13% vs 12% in the rFVIIa and control groups, respectively) (OR 1.14; 95% CI 0.65 to 2.01) was not different between the groups. All 6 studies reported reduction in blood loss with rFVIIa; however, due to the different methods of measurement, the results could not be compared between the studies.

Additionally, the use of recombinant activated factor VII (rFVIIa) in patients who bleed after cardiac surgery was effective in a phase II, multicenter, randomized, double-blind, placebo-controlled trial (n=172); however, however, the incidence of serious adverse events was higher in the rFVIIa group (Gill et al). Patients who were bleeding after cardiac surgery requiring cardiopulmonary bypass (CPB) and needing conventional transfusion therapy or surgical reexploration were randomized to receive placebo (n=68), 40 micrograms per kilogram (mcg/kg) rFVIIa (n=35), or 80 mcg)/kg rFVIIa (n=69). The study reported that rFVIIa reduced bleeding and patients receiving rFVIIa had significantly fewer reoperations (p=0.03) (placebo, 25%; 40 mcg/kg, 14%; 80 mcg/kg 12%), and less transfusion requirements compared

with patients receiving placebo (p=0.01). The primary end point of the study was the number of patients experiencing serious adverse events (SAEs), and the results showed that there were more SAEs (death, acute myocardial infarction, cerebral infarction, pulmonary embolus and other thrombotic events) in the rFVIIa groups than in the placebo group; however, the differences were not statistical significant (placebo, 7%; 40 mcg/kg, 14%; p=0.25; 80 mcg/kg, 12%; p=0.43). There was a total of 14 deaths, with 6% of the placebo group and 10% of the combined rFVIIa dose groups. The major limitation of the study was its small sample size with some of the patients who received rFVIIa were older, were on CPB longer, and received more transfusions before randomization. These factors were strong predictors of the SAEs and mortality and may partially account for its increased number (although statistically insignificant) in rFVIIa-treated patient.

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Reference number(s)
2063-A

Standard Medicare Part B Management
Nucala

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Nucala	mepolizumab

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

Maintenance Treatment of Severe Asthma

Nucala is indicated for the add-on maintenance treatment of adult and pediatric patients aged 6 years and older with severe asthma and with an eosinophilic phenotype.

Limitations of Use:

Not for relief of acute bronchospasm or status asthmaticus

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Nucala is indicated for the add-on maintenance treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) in adult patients 18 years of age and older with inadequate response to nasal corticosteroids.

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Nucala is indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).

Hypereosinophilic Syndrome (HES)

Nucala is indicated for the treatment of adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome (HES) for $\geq$ 6 months without an identifiable non-hematologic secondary cause.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Asthma:

- For initial requests:
  - Chart notes or medical record documentation showing baseline blood eosinophil count, or dependance on inhaled corticosteroids, if applicable.
  - Chart notes, medical record documentation, or claims history supporting previous medications tried including drug, dose, frequency, and duration. If therapy is not advisable, documentation of clinical reason to avoid therapy.
- For continuation requests: Chart notes or medical record documentation supporting improvement in asthma control.

CRSwNP:

- For initial requests:
  - Chart notes or medical record documentation showing nasal endoscopy, anterior rhinoscopy, or computed tomography (CT) details (e.g., polyps location, size), or Meltzer Clinical Score or endoscopic nasal polyps score (NPS) (where applicable).
  - Chart notes, medical record documentation, or claims history supporting previous medications tried (if applicable), including response to therapy. If therapy is not advisable, documentation of clinical reason to avoid therapy.
- For continuation requests: Chart notes or medical record documentation supporting positive clinical response.

EGPA:

- For initial requests:
  - Chart notes or medical record documentation showing pre-treatment blood eosinophil count.
  - Chart notes, medical record documentation, or claims history supporting previous medications tried including drug, dose, frequency, and duration. If therapy is not advisable, documentation of clinical reason to avoid therapy.
- For continuation requests: Chart notes or medical record documentation supporting improvement in EGPA control.

HES:

- For initial requests:

  - FIP1L1-PDGFRA fusion gene test results.
  - Chart notes or medical record documentation showing pre-treatment blood eosinophil count.
- For continuation requests:
  - FIP1L1-PDGFRA fusion gene test results.
  - Chart notes or medical record documentation supporting improvement in HES control.

Exclusions

Coverage will not be provided for treatment of HES for members with any of the following exclusions:

- HES secondary to a non-hematologic cause (e.g., drug hypersensitivity, parasitic helminth infection, [human immunodeficiency virus] HIV infection, non-hematologic malignancy).
- FIP1L1-PDGFRA kinase-positive HES.

Coverage Criteria

Eosinophilic Asthma[1-4,7]

Authorization of 12 months may be granted for treatment of eosinophilic asthma when all of the following criteria are met:

- Member is 6 years of age or older.
- Member has a baseline blood eosinophil count (pre-treatment with a biologic indicated for asthma) of at least 150 cells per microliter.
- Member has a history of severe asthma despite current treatment with both of the following medications at optimized doses, unless the member has a clinical reason to avoid these therapies:
  - Inhaled corticosteroid.
  - Additional controller (i.e., long-acting beta$_2$-agonist, long-acting muscarinic antagonist, leukotriene modifier, or sustained-release theophylline).
- Member will not use the requested medication concomitantly with other biologics indicated for asthma (e.g., Cinqair, Dupixent, Fasenra, Tezspire, or Xolair).

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)[1,6,8,9]

Authorization of 12 months may be granted for treatment of CRSwNP when all of the following criteria are met:

- Member is 18 years of age or older
- Member has bilateral nasal polyposis and chronic symptoms of sinusitis despite intranasal corticosteroid treatment for at least 2 months unless contraindicated or not tolerated.
- The member has CRSwNP despite one of the following:
  - Prior sino-nasal surgery.
  - Prior treatment with systemic corticosteroids within the last two years was ineffective, unless contraindicated or not tolerated

- Member has one of the following:
  - A bilateral nasal endoscopy, anterior rhinoscopy, or computed tomography (CT) showing polyps reaching below the lower border of the middle turbinate or beyond in each nostril.
  - Meltzer Clinical Score of 2 or higher in both nostrils.
  - A total endoscopic nasal polyp score (NPS) of at least 5 with a minimum score of 2 for each nostril.
- Member has symptoms of nasal blockage, congestion, or obstruction plus one of the following additional symptoms:
  - Rhinorrhea (anterior/posterior)
  - Reduction or loss of smell
  - Facial pain or pressure
- Member will continue to use a daily intranasal corticosteroid while being treated with the requested medication, unless contraindicated or not tolerated.
- Member will not use Nucala concomitantly with other biologics indicated for chronic rhinosinusitis with nasal polyps (e.g., Dupixent or Xolair).

Eosinophilic Granulomatosis with Polyangiitis (EGPA)[1,5]

Authorization of 12 months may be granted for treatment of EGPA when all of the following criteria are met:

- Member is 18 years of age or older.
- Member has a history or the presence of an eosinophil count of more than 1000 cells per microliter or a blood eosinophil level of greater than 10%.
- Member is currently taking oral corticosteroids, unless contraindicated or not tolerated.

Hypereosinophilic Syndrome (HES)[1]

Authorization of 12 months may be granted for treatment of HES when all of the following criteria are met:

- Member is 12 years of age or older.
- Member has a history or presence of a blood eosinophil count of at least 1000 cells per microliter.
- Member has been on a stable dose of HES therapy (e.g., oral corticosteroid, immunosuppressive, and/or cytotoxic therapy).
- Member has had HES for at least 6 months.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication.

Eosinophilic Asthma[1-4,7]

Authorization of 12 months may be granted for continuation of treatment of eosinophilic asthma when all of the following criteria are met:

- Member is 6 years of age or older.

- The member is currently receiving therapy with the requested medication.
- Nucala is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy as defined by reduction in the frequency and/or severity of symptoms and exacerbations.
- Member will not use Nucala concomitantly with other biologics indicated for asthma (e.g., Cinqair, Dupixent, Fasenra, Tezspire, or Xolair).

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)[1]

Authorization of 12 months may be granted for continuation of treatment of CRSwNP when all of the following criteria are met:

- Member is 18 years of age or older.
- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy as defined by achieving or maintaining a positive clinical response with the requested medication as evidenced by improvement in signs and symptoms of CRSwNP (e.g., improvement in nasal congestion, nasal polyp size, loss of smell, anterior or posterior rhinorrhea, sino-nasal inflammation, hyposmia and/or facial pressure or pain or reduction in corticosteroid use).
- Member will not use the requested medication concomitantly with other biologics indicated for chronic rhinosinusitis with nasal polyps (e.g., Dupixent or Xolair).

Eosinophilic Granulomatosis with Polyangiitis (EGPA)[1]

Authorization of 12 months may be granted for continuation of treatment of EGPA when all of the following criteria are met:

- Member is 18 years of age or older.
- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy as defined by reduction in the frequency and/or severity of symptoms and exacerbations.

Hypereosinophilic Syndrome (HES)[1]

Authorization of 12 months may be granted for continuation of treatment of HES when all of the following criteria are met:

- Member is 12 years of age or older.
- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy as defined by reduction in the frequency and/or severity of symptoms and exacerbations.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Nucala.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Global Initiative for Asthma (GINA): Global strategy for asthma management and prevention. 2023 update.
- National Asthma education and Prevention Program Expert Panel 3: Guidelines for the diagnosis and management of asthma
- Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program
- EAACI biologicals guidelines- recommendations for severe asthma
- American College of Rheumatology/Vasculitis Foundation Guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis
- European Position Paper on Rhinosinusitis and Nasal Polyps

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Nucala are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Nucala for allergic asthma can be found in the manufacturer's prescribing information, the Global Initiative for Asthma (GINA): Global strategy for asthma management and prevention guidelines, and the guideline update from the National Asthma Education and Prevention Program. The prescribing information indicates the minimum labeled age for Nucala is six years of age. Nucala should be used in patients whose symptoms are inadequately controlled with inhaled corticosteroids. According to the 2023 update of the GINA Global Strategy for asthma management and prevention, Nucala should be considered as an add-on therapy that is uncontrolled on other medications such as long-acting beta2-agonists, leukotriene receptor antagonists, tiotropium, or inhaled corticosteroids-formoterol maintenance and reliever therapy (MART).

According to the EAACI biologicals guidelines, Nucala should be given as add-on therapy in adults and pediatric patients 12 years and older with uncontrolled severe eosinophilic asthma (blood eosinophil cell counts 300 cells/mcL or more in the past 12 months or 150 cells/mcL or more at initiation) to decrease severe asthma exacerbations (strong recommendation for adults; conditional for pediatric patients), decrease or withdraw corticosteroids (strong recommendation for adults; conditional for pediatric patients), and improve lung function (may be relevant in severe asthma with very low lung function), quality of life, and asthma control (conditional recommendation for all).

Support for using Nucala to treat chronic rhinosinusitis can be found in the prescribing information. The addition of mepolizumab versus placebo to standard of care significantly improved the change from baseline to week 52 in total

endoscopic nasal polyp score (median change, -1 vs 0 on an 8-point scale; difference, -0.73; 95% CI, -1.11 to -0.34) and nasal obstruction visual analog scale (VAS) score (median change, -4.41 vs -0.82 on a 10-point scale; difference, -3.14; 95% CI, -4.09 to -2.18) in the randomized SYNAPSE trial (N=407). The study enrolled adults with recurrent, refractory, severe, bilateral nasal polyp symptoms despite standard of care treatment who were eligible for repeat nasal surgery. Nucala significantly reduced the proportion of patients who required nasal surgery (9% vs 23%) and who required systemic corticosteroids (25% vs 37%). The change in the following scores were also significantly reduced with Nucala: overall symptom VAS score (-4.48 vs -0.9), Sino-Nasal Outcome Test (SNOT)-22 total score (-30 vs -14), composite VAS score (combined nasal obstruction, nasal discharge, throat mucus, and loss of smell scores; -3.96 vs -0.89) and smell VAS score (-0.53 vs 0). Adverse events reported more frequently with Nucala included nasopharyngitis (25% vs 23%), oropharyngeal pain (8% vs 5%), and arthralgia (6% vs 2%). Patients had at least 1 nasal surgery in the past 10 years and required stable maintenance therapy with mometasone furoate intranasal spray for at least 8 weeks before screening.

Support for using Nucala to treat eosinophilic granulomatosis with polyangiitis can be found in a study by Wechsler et al. (2017). In adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA), a randomized trial (N=136) evaluated the addition of mepolizumab versus placebo to stable doses of prednisolone or prednisone with or without additional immunosuppressive therapy. Enrolled participants were at least 18 years of age, had received a diagnosis of relapsing or refractory eosinophilic granulomatosis with polyangiitis at least 6 months previously, and had been taking a stable dose of prednisolone or prednisone (≥7.5 to ≤50.0 mg per day, with or without additional immunosuppressive therapy) for at least 4 weeks before the baseline visit. Eosinophilic granulomatosis with polyangiitis was defined as a history or presence of asthma, a blood eosinophil level of 10% or an absolute eosinophil count of more than 1000 cells per cubic millimeter, and the presence of two or more criteria that are typical of eosinophilic granulomatosis with polyangiitis. Nucala was given as a 300 mg subcutaneous injection every 4 weeks. In co-primary outcomes, the total accrued weeks of remission over 52 weeks was significantly greater with mepolizumab versus placebo (OR, 5.91; 95% CI, 2.68 to 13.03) and remission at both week 36 and 48 was also significantly improved (32% vs 3%; OR, 16.74; 95% CI, 3.61 to 77.56). Remission for at least 24 weeks was achieved in 28% with Nucala and 3% with placebo; although, in subgroup analyses, the outcome was not significantly different with Nucala versus placebo in patients with an absolute eosinophil count (AEC) less than 150/mm(3) (n=57; 21% vs 7%) but was significantly greater with Nucala in patients with an AEC of 150/mm(3) or greater (n=79; 33% vs 0%). Remission within the first 23 weeks that continued until week 52 (secondary outcome) was also significantly greater with Nucala (19% vs 1%). Remission was defined as a Birmingham Vasculitis Activity Score (BVAS) of 0 (on a 63-point scale) and a prednisolone/prednisone dose of 4 mg/day or less. The time to first relapse was significantly reduced with Nucala versus placebo (HR, 0.32; 95% CI, 0.21 to 0.5); a relapse within the 52-week study period was reported in 56% with Nucala and 82% with placebo (major relapses, 22% vs 35%). The annualized relapse rate was significantly reduced with Nucala (1.14 vs 2.27). Relapses with Nucala and placebo, respectively, were vasculitis (43% and 65%), asthma (37% and 60%), and sino-nasal (35% and 51%). Relapse was defined as active vasculitis (BVAS greater than 0), active asthma signs or symptoms and a worsening Asthma Control Questionnaire score, or active nasal or sinus disease with worsening in at least 1 of the sino-nasal-symptom items leading to an increase in glucocorticoid dose to more than 4 mg/day of prednisolone (or equivalent), initiation of or increase in immunosuppressive therapy, or hospitalization. During weeks 48 through 52, the average prednisolone/prednisone dose was significantly reduced with Nucala versus placebo (OR, 0.2; 95% CI, 0.09 to 0.41), a dosage of 4 mg/day or less was achieved in 44% versus 7%, and discontinuation was achieved in 18% versus 3%. Over the 52-week study period, the mean daily dose was 9.2 mg with mepolizumab and 13.5 mg with placebo. Adverse events were reported in 97% with Nucala and 94% with placebo and included headache (32% vs 18%), nasopharyngitis (18% vs 24%), arthralgia (22% vs 18%), sinusitis (21% vs 16%), and upper respiratory tract infection (21% vs 16%). Serious adverse events were reported in 18% with Nucala and 26% with placebo and included exacerbation or worsening of asthma (3% vs 6%).

Support for using Nucala to treat hypereosinophilic syndrome (HES) can be found in the prescribing information. Nucala compared with placebo significantly reduced HES flares at 32 weeks (28% vs 56%; OR, 0.28; 95% CI, 0.12 to 0.64) in a randomized, double-blind trial (N=108) of adults and adolescents. HES flares were defined as worsening of clinical HES signs and symptoms or increasing eosinophils on at least 2 occasions that resulted in the need to increase oral corticosteroids or increase/add cytotoxic or immunosuppressive therapy. Nucala (300 mg every 4 weeks) versus placebo was also associated with significant reductions in the annualized rate of HES flares (0.5 vs 1.46; RR, 0.34; 95% CI, 0.19 to 0.63), HES flares during week 20 through week 32 (17% vs 35%; OR, 0.33; 95% CI, 0.13 to 0.85), and change from baseline in the median Brief Fatigue Inventory Item 3 score (-0.66 vs +0.32 on a 10-point scale). Patients were 12 years or older (mean age, 46 years) and had HES for at least 6 months (mean duration, 5.55 years). They experienced at least 2 HES flares in the past year (worsening of clinical symptoms or blood eosinophil counts that required an escalation in therapy) and had a blood eosinophil count of 1000 cell/mcL or higher during screening. All patients were on stable HES therapy for at least 4 weeks before randomization, which could include chronic or episodic oral corticosteroids, immunosuppressive, or cytotoxic therapy. Patients with non-hematologic secondary HES or FIP1L1-PDGFR-alpha kinase-positive HES were excluded.

References

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Reference number(s)
4582-A

Standard Medicare Part B Management Nulibry

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Nulibry	fosdenopterin

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indication[1]

Nulibry is indicated to reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Initial requests

- Genetic testing results documenting pathogenic variant(s) in the molybdenum cofactor synthesis 1 (MOCS1) gene, where applicable.

Continuation requests (where applicable)

- Genetic testing results documenting pathogenic variant(s) in the molybdenum cofactor synthesis 1 *(MOCS1)* gene.
- Chart notes or medical records documenting a benefit from therapy (e.g., improvement, stabilization, or slowing of disease progression for encephalopathy and/or seizure activity, improved or normalized uric acid, urinary S-sulfocysteine, and xanthine levels).

Coverage Criteria

Molybdenum cofactor deficiency (MoCD) Type A

Authorization of 12 months may be granted for treatment of MoCD Type A when the diagnosis was confirmed by genetic testing documenting pathogenic variant(s) in the molybdenum cofactor synthesis 1 (MOCS1) gene.

Authorization of 3 months may be granted for treatment of MoCD Type A when both of the following criteria are met:

- Member has a presumed diagnosis of MoCD Type A and genetic test results are pending.
- Member has clinical signs and symptoms associated with MoCD Type A (e.g., encephalopathy, intractable seizures, developmental delay, decreased uric acid levels, elevated urinary S-sulfocysteine and/or xanthine levels).

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member meets one of the following criteria:
    - The member has received less than 12 months of therapy and has genetic testing results documenting pathogenic variant(s) in the molybdenum cofactor synthesis 1 (MOCS1) gene.
    - The member has received 12 months of therapy or more and is experiencing benefit from therapy (e.g., improvement, stabilization, or slowing of disease progression for encephalopathy and/or seizure activity, improved or normalized uric acid, urinary S-sulfocysteine, and xanthine levels).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Nulibry.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Nulibry are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Nulibry [package insert]. Solana Beach, CA: Sentynl Therapeutics, Inc.; October 2022.
2. Atwal PS, Scaglia F. Molybdenum cofactor deficiency. Mol Genet Metab. 2016;117(1):1-4.
3. Schwahn BC, Van Spronsen FJ, Belaidi AA, et al. Efficacy and safety of cyclic pyranopterin monophosphate substitution in severe molybdenum cofactor deficiency type A: a prospective cohort study. Lancet. 2015; 386: 1955-1963.
4. ClinicalTrials.gov. Study of ORGN001 (formerly ALXN1101) in neonates with molybdenum cofactor deficiency (MOCD) type A. Available at: https://clinicaltrials.gov/study/NCT02629393. Accessed: November 11, 2023.
5. ClinicalTrials.gov. Safety & efficacy study of ORGN001 (formerly ALXN1101) in pediatric patients with MoCD type A currently treated with rcPMP. Available at: https://clinicaltrials.gov/ct2/show/NCT02047461. Accessed: November 11, 2024.

Reference number(s)
4850-A

Standard Medicare Part B Management
Obizur

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Obizur	antihemophilic factor [recombinant], porcine sequence

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Obizur is indicated for the on-demand treatment and control of bleeding episodes in adults with acquired hemophilia A.

Limitations of Use

- Safety and efficacy of Obizur has not been established in patients with a baseline anti-porcine factor VIII inhibitor titer of greater than 20 Bethesda units (BU).
- Obizur is not indicated for the treatment of von Willebrand disease.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Acquired hemophilia A[1-3]

Authorization of 1 month may be granted for treatment of acquired hemophilia A.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must meet all requirements in the coverage criteria.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Obizur.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Obizur are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Obizur [package insert]. Lexington, MA: Takeda Pharmaceuticals U.S.A., Inc.; March 2023.
2. National Hemophilia Foundation. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised October 2024. MASAC Document #290. https://www.hemophilia.org/sites/default/files/document/files/ MASAC-Products-Licensed.pdf. Accessed December 10, 2024.
3. Gomperts E. Recombinant B domain deleted porcine factor VIII for the treatment of bleeding episodes in adults with acquired hemophilia A. Expert Review of Hematology. 2015 Aug;8(4):427-32.

Reference number(s)
6242-A

Standard Medicare Part B Management Omvoh Intravenous (IV)

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name	Dosage Form
Omvoh	mirikizumab-mrkz	intravenous (IV)

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met, the member has no exclusions to the prescribed therapy, and the drug or biological is usually not self-administered. The criteria outlined in this policy is only applicable to drugs not usually self-administered and are furnished incident to a physician's service. Requests for drugs on a region's self-administered drug list are not covered. Members enrolled in Medicare Part D may seek coverage under their Medicare Part D plan.

FDA-approved Indications[1]

- Treatment of moderately to severely active ulcerative colitis in adults.
- Treatment of moderately to severely active Crohn's disease in adults.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Ulcerative colitis (UC) and Crohn's disease (CD)

For continuation requests: Chart notes or medical record documentation supporting benefit of therapy.

Reference number(s)
6242-A

Coverage Criteria

Ulcerative colitis (UC)[1]

Authorization of 12 months may be granted for treatment of moderately to severely active ulcerative colitis.

Crohn's disease (CD)[1]

Authorization of 12 months may be granted for treatment of moderately to severely active Crohn's disease.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Omvoh.
- Omvoh is being used to treat an indication listed in the coverage criteria.
- The member is receiving benefit from therapy.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Omvoh.
- The available compendium:
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- American College of Gastroenterology (ACG) Clinical Guideline: Ulcerative Colitis in Adults
- American Gastroenterological Association (AGA) Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis
- ACG Clinical Guideline: Management of Crohn's Disease in Adults
- AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Omvoh are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Omvoh [package insert]. Indianapolis, IN: Eli Lilly and Company.; January 2025.
2. Self-Administered Drug Exclusion List: and Biologicals Excluded from Coverage- Medical Policy Article (A52527) Version R57. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 22, 2025.
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10. Self-Administered Drug Exclusion List: Medical Policy Article (A53022) Version R38. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 22, 2025.

Reference number(s)
4238-A

Standard Medicare Part B Management Onpattro

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Onpattro	patisiran

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Onpattro is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

All other indications will be assessed on an individual basis. Submissions for indications other than those in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- Initial Requests:
  - Testing or analysis confirming a mutation of the TTR gene.
  - Medical record documentation confirming the member demonstrates signs and symptoms of polyneuropathy.
- Continuation Requests: Chart notes or medical record documentation supporting clinical benefit of therapy compared to baseline.

Reference number(s)
4238-A

Coverage Criteria

Polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis

Authorization of 12 months may be granted for treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (also called transthyretin-type familial amyloid polyneuropathy [ATTR-FAP]) when all of the following criteria are met:

- The diagnosis is confirmed by detection of a mutation in the TTR gene.
- Member exhibits clinical manifestations of ATTR-FAP (e.g., amyloid deposition in biopsy specimens, TTR protein variants in serum, progressive peripheral sensory-motor polyneuropathy).
- The requested medication will not be used in combination with any other medication approved for the treatment of hereditary transthyretin-mediated amyloidosis (e.g., Amvuttra, Tegsedi, Vyndamax, Vyndaqel, Wainua).

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving treatment with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- There is a clinical benefit from therapy with the requested medication compared to baseline (e.g., improvement of neuropathy severity and rate of disease progression as demonstrated by the modified Neuropathy Impairment Scale+7 (mNIS+7) composite score, the Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score, polyneuropathy disability (PND) score, FAP disease stage, manual grip strength).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Onpattro.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Guideline of transthyretin-related hereditary amyloidosis for clinicians.
- Hereditary Transthyretin Amyloidosis. In: GeneReviews.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Onpattro are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using the above initial criteria can be found in a guideline from Ando and colleagues and a Gene Reviews chapter discussing hereditary transthyretin amyloidosis. The diagnosis of ATTR should be suspected in patients with progressive sensorimotor and/or autonomic neuropathy. The diagnosis of hereditary ATTR is established when characteristic clinical features are present, a biopsy shows amyloid deposits that bind to anti-TTR antibodies, and there is identification of mutations in the TTR gene.

The treatment for peripheral and autonomic neuropathy is orthotopic liver transplantation, TTR tetramer stabilizers, and gene-silencing therapies. Liver transplantation provides a wild type gene expressing normal TTR in the liver. Successful liver transplantation results in the disappearance of the variant TTR protein and thus halts the progression of peripheral and/or autonomic neuropathy.

Pharmacologic treatment approaches for hereditary TTR amyloidosis (ATTR) include ribonucleic acid (RNA)-targeted therapies (e.g., Amvuttra, Onpattro, Tegsedi, Wainua) that interfere with hepatic TTR synthesis, and transthyretin tetramer stabilizers (e.g., Vyndaqel, Vyndamax) that reduce formation of TTR amyloid through stabilization of the tetramer configuration and subsequently prevent the release of amyloidogenic monomers. These therapies work to decrease TTR production. Currently, there is no literature supporting the combination use of any therapies approved for ATTR.

References

1. Onpattro [package insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; January 2023.
2. Adams, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018 Jul 5; 379(1):11-21.
3. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013; 8:31.
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Reference number(s)
2345-A

Standard Medicare Part B Management Opdivo

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Opdivo	nivolumab

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Unresectable or Metastatic Melanoma

Opdivo (nivolumab), as a single agent or in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic melanoma.

Adjuvant Treatment of Melanoma

Opdivo is indicated for the adjuvant treatment of adult and pediatric patients 12 years and older with completely resected stage IIB, stage IIC, stage III, or stage IV melanoma.

Metastatic Non-Small Cell Lung Cancer

Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

Opdivo, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations.

Opdivo is indicated for the treatment of adult patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo.

Neoadjuvant and Adjuvant Treatment of Resectable Non-Small Cell Lung Cancer

Opdivo, in combination with platinum-doublet chemotherapy, is indicated as neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC) and no known epidermal growth

factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, followed by single-agent OPDIVO as adjuvant treatment after surgery.

Neoadjuvant Treatment of Resectable Non-Small Cell Lung Cancer

Opdivo, in combination with platinum-doublet chemotherapy, is indicated as neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC).

Malignant Pleural Mesothelioma

Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

Advanced Renal Cell Carcinoma

- Opdivo as a single agent is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.
- Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with intermediate or poor risk advanced RCC.
- Opdivo, in combination with cabozantinib, is indicated for the first-line treatment of adult patients with advanced RCC.

Classical Hodgkin Lymphoma

Opdivo is indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after:

- Autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
- Three or more lines of systemic therapy that includes autologous HSCT.

Squamous Cell Carcinoma of the Head and Neck

Opdivo (nivolumab) is indicated for the treatment of adult patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

Urothelial Carcinoma

- Opdivo is indicated for the adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC.
- Opdivo, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.
- Opdivo is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:
    - Have disease progression during or following platinum-containing chemotherapy
    - Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer

Opdivo, as a single agent or in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Hepatocellular Carcinoma

Opdivo, in combination with ipilimumab, is indicated for the treatment of adult patients with hepatocellular carcinoma (HCC) who have previously been treated with sorafenib.

Esophageal Cancer

- Opdivo is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult patients who have received neoadjuvant chemoradiotherapy (CRT).
- Opdivo, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).
- Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).
- Opdivo is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

Opdivo, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

Compendial Uses

- Cutaneous melanoma
- Non-small cell lung cancer
- Colorectal cancer, including appendiceal adenocarcinoma
- Urothelial carcinoma
    - Bladder cancer
    - Primary carcinoma of the urethra
    - Upper genitourinary tract tumors
    - Urothelial carcinoma of the prostate
- Renal cell carcinoma
- Head and neck cancers
    - Very advanced head and neck cancer
    - Mucosal melanoma
    - Cancer of the nasopharynx
- Classical Hodgkin lymphoma
- Hepatocellular carcinoma
- Uveal melanoma
- Anal carcinoma
- Merkel cell carcinoma
- Central nervous system (CNS) brain metastases
- Pleural mesothelioma
- Peritoneal mesothelioma
- Gestational trophoblastic neoplasia
- Diffuse large B-cell lymphoma

    - Primary mediastinal large B-cell lymphoma
    - Histologic (Richter's) transformation to diffuse large B-cell lymphoma
- Small bowel adenocarcinoma
- Ampullary adenocarcinoma
- Extranodal NK/T-cell lymphoma
- Neuroendocrine tumors
    - Poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma
    - Well-differentiated grade 3 neuroendocrine tumors
- Endometrial carcinoma
- Vulvar Cancer
- Gastric cancer
- Esophageal and esophagogastric junction cancers
- Biliary tract cancers
    - Gallbladder cancer
    - Intrahepatic cholangiocarcinoma
    - Extrahepatic cholangiocarcinoma
- Cervical cancer
- Small cell lung cancer
- Kaposi Sarcoma
- Bone Cancer
- Pediatric Diffuse High-Grade Gliomas
- Pancreatic adenocarcinoma
- Soft Tissue Sarcoma
    - Extremity/body wall sarcoma
    - Head/neck sarcoma
    - Retroperitoneal/intra-abdominal sarcoma
    - Rhabdomyosarcoma
    - Angiosarcoma
- Anaplastic thyroid carcinoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- Documentation of laboratory report confirming microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) or polymerase epsilon/delta (POLE/POLD1) tumor status, where applicable.
- Documentation of the presence of EGFR exon 19 deletions or exon 21 L858R mutations or ALK rearrangements, where applicable.

Coverage Criteria

Cutaneous melanoma

Authorization of 12 months may be granted for treatment of cutaneous melanoma in either of the following settings:

- For treatment of unresectable or metastatic disease.
- The requested medication will be used as adjuvant treatment of stage III or IV disease following complete resection or no evidence of disease.
- The requested medication will be used as a single agent as adjuvant treatment of stage IIB and IIC disease following complete resection.
- The requested medication will be used as neoadjuvant treatment of resectable disease.

Non-small cell lung cancer

- Authorization of 12 months may be granted for treatment of recurrent, advanced, or metastatic NSCLC when either of the following conditions is met:
    - There are no EGFR exon 19 deletions or exon 21 L858R mutations or ALK rearrangements (unless testing is not feasible due to insufficient tissue) and the requested medication will be used in a regimen containing ipilimumab.
    - The requested medication will be used as a single agent as subsequent therapy.
- Authorization of 3 months (for up to 3 cycles total) may be granted for neoadjuvant treatment of resectable non-small cell lung cancer (NSCLC) in combination with platinum-doublet chemotherapy.
- Authorization of 12 months may be granted for neoadjuvant treatment of resectable non-small cell lung cancer (NSCLC) when both of the following conditions are met:
    - There are no EGFR exon 19 deletions or exon 21 L858R mutations or ALK rearrangements (unless testing is not feasible due to insufficient tissue)
    - The requested medication is used in combination with platinum-doublet chemotherapy (for up to 4 cycles total), followed by single agent adjuvant therapy (for up to 13 cycles)

Colorectal cancer

Authorization of 12 months may be granted for treatment of colorectal cancer, including appendiceal adenocarcinoma and anal adenocarcinoma, when member has microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) or polymerase epsilon/delta (POLE/POLD1) tumors.

Urothelial carcinoma

Authorization of 12 months may be granted for treatment of urothelial carcinoma, including bladder cancer, upper genitourinary tract tumors, urothelial carcinoma of the prostate, and primary carcinoma of the urethra.

Renal cell carcinoma

Authorization of 12 months may be granted for treatment of renal cell carcinoma for relapsed, advanced or stage IV disease.

Head and neck cancers

Authorization of 12 months may be granted for treatment of head and neck cancers, including very advanced head and neck cancer, mucosal melanoma, and cancer of the nasopharynx.

Classical Hodgkin lymphoma (cHL)

Authorization of 12 months may be granted for the treatment of classical Hodgkin lymphoma.

Hepatocellular carcinoma

Authorization of 12 months may be granted for treatment of hepatocellular carcinoma.

Uveal melanoma

Authorization of 12 months may be granted for treatment of uveal melanoma.

Anal carcinoma

Authorization of 12 months may be granted for treatment of anal carcinoma.

Merkel cell carcinoma

Authorization of 12 months may be granted for treatment of Merkel cell carcinoma.

CNS brain metastases

Authorization of 12 months may be granted for treatment of CNS brain metastases in patients with melanoma or NSCLC.

Pleural or peritoneal mesothelioma

Authorization of 12 months may be granted for treatment of pleural or peritoneal mesothelioma, including pericardial mesothelioma and tunica vaginalis testis mesothelioma, in either of the following settings:

- The requested medication will be used as first-line therapy in combination with ipilimumab.
- The requested medication will be used as subsequent therapy as a single agent or in combination with ipilimumab.

Gestational Trophoblastic Neoplasia

Authorization of 12 months may be granted for treatment of gestational trophoblastic neoplasia.

Diffuse large B-cell lymphoma

Authorization of 12 months may be granted for treatment of either of the following:

- Primary mediastinal large B-cell lymphoma
- Histologic (Richter's) transformation to diffuse large B-cell lymphoma.

Esophageal and esophagogastric junction cancer

- Authorization of 12 months may be granted for treatment of esophageal and esophagogastric junction cancer in members who are not surgical candidates or have unresectable, recurrent, or metastatic disease when the requested medication will be used in combination with ipilimumab or chemotherapy, or will be used as subsequent therapy.
- Authorization of 12 months may be granted for adjuvant treatment of completely resected esophageal or esophagogastric junction cancer with residual pathologic disease.
- Authorization of 12 months may be granted as a single agent or in combination with ipilimumab for neoadjuvant or perioperative treatment of esophageal or esophagogastric junction adenocarcinoma if tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and member is medically fit for surgery.

Small bowel adenocarcinoma

Authorization of 12 months may be granted for treatment of advanced or metastatic small bowel adenocarcinoma for microsatellite-instability high (MSI-H), mismatch repair deficient (dMMR) or polymerase epsilon/delta (POLE/POLD1) tumors, as a single agent or in combination with ipilimumab.

Ampullary adenocarcinoma

Authorization of 12 months may be granted for treatment of progressive, unresectable, or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) ampullary adenocarcinoma in combination with ipilimumab.

Extranodal NK/T-cell lymphoma

Authorization of 12 months may be granted for treatment of extranodal NK/T-cell lymphoma.

Neuroendocrine tumors

Authorization of 12 months may be granted for treatment of neuroendocrine tumors, including poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma and well-differentiated grade 3 neuroendocrine tumors, in combination with ipilimumab.

Endometrial carcinoma

Authorization of 12 months may be granted for treatment of endometrial carcinoma with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors.

Vulvar cancer

Authorization of 12 months may be granted for treatment of human papillomavirus (HPV)-related vulvar cancer.

Gastric cancer

Authorization of 12 months may be granted for treatment of gastric cancer in any of the following settings:

- When the requested medication is being used in members who are not surgical candidates or have unresectable, recurrent, or metastatic disease, when the requested medication will be used in combination with ipilimumab or chemotherapy.
- When the requested medication will be used as a single agent or in combination with ipilimumab for neoadjuvant or perioperative treatment of gastric adenocarcinoma if tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and member is medically fit for surgery.
- When the requested medication will be used in combination with ipilimumab or chemotherapy in members with early stage microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors and completed endoscopic resection.
- When the requested medication will be used in combination with chemotherapy in members with early stage HER-2 overexpression negative disease and completed endoscopic resection.

Biliary tract cancers

Authorization of 12 months may be granted for treatment of biliary tract cancers, including gallbladder cancer, intrahepatic cholangiocarcinoma, and extrahepatic cholangiocarcinoma.

Cervical cancer

Authorization of 12 months may be granted for subsequent treatment of recurrent or metastatic cervical cancer.

Small cell lung cancer

Authorization of 12 months may be granted for subsequent treatment of relapsed or progressive small cell lung cancer.

Kaposi Sarcoma

Authorization of 12 months may be granted in combination with ipilimumab for subsequent treatment of relapsed/refractory classic Kaposi Sarcoma.

Bone Cancer

Authorization of 12 months may be granted in combination with ipilimumab for unresectable or metastatic bone cancer with tumor mutation burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors.

Pediatric Diffuse High-Grade Gliomas

Authorization of 12 months may be granted for hypermutant tumor pediatric diffuse high-grade glioma as adjuvant treatment or for recurrent or progressive disease.

Soft Tissue Sarcoma

Authorization of 12 months may be granted for treatment of soft tissue sarcoma in the following settings:

- The requested medication will be used as a single agent or in combination with ipilimumab for treatment of extremity/body wall sarcomas, head/neck sarcomas and retroperitoneal/intra-abdominal sarcomas and rhabdomyosarcoma.
- The requested medication will be used in combination with ipilimumab for the treatment of angiosarcoma.

Pancreatic Adenocarcinoma

Authorization of 12 months may be granted in combination with ipilimumab for treatment of locally advanced, metastatic, or recurrent pancreatic adenocarcinoma with tumor mutation burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors.

Anaplastic Thyroid Carcinoma

Authorization of 6 months may be granted as a single agent for treatment of stage IVC anaplastic thyroid carcinoma.

Continuation of Therapy

Adjuvant treatment of melanoma

Authorization for 12 months total therapy may be granted for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used as adjuvant treatment for a member with melanoma.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease recurrence while on the current regimen.

Non-small cell lung cancer or pleural or peritoneal mesothelioma

Authorization for 12 months may be granted for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen.

Therapy durations will be limited to the following:

- Non-small cell lung cancer or pleural or peritoneal mesothelioma, including pericardial mesothelioma and tunica vaginalis testis mesothelioma subtypes, will be approved for up to 24 months when used in combination with ipilimumab.
- Neoadjuvant treatment of resectable NSCLC will be approved for a total of 3 months of therapy (up to 3 cycles).
- Authorization of 12 months may be granted for neoadjuvant treatment of resectable NSCLC (up to 4 cycles in combination with chemotherapy, followed by single agent adjuvant treatment up to 13 cycles).

Urothelial carcinoma

- Authorization for up to 12 months total may be granted for continued adjuvant treatment of urothelial carcinoma in all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:
    - The member is currently receiving therapy with the requested medication.
    - The requested medication is being used to treat urothelial carcinoma.

    - The member is receiving benefit from therapy. Benefit is defined as:
        - No evidence of unacceptable toxicity while on the current regimen AND
        - No evidence of disease progression while on the current regimen.
- Authorization for 12 months may be granted up to 24 months total when used in combination with gemcitabine and cisplatin for up to 6 cycles followed by nivolumab maintenance therapy for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:
    - The member is currently receiving therapy with the requested medication.
    - The requested medication is being used to treat urothelial carcinoma.
    - The member is receiving benefit from therapy. Benefit is defined as:
        - No evidence of unacceptable toxicity while on the current regimen AND
        - No evidence of disease progression while on the current regimen.

Renal cell carcinoma

Authorization for 12 months may be granted (up to 24 months total when used in combination with cabozantinib) for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat renal cell carcinoma.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen.

Gastric cancer, esophageal cancer, and esophagogastric junction carcinoma

Authorization of 12 months may be granted for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen.

Therapy durations will be limited to the following:

- Esophageal squamous cell carcinoma in combination with ipilimumab or chemotherapy for up to 24 months
- Unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma as a single agent until disease progression or unacceptable toxicity
- Adjuvant treatment of resected esophageal or esophagogastric junction cancer as a single agent for up to 12 months
- Gastric cancer, esophagogastric junction cancer, and esophageal adenocarcinoma in combination with chemotherapy for up to 24 months
- Gastric cancer in members who have completed endoscopic resection for up to 24 months

All other indications

Authorization for 12 months may be granted for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat any other diagnosis or condition enumerated in Section III.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Opdivo.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Hodgkin lymphoma
- NCCN Guideline: Small cell lung cancer
- NCCN Guideline: Vulvar cancer
- NCCN Guideline: Cervical cancer
- NCCN Guideline: Gestational trophoblastic neoplasia
- NCCN Guideline: Small bowel adenocarcinoma
- NCCN Guideline: Peritoneal mesothelioma
- NCCN Guideline: Pleural mesothelioma
- NCCN Guideline: T-cell lymphomas
- NCCN Guideline: Pediatric Hodgkin lymphoma
- NCCN Guideline: Cutaneous melanoma
- NCCN Guideline: Merkel cell carcinoma
- NCCN Guideline: Non-small cell lung cancer
- NCCN Guideline: Hepatocellular carcinoma
- NCCN Guideline: Anal carcinoma
- NCCN Guideline: Uveal melanoma
- NCCN Guideline: Gastric cancer
- NCCN Guideline: Esophageal and esophagogastric junction
- NCCN Guideline: Central nervous system cancers
- NCCN Guideline: Biliary tract cancers
- NCCN Guideline: Ampullary adenocarcinoma
- NCCN Guideline: Bladder cancer
- NCCN Guideline: Colon cancer
- NCCN Guideline: Rectal cancer
- NCCN Guideline: Head and neck cancers
- NCCN Guideline: Kidney cancer
- NCCN Guideline: Pediatric central nervous system cancers
- NCCN Guideline: Pancreatic adenocarcinoma
- NCCN Guideline: Chronic lymphocytic leukemia/Small lymphocytic lymphoma

- NCCN Guideline: Pediatric aggressive mature b-cell lymphomas
- NCCN Guideline: Thyroid carcinoma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Opdivo and are included in addition to the following:

- Cutaneous melanoma
- Non-small cell lung cancer
- Colorectal cancer, including appendiceal adenocarcinoma
- Urothelial carcinoma
- Renal cell carcinoma
- Head and neck cancers
- Classical Hodgkin lymphoma
- Hepatocellular carcinoma
- Uveal melanoma
- Anal carcinoma
- Merkel cell carcinoma
- Central nervous system (CNS) brain metastases
- Pleural mesothelioma
- Peritoneal mesothelioma
- Gestational trophoblastic neoplasia
- Diffuse large B-cell lymphoma
- Small bowel adenocarcinoma
- Ampullary adenocarcinoma
- Extranodal natural killer (NK)/T-cell lymphoma
- Neuroendocrine tumors
- Endometrial carcinoma
- Vulvar carcinoma
- Gastric cancer
- Esophageal and esophagogastric junction cancers
- Cervical cancer
- Small cell lung cancer
- Kaposi sarcoma
- Bone cancer
- Pediatric diffuse high-grade gliomas
- Biliary tract cancers
- Soft tissue sarcoma
- Pancreatic adenocarcinoma
- Histologic (Richter's) transformation to diffuse large B-cell lymphoma
- Primary mediastinal large b-cell lymphoma
- Anaplastic thyroid carcinoma

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer’s prescribing information.

Support for using Opdivo to treat the indications in section V can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals

in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

References

1. Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; October 2024.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed March 4, 2024.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Anal Carcinoma. Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf Accessed March 4, 2024

Reference number(s)
6796-A

Standard Medicare Part B Management Opdivo Qvantig

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Opdivo Qvantig	nivolumab and hyaluronidase-nvhy

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Advanced Renal Cell Carcinoma

- Opdivo Qvantig, as monotherapy, is indicated for the the first-line treatment of adult patients with intermediate or poor risk advanced renal cell carcinoma (RCC) following treatment with intravenous nivolumab and ipilimumab combination therapy.
- Opdivo Qvantig, in combination with cabozantinib, is indicated for the first-line treatment of adult patients with advanced RCC.
- Opdivo Qvantig, as monotherapy, is indicated for the treatment of adult patients with advanced RCC who have received prior anti-angiogenic therapy.

Unresectable or Metastatic Melanoma

- Opdivo Qvantig, as monotherapy, is indicated for the treatment of adult patients with unresectable or metastatic melanoma.
- Opdivo Qvantig, as monotherapy, is indicated for the treatment of adult patients with unresectable or metastatic melanoma following treatment with intravenous nivolumab and ipilimumab combination therapy.

Adjuvant Treatment of Melanoma

Opdivo Qvantig, as monotherapy, is indicated for the adjuvant treatment of adult patients with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma.

Neoadjuvant Treatment of Resectable Non-Small Cell Lung Cancer

Opdivo Qvantig, in combination with platinum-doublet chemotherapy, is indicated as neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC).

Neoadjuvant and Adjuvant Treatment of Resectable Non-Small Cell Lung Cancer

Opdivo Qvantig, in combination with platinum-doublet chemotherapy, is indicated for the neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) NSCLC and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, followed by Opdivo Qvantig as monotherapy in the adjuvant setting after surgical resection.

Metastatic Non-Small Cell Lung Cancer

Opdivo Qvantig, as monotherapy, is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo Qvantig.

Squamous Cell Carcinoma of the Head and Neck

Opdivo Qvantig, as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

Urothelial Carcinoma

- Opdivo Qvantig, as monotherapy, is indicated for the adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC.
- Opdivo Qvantig, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with unresectable or metastatic UC.
- Opdivo Qvantig, as monotherapy, is indicated for the treatment of adult patients with locally advanced or metastatic UC who:
    - have disease progression during or following platinum-containing chemotherapy
    - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer

Opdivo Qvantig, as monotherapy or as monotherapy following treatment with intravenous nivolumab and ipilimumab combination therapy, is indicated for the treatment of adult patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Hepatocellular Carcinoma

Opdivo Qvantig, as monotherapy, is indicated for the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib and following treatment with intravenous nivolumab and ipilimumab.

Esophageal Carcinoma

- Opdivo Qvantig, as monotherapy, is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult patients who have received neoadjuvant chemoradiotherapy (CRT).
- Opdivo Qvantig, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).
- Opdivo Qvantig, as monotherapy, is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy.

Gastric Cancer, Gastroesophageal Junction Cancer, Esophageal Adenocarcinoma

Opdivo Qvantig, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

Limitations of use:

Opdivo Qvantig is not indicated in combination with ipilimumab for the treatment of renal cell carcinoma, unresectable or metastatic melanoma, metastatic NSCLC, MSI-H or dMMR metastatic CRC, HCC, or unresectable advanced or metastatic ESCC.

Compendial Use[2]

Renal cell carcinoma as substitute for IV nivolumab

Documentation

The following documentation must be available, upon request, for all submissions:

- Documentation of laboratory report confirming MSI-H or mismatch repair deficient (dMMR) tumor status, where applicable.
- Documentation of EGFR mutation or ALK rearrangement status, where applicable.

Exclusions

Coverage will not be provided for members who have experienced disease progression while on programmed death receptor-1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitor therapy.

Coverage Criteria

Renal Cell Carcinoma[1,2]

Authorization of 12 months may be granted for treatment of renal cell carcinoma when the requested medication will be used in any of the following settings:

- As a single agent for the first-line treatment of intermediate or poor risk advanced renal cell carcinoma (RCC) following treatment with intravenous nivolumab and ipilimumab combination therapy.
- As a single agent for clear cell histology as subsequent therapy.
- As a single agent for non-clear cell histology.
- In combination with cabozantinib.

Melanoma[1]

Authorization of 12 months may be granted for treatment of melanoma when the requested medication will be used in either of the following settings:

- As a single agent for unresectable or metastatic disease.

- As a single agent for adjuvant treatment of completely resected Stage IIB, Stage IIC, Stage III, or Stage IV disease.

Non-Small Cell Lung Cancer (NSCLC)[1]

- Authorization of 12 months may be granted for treatment of metastatic non-small cell lung cancer when all of the following criteria are met:
  - If member has EGFR mutations or ALK rearrangements, disease has progressed on FDA-approved targeted therapy
  - The member had disease progression on or after platinum based chemotherapy.
  - The requested medication will be used as a single agent.
- Authorization of 3 months (for up to 3 cycles total) may be granted for neoadjuvant treatment of resectable non-small cell lung cancer (NSCLC) in combination with platinum based chemotherapy when there are no EGFR mutations or ALK rearrangements.
- Authorization of 12 months may be granted for neoadjuvant and adjuvant treatment of resectable non-small cell lung cancer (NSCLC) when both of the following criteria are met:
  - There are no EGFR mutations or ALK rearrangements.
  - The requested medication is used in combination with platinum based chemotherapy (for up to 4 cycles total), followed by single agent adjuvant therapy (for up to 13 cycles).

Head and Neck Cancer[1]

Authorization of 12 months may be granted for treatment of squamous cell head and neck carcinoma when all of the following criteria are met:

- The member has recurrent or metastatic disease.
- The member had disease progression on or after platinum based chemotherapy.
- The requested medication will be used as a single agent.

Urothelial Carcinoma[1]

- Authorization of 12 months may be granted in combination with gemcitabine and cisplatin for up to 6 cycles for first-line treatment of unresectable or metastatic urothelial carinoma.
- Authorization of 12 months may be granted as a single agent for treatment of urothelial carinoma when any of the following conditions are met:
  - The requested medication will be used to treat locally advanced or metastatic disease in members who:
    - have disease progression during or following platinum-containing chemotherapy.
    - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
  - The requested medication will be used as adjuvant therapy in members who are at high risk of recurrence after undergoing radical resection.

Colorectal Cancer[1]

Authorization of 12 months may be granted as a single agent for treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer when the disease has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Hepatocellular Carcinoma[1]

Authorization of 12 months may be granted as a single agent for treatment of hepatocellular carcinoma when member has been previously treated with sorafenib and following treatment with intravenous nivolumab and ipilimumab.

Esophageal Carcinoma[1]

- Authorization of 12 months may be granted as a single agent for adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in members who have received neoadjuvant chemoradiotherapy (CRT).
- Authorization of 12 months may be granted as a single agent for treatment of unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.
- Authorization of 12 months may be granted in combination with fluoropyrimidine- and platinum-containing chemotherapy, for first-line treatment of unresectable advanced or metastatic ESCC.

Gastric Cancer, Gastroesophageal Junction Cancer, Esophageal Adenocarcinoma[1]

Authorization of 12 months may be granted in combination with fluoropyrimidine- and platinum-containing chemotherapy for treatment of advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

Continuation of Therapy

Adjuvant treatment of melanoma

Authorization for 12 months total therapy may be granted for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used as adjuvant treatment for a member with melanoma.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease recurrence while on the current regimen.

Non-small cell lung cancer

Authorization for 12 months may be granted for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen.

Therapy durations in the following scenarios will be applied:

- Neoadjuvant treatment of resectable NSCLC will be approved for a total of 3 months of therapy (up to 3 cycles).

- Neoadjuvant treatment of resectable NSCLC (up to 4 cycles in combination with chemotherapy), followed by single agent adjuvant treatment (up to 13 cycles) will be approved for a total of 12 months.

Urothelial carcinoma

- Authorization for up to 12 months total may be granted for continued treatment of urothelial carcinoma in all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:
    - The member is currently receiving therapy with the requested medication.
    - The requested medication is being used as adjuvant treatment of urothelial carcinoma.
    - The member has not experienced unacceptable toxicity while on the current regimen.
    - The member has not experienced disease recurrence while on the current regimen.
- Authorization for 12 months may be granted up to 24 months total when used in combination with gemcitabine and cisplatin for up to 6 cycles followed by nivolumab maintenance therapy for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:
    - The member is currently receiving therapy with the requested medication.
    - The requested medication is being used to treat urothelial carcinoma.
    - The member is receiving benefit from therapy. Benefit is defined as:
        - No evidence of unacceptable toxicity while on the current regimen AND
        - No evidence of disease progression while on the current regimen.

Renal Cell Carcinoma

Authorization for 12 months may be granted (up to 24 months total when used as a single agent) for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat renal cell carcinoma.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen.

Esophageal Squamous Cell Carcinoma, Gastric Cancer, Gastroesophageal Junction Cancer, Esophageal Adenocarcinoma

Authorization of 12 months may be granted for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat esophageal squamous cell carcinoma, gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen.

Therapy durations in the following scenarios will be applied:

- 24 months total therapy for esophageal squamous cell carcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy

- 12 months total therapy for adjuvant treatment of resected esophageal or gastroesophageal junction cancer.
- 24 months total therapy for gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma that has not been resected.

All other indications

Authorization for 12 months may be granted for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat any other diagnosis or condition listed in the coverage criteria section.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Opdivo Qvantig.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Cutaneous melanoma
- NCCN Guideline: Non-small cell lung cancer
- NCCN Guideline: Hepatocellular carcinoma
- NCCN Guideline: Gastric cancer
- NCCN Guideline: Esophageal and esophagogastric junction cancers
- NCCN Guideline: Colon cancer
- NCCN Guideline: Rectal cancer
- NCCN Guideline: Head and neck cancers
- NCCN Guideline: Kidney cancer

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer’s prescribing information.

Support for using Opdivo to treat renal cell carcinoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

References

1. Opdivo Qvantig [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; December 2024.
2. The NCCN Drugs & Biologics Compendium® © 2025 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed January 9, 2025.

Reference number(s)
5326-A

Standard Medicare Part B Management Opdualag

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Opdualag	nivolumab and relatlimab-rmbw

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indication[1]

Opdualag is indicated for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Compendial Uses[2]

- Resectable melanoma
- Limited resectable melanoma

Coverage Criteria

Melanoma[1,2]

- Authorization of 6 months may be granted for treatment of adult members and children 12 years of age and older weighing at least 40 kg, with unresectable or metastatic melanoma.

- Authorization of 6 months may be granted for neoadjuvant treatment of resectable or limited resectable melanoma.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 6 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat an indication in the coverage criteria section
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Opdualag.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Cutaneous melanoma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Opdualag are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Opdualag to treat resectable and limited resectable melanoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Reference number(s)
5326-A

References

1. Opdualag [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; March 2024.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed November 14, 2024.

Reference number(s)
2210-A

Standard Medicare Part B Management Orencia

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Orencia	abatacept

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met, the member has no exclusions to the prescribed therapy, and the drug or biological is usually not self-administered. The criteria outlined in this policy is only applicable to drugs not usually self-administered and are furnished incident to a physician's service. Requests for drugs on a region's self-administered drug list are not covered. Members enrolled in Medicare Part D may seek coverage under their Medicare Part D plan.

FDA-approved Indications

- Treatment of moderately to severely active rheumatoid arthritis (RA) in adults
- Treatment of moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older
- Treatment of active psoriatic arthritis (PsA) in patients 2 years of age and older
- Prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated-donor

Limitations of Use:

Concomitant use of Orencia with other potent immunosuppressants [e.g., biologic disease-modifying antirheumatic drugs (bDMARDs), Janus kinase (JAK) inhibitors] is not recommended.

Compendial Uses

- Methotrexate-naive, early rheumatoid arthritis patients with poor prognostic factors
- Giant cell arteritis
- Chronic graft versus host disease
- Immune checkpoint inhibitor-related toxicity
- Oligoarticular juvenile idiopathic arthritis

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Rheumatoid arthritis (RA), articular juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), and giant cell arteritis

For Continuation requests:

- Chart notes or medical record documentation supporting benefit from therapy

Chronic graft versus host disease

For Initial requests:

- Chart notes, medical record documentation, or claims history supporting previous medications tried (if applicable), including response to therapy. If therapy is not advisable, documentation of clinical reason to avoid therapy.

For Continuation requests:

- Chart notes or medical record documentation supporting benefit from therapy.

Immune checkpoint inhibitor-related toxicity

For Initial requests:

- Chart notes, medical record documentation, or claims history supporting previous medications tried (if applicable), including response to therapy. If therapy is not advisable, documentation of clinical reason to avoid therapy.

Reference number(s)
2210-A

Coverage Criteria

Rheumatoid arthritis (RA)

Authorization of 12 months may be granted for treatment of active rheumatoid arthritis.

Articular juvenile idiopathic arthritis (JIA)

Authorization of 12 months may be granted for treatment of active articular juvenile idiopathic arthritis.

Psoriatic arthritis (PsA)

Authorization of 12 months may be granted for treatment of active psoriatic arthritis.

Prophylaxis of acute graft versus host disease

Authorization of 1 month may be granted for prophylaxis of acute graft versus host disease when both of the following criteria are met:

- Member is undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated-donor.
- The requested medication will be used in combination with a calcineurin inhibitor (e.g., cyclosporine, tacrolimus) and methotrexate.

Giant cell arteritis

Authorization of 12 months may be granted for treatment of giant cell arteritis.

Chronic graft versus host disease

Authorization of 12 months may be granted for treatment of chronic graft versus host disease when either of the following criteria is met:

- Member has had an inadequate response to systemic corticosteroids.
- Member has an intolerance or contraindication to corticosteroids.

Immune checkpoint inhibitor-related toxicity

Authorization of 6 months may be granted for treatment of immune checkpoint inhibitor-related toxicity when the member has myocarditis and meets any of the following:

- Member has had an inadequate response to systemic corticosteroids.
- Member has an intolerance or contraindication to corticosteroids.
- Member has concomitant myositis and the requested medication will be used in combination with ruxolitinib.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Prophylaxis of acute graft versus host disease and immune checkpoint inhibitor-related toxicity

All members (including new members) requesting authorization for continuation of therapy must meet all requirements in the coverage criteria.

All other indications

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Orencia.
- Orencia is being used to treat an indication listed in the coverage criteria section.
- The member is receiving benefit from therapy.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Orencia.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update.
- 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis.
- American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis.
- 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features.
- 2013 Update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis.
- 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis.
- 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis.

- 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis.
- 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis.
- EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Orencia are covered in addition to the following:

- Methotrexate-naive, early rheumatoid arthritis patients with poor prognostic factors
- Giant cell arteritis
- Chronic graft versus host disease
- Immune checkpoint inhibitor-related toxicity
- Oligoarticular juvenile idiopathic arthritis

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Orencia to treat methotrexate-naïve, early rheumatoid arthritis patients with poor prognostic factors can be found in a study by Westhovens et al. Abatacept plus methotrexate compared with placebo plus methotrexate significantly improved the rate of remission at 1 year (41.4% vs 23.3%) and the extent of structural damage (mean change from baseline in Genant-modified Sharp scoring system total score [TS], 0.63 vs 1.06), in a randomized trial (N=509) of methotrexate-naïve patients with rheumatoid arthritis. Remission was defined as a disease activity score in 28 joints (DAS28; C-reactive protein [CRP]) of less than 2.6. At 1 year, abatacept plus methotrexate compared with methotrexate alone was associated with significant differences in mean change from baseline to 1 year in DAS28 (CRP)(-3.22 vs -2.49), American College of Rheumatology 50% improvement (ACR50; 57.4% vs 42.3%), ACR70 (42.6% vs 27.3%), ACR90 (16.4% vs 6.7%), and major clinical response (ACR70 for at least 6 months, 27.3% vs 11.9%). At 1 year, abatacept plus methotrexate was also associated with a significant difference in Genant-modified Sharp erosion score (mean change from baseline, 0.5 vs 0.89) but not joint-space narrowing score (mean change from baseline, 0.13 vs 0.17), and there was no significant difference in the proportion of patients with no radiographic progression (TS 0 or less; 61.2% vs 52.9%). A health assessment questionnaire disability index (HAQ-DI) change from baseline of 0.3 or more units was achieved by significantly more patients with abatacept and methotrexate (71.9% vs 62.1%). Adverse events were reported in 84.8% with abatacept plus methotrexate versus 83.4% with placebo plus methotrexate, with infections being the most common (51.6% vs 54.9%); serious adverse events were reported in 7.8% and 7.9%, respectively. Adults enrolled in the study had rheumatoid arthritis for 2 years or less, at least 12 tender and 10 swollen joints, CRP of 0.45 mg/dL or higher, rheumatoid factor of anti-cyclic citrullinated protein type 2 positivity, and radiographic evidence of bone erosion of hands/wrists/feet. Abatacept 10 mg/kg IV infusion was given on days 1, 15, and 29, then every 4 weeks. Methotrexate 7.5 mg/week was increased to 15 mg/week at week 4, then to 20 mg/week at week 8. Oral corticosteroids (10 mg predniSONE equivalent or less daily) and up to 2 corticosteroid pulses (more than 10 mg predniSONE or equivalent orally for at least 3 consecutive days or injectable corticosteroids) were permitted during any 6-month period. A non-biological disease modifying antirheumatic drug (DMARD) was allowed after 6 months.

Support for using Orencia to treat giant cell arteritis can be found in a study by Langford et al. During a randomized, double-blind trial (N=41), the relapse-free survival rate at 1 year was significant in patients who received abatacept (48%) compared with patients who received placebo (31%), and the median duration of remission was significantly longer (9.9 vs 3.9 months, respectively). Patients with newly diagnosed or relapsing giant cell arteritis were treated with abatacept 10 mg/kg (500 mg for body weight less 60 kg, 750 mg for 60 to 100 kg, and 1000 mg for greater than 100 kg) IV infusion on days 1, 15, 29 and week 8, in combination with oral predniSONE 40 to 60 mg/day. Those who achieved remission after 12 weeks of treatment were randomized to continue abatacept every 4 weeks or switch to placebo, in combination with oral predniSONE 20 mg/day, which was tapered after randomization so that all patients discontinued predniSONE at week 28. Seven of the 41 randomized patients withdrew prior to week 64, and a subset analysis performed on the remaining 34 patients at week 64 demonstrated a significant relapse-free survival rate at 1 year for abatacept (52.9%) vs placebo (23.5%). There was no difference in the severity or frequency of adverse events between treatment groups.

Support for using Orencia to treat chronic graft-versus-host disease can be found in the National Comprehensive Cancer Network's guideline for hematopoietic cell transplantation. The NCCN Guideline supports the use of Orencia for chronic graft-versus-host disease as an additional therapy in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options.

Support for using Orencia to treat immune checkpoint inhibitor-related toxicity can be found in the National Comprehensive Cancer Network's guideline for the management of immunotherapy-related toxicities. The NCCN Guideline supports the use of Orencia as a further intervention for the management of myocarditis if no improvement within 24 to 48 hours of starting high-dose methylprednisolone. Orencia with ruxolitinib has also been used in concomitant myositis and myocarditis.

Support for using Orencia to treat oligoarticular juvenile idiopathic arthritis can be found in the 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis. In children with oligoarticular JIA, give biologic disease-modifying antirheumatic drugs (DMARDs). This approach is preferred instead of combining or switching conventional synthetic DMARDs due to reported greater probability of achieving rapid and sustained response.

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Reference number(s)
4397-A

Standard Medicare Part B Management
Oxlumo

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Oxlumo	lumasiran

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

Oxlumo is indicated for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary and plasma oxalate levels in pediatric and adult patients.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Initial requests:

- Molecular genetic test results demonstrating a mutation in the alanine:glyoxylate aminotransferase (AGXT) gene or liver enzyme analysis results demonstrating absent or significantly reduced alanine:glyoxylate aminotransferase (AGT) activity.

Continuation requests:

- Chart notes or medical records demonstrating a benefit from therapy.

Reference number(s)
4397-A

Coverage Criteria

Primary Hyperoxaluria Type 1[1-4]

Authorization of 12 months may be granted for the treatment of primary hyperoxaluria type 1 (PH1) when the diagnosis is confirmed by either of the following:

- Molecular genetic test results demonstrating a mutation in the alanine:glyoxylate aminotransferase (AGXT) gene.
- Liver enzyme analysis results demonstrating absent or significantly reduced alanine:glyoxylate aminotransferase (AGT) activity.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Oxlumo.
- Oxlumo is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy (e.g., decrease or normalization of urinary and/or plasma oxalate levels, improvement in kidney function).

Summary of Evidence

The contents of this document were created after examining the following resources:

- The prescribing information for Oxlumo.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- The primary hyperoxalurias: an algorithm for diagnosis

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Oxlumo are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the diagnostic criteria for primary hyperoxaluria type 1 can be found in a review article by Cochat and Rumsby. A definitive diagnosis of primary hyperoxaluria in a patient with clinical signs and symptoms requires genetic testing to detect a mutation in the alanine:glyoxylate aminotransferase (AGXT) gene. In some cases, the phenotype is typical of primary hyperoxaluria, but no mutation is detected, either because the mutation lies in a promoter or other regulatory sequence or because some other, as yet undefined, metabolic defect is present (i.e., "uncategorized" primary hyperoxaluria). In such cases, a liver biopsy can be performed to test for levels of AGT and GRHPR activity; if the results are negative, primary hyperoxaluria types 1 and 2 can be ruled out.

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Reference number(s)
6203-A

Standard Medicare Part B Management Pombiliti

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter(OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Pombiliti	cipaglucosidase alfa-atga

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Pombiliti is indicated, in combination with Opfolda, for the treatment of adult patients with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency) weighing greater than or equal to 40 kg and who are not improving on their current enzyme replacement therapy (ERT).

All other indications will be assessed on an individual basis.Submissions for indications other than those listed in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- Initial requests: acid alpha-glucosidase enzyme assay or genetic testing results supporting diagnosis.
- Continuation or therapy: chart notes documenting a positive response to therapy.

Reference number(s)
6203-A

Coverage Criteria

Late-onset Pompe disease[1]

Authorization of 12 months may be granted for treatment of late-onset Pompe disease when all of the following criteria are met:

- Member is 18 years of age or older.
- Member weighs greater than or equal to 40 kg.
- Diagnosis was confirmed by enzyme assay demonstrating a deficiency of acid alpha-glucosidase enzyme activity or by genetic testing.
- Member is not improving on current enzyme replacement therapy (ERT) (e.g., Lumizyme, Nexviazyme).
- The requested medication will be taken in combination with Opfolda (miglustat).

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy (e.g., improvement, stabilization, or slowing of disease progression for motor function, walking capacity, respiratory function, or muscle strength).
- The requested medication will be taken in combination with Opfolda (miglustat).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Pombiliti
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service-Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Pompe Disease, Gene Reviews article.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Pombiliti are covered.

Reference number(s)
6203-A

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using enzyme assay and genetic testing to diagnose Pompe disease can be found in a Gene Reviews article. The diagnosis of Pompe disease is established in a patient with either deficiency of acid alpha-glucosidase enzyme activity or biallelic pathogenic variants in GAA on molecular genetic testing.

References

1. Pombiliti [package insert]. Philadelphia, PA: Amicus Therapeutics US, LLC; September 2023.
2. Leslie N, Bailey L. Pompe Disease. 2007 Aug 31 [Updated Nov 2, 2023]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2023

Reference number(s)
2390-A

Standard Medicare Part B Management Prolia and Biosimilars

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Prolia	denosumab
Conexxence	denosumab-bnht
Jubbonti	denosumab-bbdz
Opsomyv	denosumab-dssb
Stoboclo	denosumab-bmwo

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1-5]

- Treatment of postmenopausal women with osteoporosis 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.
- Treatment to increase bone mass in men with osteoporosis 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.
- Treatment of glucocorticoid-induced osteoporosis 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.
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy (ADT) for nonmetastatic prostate cancer.

- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

Compendial Uses[6,7]

- Prophylaxis of osteoporosis in osteopenic postmenopausal women.
- For treatment-related bone loss in patients with prostate cancer receiving androgen deprivation therapy (ADT).
- Treatment in postmenopausal (natural or induced) patients with breast cancer receiving adjuvant aromatase inhibition therapy to maintain or improve bone mineral density and reduce risk of fractures.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in the coverage criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Osteoporosis Treatment[1-5]

Authorization of 12 months may be granted for treatment of osteoporosis in men or postmenopausal women at high risk for fracture.

Osteoporosis Prevention[6,8]

Authorization of 12 months may be granted for prevention of osteoporosis in osteopenic postmenopausal women.

Increasing Bone Mass in Prostate Cancer[1-5,7]

Authorization of 12 months may be granted to increase bone mass in men at high risk for fracture who are receiving androgen deprivation therapy (ADT) for prostate cancer.

Increasing Bone Mass in Breast Cancer[1-5,7]

Authorization of 12 months may be granted to increase bone mass in women at high risk for fracture who are receiving adjuvant aromatase inhibition therapy for breast cancer.

Glucocorticoid-Induced Osteoporosis[1-5]

Authorization of 12 months may be granted to increase bone mass in men and women with glucocorticoid-induced osteoporosis at high risk for fracture.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with a denosumab product.
- The requested drug is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy. Benefit is defined as:
    - Disease stability, or
    - Disease improvement

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for the requested drug.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Prostate cancer
- NCCN Guideline: Breast cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for the requested drug are covered in addition to the following:

- Prophylaxis of osteoporosis in osteopenic postmenopausal women
- For treatment-related bone loss in those receiving androgen deprivation therapy (ADT) for prostate cancer when the absolute fracture risk warrants drug therapy
- Maintenance or improvement in bone mineral density in postmenopausal patients with breast cancer receiving adjuvant aromatase inhibition therapy

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using denosumab for prevention of osteoporosis in osteopenic postmenopausal women as an approvable indication is evidenced by a multicenter, randomized, placebo-controlled study of 332 postmenopausal women with low bone mineral density (BMD) by Bone et al. Treatment with denosumab given once every 6 months improved BMD from baseline compared with placebo at 2 years. Postmenopausal women (mean age, 59.4 +/- 7.5 years) were eligible for enrollment if they had a lumbar spine (LS)-BMD T-score of -1 to -2.5 (mean T-score, -1.61 +/- 0.42), no history of fracture after age 25 years, and had not received IV bisphosphonates, fluoride, or strontium within the previous 5 years or parathyroid hormone agents (including derivatives), steroids, hormone-replacement therapy, selective estrogen-receptor modulators, calcitonin, or calcitriol within the previous 6 weeks. Patients were randomized to receive either denosumab 60 mg (n=166) or placebo (n=166) given subcutaneously every 6 months. All patients also received oral calcium (1000 mg) and vitamin D (400 to 800 international units or greater) daily. Approximately 86% of patients

completed 24 months of study treatment. At 24 months, patients in the denosumab arm had a mean percentage LS-BMD increase over baseline (6.5%; 97.5% CI, 5.8% to 7.2%) and patients in the placebo arm had a mean percentage LS-BMD decrease over baseline (-0.6%; 97.5% CI, -1.2% to 0.1%); additionally, the mean percentage LS-BMD difference between the 2 arms was significant (7%; 97.5% CI, 6.2% to 7.8%; p less than 0.0001). In patients who received denosumab, mean percentage BMDs were all increased from baseline at 24 months for the total hip (3.4%; 97.5% CI, 3% to 3.7%), femoral neck (2.8%; 97.5% CI, 2.3% to 3.3%), trochanter (5.2%; 97.5% CI, 4.7% to 5.6%), and distal third of the radius (1.4%; 97.5% CI, 0.9% to 1.9%), and the mean percent BMD differences compared with placebo were significant (p less than 0.0001). Markers of bone turnover were reduced from baseline in patients receiving denosumab (mean percent reduction: C-telopeptide I, 63% to 88%; tartrate-resistant acid phosphatase 5b, 40% to 50%; intact N-terminal propeptide of type 1 procollagen, 65% to 76%).

Support for using denosumab for the prevention or treatment of osteoporosis during androgen deprivation therapy is found in the National Comprehensive Cancer Network's guideline for prostate cancer. The NCCN Guideline for prostate cancer supports the use of denosumab as prevention or treatment of osteoporosis during androgen deprivation therapy in patients with high fracture risk.

Support for using denosumab to maintain or improve bone mineral density and reduce the risk of fractures in postmenopausal patients receiving adjuvant aromatase inhibition therapy is found in the National Comprehensive Cancer Network's guideline for breast cancer. The NCCN Guideline for breast cancer supports the use of denosumab in postmenopausal (natural or induced) patients receiving adjuvant aromatase inhibition therapy along with calcium and vitamin D supplementation to maintain or improve bone mineral density and reduce the risk of fractures.

References

1. Prolia [package insert]. Thousand Oaks, CA: Amgen Inc.; March 2024.
2. Conexxence [package insert]. Lake Zurich, IL: Fresenius Kabi USA, LLC.; March 2025
3. Jubbonti [package insert]. Princeton, NJ: Sandoz Inc.; April 2024.
4. Ospomyv [package insert]. Incheon, South Korea: Samsung Bioepis; February 2025.
5. Stoboclo [package insert]. Incheon, South Korea: Celltrion, Inc.; February 2025.
6. Micromedex® (electronic version). IBM Watson Health, Greenwood Village, Colorado. Available at https://www.micromedexsolutions.com Accessed October 10, 2024.
7. The NCCN Drugs & Biologics Compendium© 2025 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed April 8, 2025.
8. Bone HG, Bolognese MA, Yuen CK, et al: Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. *J Clin Endocrinol Metab*. 2008; 93(6):2149-2157

Reference number(s)
5915-A

Standard Medicare Part B Management Qalsody

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Qalsody	tofersen

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Qalsody is indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the superoxide dismutase 1 (SOD1) gene.

This indication is approved under accelerated approval based on reduction in plasma neurofilament light chain observed in patients treated with Qalsody. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available upon request for all submissions: Supporting chart notes, medical record documentation, and/or laboratory results as applicable to the coverage criteria and continuation of therapy sections.

- Initial Requests:
  - Weakness attributable to ALS.
  - Genetic testing confirming SOD1 mutation.

- Continuation Requests:
    - Documentation of clinical benefit from therapy with the requested medication.

Coverage Criteria

Amyotrophic Lateral Sclerosis (ALS)

Authorization of 12 months may be granted for treatment of ALS when all of the following criteria are met:

- Member is 18 years of age or older.
- Member has weakness attributable to ALS (e.g., medical history and/or diagnostic testing including nerve conduction studies, imaging and laboratory values to support the diagnosis).
- Member has an SOD1 mutation confirmed via genetic testing.

Continuation Of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving treatment with the requested medication.
- The requested medication is being used for the treatment of weakness associated with ALS in members who have a mutation in the SOD1 gene.
- Member has a documented clinical benefit from therapy with the requested medication.

Summary Of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Qalsody.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) – revised report of an EFNS task force

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Qalsody are covered.

Explanation Of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Qalsody [package insert]. Cambridge, MA: Biogen MA, Inc.; April 2023.
2. EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis; Andersen PM, et al. EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) – revised report of an EFNS task force. Eur J Neurol. 2012;19(3):360-75.

Reference number(s)
2066-A

Standard Medicare Part B Management Radicava

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Radicava	edaravone

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Radicava is indicated for the treatment of amyotrophic lateral sclerosis (ALS).

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available upon request for all submissions:

Chart notes or medical record documentation supporting use as applicable in the coverage criteria and continuation of therapy sections.

- Initial Requests:
  - Diagnosis of definite or probable ALS.
  - ALS Functional Rating Scale (ALSFRS-R) results.
- Continuation Requests:
  - Documentation of clinical benefit from therapy with the requested medication.

Reference number(s)
2066-A

Coverage Criteria

Amyotrophic Lateral Sclerosis (ALS)

Authorization of 12 months may be granted for treatment of ALS when both of the following criteria are met:

- Member has a diagnosis of definite or probable ALS (e.g., medical history and diagnostic testing including, nerve conduction studies, imaging and laboratory values to support the diagnosis).
- Member has scores of at least 2 points on all 12 areas of the revised ALS Functional Rating Scale (ALSFRS-R).

Continuation Of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving treatment with the requested medication.
- The requested medication is being used for the treatment of definite or probable ALS.
- There is a clinical benefit from therapy with the requested medication.

Summary Of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Radicava.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) – revised report of an EFNS task force

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Radicava are covered.

Explanation Of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Radicava [package insert]. Jersey City, NJ: MT Pharma America, Inc.; November 2022.
2. EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis; Andersen PM, et al. EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) – revised report of an EFNS task force. Eur J Neurol. 2012;19(3):360-75.

Reference number(s)
4717-A

Standard Medicare Part B Management Reblozyl

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Reblozyl	luspatercept-aamt

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Indicated for:

- Treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions
- Treatment of anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions
- Treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)

Compendial Use

Myelofibrosis-associated anemia

Limitations of Use

Reblozyl is not indicated for use as a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anemia.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Anemia with beta thalassemia

Initial requests:

- Pretreatment or pretransfusion hemoglobin (Hgb) level
- Either of the following:
  - Hemoglobin electrophoresis or high-performance liquid chromatography (HPLC) results OR molecular genetic testing results, or
  - Chart notes or medical record documentation stating diagnosis of beta thalassemia (β-thalassemia) or hemoglobin E/β-thalassemia was previously confirmed

Anemia of myelodysplastic syndrome or myelodysplastic/myeloproliferative neoplasm

Initial requests:

Pretreatment or pretransfusion hemoglobin (Hgb) level

Exclusions

Coverage will not be provided for treatment of anemia with beta thalassemia in members with hemoglobin S/β-thalassemia or alpha-thalassemia.

Coverage Criteria

Anemia with beta thalassemia

Authorization of 16 weeks may be granted for treatment of anemia with beta thalassemia in members 18 years of age or older when all of the following criteria are met:

- The member has symptomatic anemia evidenced by a pretreatment or pretransfusion Hgb level less than or equal to 11 grams per deciliter (g/dL).
- The member has a diagnosis of beta thalassemia (β-thalassemia) or hemoglobin E/β-thalassemia (β-thalassemia with mutation and/or multiplication of alpha globin is allowed) confirmed by one of the following:
    - Hemoglobin electrophoresis or high-performance liquid chromatography (HPLC)
    - Molecular genetic testing
- The member required at least 6 red blood cell (RBC) units to be transfused in the previous 24 weeks.

Note: If a red blood cell (RBC) transfusion occurred prior to dosing, the pretransfusion hemoglobin (Hgb) level must be considered for dosing purposes.

Anemia of myelodysplastic syndrome or myelodysplastic/myeloproliferative neoplasm

Authorization of 24 weeks may be granted for treatment of anemia of myelodysplastic syndrome or myelodysplastic/myeloproliferative neoplasm in patients 18 years of age or older when all of the following criteria are met:

- The member has one of the following:
    - Very low- to intermediate-risk myelodysplastic syndrome
    - Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
- The member has symptomatic anemia evidenced by a pretreatment or pretransfusion Hgb level less than or equal to 11 g/dL.
- The member has been receiving regular red blood cell (RBC) transfusions as defined by greater than or equal to 2 units per 8 weeks.

Myelofibrosis-associated anemia

Authorization of 12 months may be granted for the treatment of myelofibrosis-associated anemia.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Reblozyl
- Reblozyl is being used to treat an indication listed in the coverage criteria section
- The member is receiving benefit from therapy. Benefit is defined as meeting all of the following criteria:
    - Achieving or maintaining red blood cell transfusion burden reduction
    - No evidence of unacceptable toxicity from Reblozyl

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Reblozyl.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- A phase 3 trial of luspatercept in patients with transfusion-dependent β-thalassemia
- Luspatercept in patients with lower-risk myelodysplastic syndromes
- 2021 Thalassaemia International Federation guidelines for the management of transfusion-dependent thalassemia
- NCCN Guideline: Myelodysplastic syndromes
- NCCN Guideline: Myelofibrosis

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Reblozyl are covered in addition to myelofibrosis-associated anemia.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using either hemoglobin electrophoresis, high-performance liquid chromatography (HPLC) or molecular genetic testing is supported by the 2021 Thalassaemia International Federation guidelines for the management of transfusion-dependent thalassemia. The diagnosis of thalassemias relies on using red blood cell indices, hemoglobin analysis, and assessing the clinical severity of anemia. Molecular genetic testing may be useful for predicting the clinical phenotype and enabling presymptomatic diagnosis of at-risk family members and prenatal diagnosis. According to the UpToDate database, the diagnostic evaluation of a thalassemia depends on the personal and family history and available laboratory results. Genetic testing is used for precise diagnosis and is especially important in carrier detection, prenatal testing, and genetic counseling. Genetic testing can be done by gene sequencing or a number of other methods. If genetic testing is not available, hemoglobin can be analyzed using a number of protein chemistry methods. The most commonly used methods are HPLC and various hemoglobin electrophoresis techniques.

Support for using Reblozyl to treat myelofibrosis-associated anemia can be found in the National Comprehensive Cancer Network's guideline for myeloproliferative neoplasms. The NCCN Guideline for myeloproliferative neoplasms supports the use of Reblozyl for myeloproliferative-associated anemia with or without symptomatic splenomegaly and/or constitutional symptoms.

References

1. Reblozyl [package insert]. Summit, NJ: Celgene Corporation, a Bristol-Myers Squibb Company; August 2023.

2. Capellini MD, Viprakasit V, Taher AT, et al. A phase 3 trial of luspatercept in patients with transfusion-dependent β-thalassemia. N Engl J Med. 2020;382:1219-31.
3. Benz EJ, Angelucci E. Diagnosis of thalassemia (adults and children). In: UpToDate, Timauer, JS (Ed), UpToDate, Waltham, MA, 2023. URL: www.uptodate.com. Accessed October 3, 2023.
4. National Comprehensive Cancer Network. The NCCN Drugs & Biologics Compendium. http://www.nccn.org. Accessed July 11, 2024.
5. Fenaux P, Platzbecker U, Mufti GJ, et.al. Luspatercept in patients with lower-risk myelodysplastic syndromes. N Engl J Med. 2020;382:140-51.
6. Farmakis D, Porter J, Taher A, Cappellini MD, Angastiniotis M, Eleftheriou A. 2021 Thalassaemia International Federation guidelines for the management of transfusion-dependent thalassemia. Hemasphere. 2022;6(8):e732.

Reference number(s)
5693-A

Standard Medicare Part B Management Rebyota

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Rebyota	fecal microbiota, live - jslm

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Rebyota is indicated for the prevention of recurrence of Clostridioides difficile infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.

Limitations of Use[1]

Rebyota is not indicated for the treatment of CDI.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- Medical records, chart notes, and/or lab test results documenting the following:
  - Recurrent CDI
  - Stool test confirming the presence of C. difficile toxin or toxigenic C. difficile

Exclusions

Coverage will not be provided for members requesting Rebyota for the treatment of CDI.

Coverage Criteria

Prevention of Recurrence of Clostridioides Difficile Infection (CDI)[1]

Authorization of 30 days for a one-time treatment may be granted for prevention of CDI when all of the following criteria are met:

- Member is 18 years of age and older
- Member has recurrent CDI including either of the following:
    - At least one recurrence after a primary episode and has had completed at least 1 round of standard-of-care oral antibiotic therapy (e.g., metronidazole, fidaxomicin)
    - Has had at least 2 episodes of severe CDI resulting in hospitalization within the last year
- Member has a positive stool test for the presence of C. difficile toxin or toxigenic C. difficile within 30 days prior to treatment
- A single, one-time 150 mL dose will be administered rectally 24 to 72 hours after the last dose of antibiotics

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Rebyota.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Rebyota are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Rebyota [package insert]. Parsippany, NJ: Ferring Pharmaceuticals Inc; November 2022.

Reference number(s)
4475-A

Standard Medicare Part B Management
Rituxan Hycela

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Rituxan Hycela	rituximab and hyaluronidase human

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

- Adult patients with follicular lymphoma (FL):
  - Relapsed or refractory, follicular lymphoma as a single agent
  - Previously untreated follicular lymphoma in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy
  - Non-progressing (including stable disease), follicular lymphoma as a single agent after first-line CVP (cyclophosphamide, vincristine, and prednisone) chemotherapy
- Adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL) in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens
- Adult patients with previously untreated and previously treated chronic lymphocytic leukemia (CLL), in combination with fludarabine and cyclophosphamide (FC)

Limitations of Use

Initiate treatment with Rituxan Hycela only after patients have received at least one full dose of a rituximab product by intravenous infusion.

Rituxan Hycela is not indicated for the treatment of non-malignant conditions

Compendial Uses

- B-cell lymphomas:
  - Castleman's disease (CD)
  - High grade B-cell lymphoma (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)
  - Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
  - Marginal zone lymphomas
    - Nodal marginal zone lymphoma
    - Extranodal Marginal Zone Lymphoma (Gastric and Nongastric mucosa associated lymphoid tissue {MALT} lymphoma)
    - Splenic marginal zone lymphoma
  - Mantle cell lymphoma
- Post-transplant lymphoproliferative disorder (PTLD)
- Hairy cell leukemia
- Primary cutaneous B-cell lymphoma (e.g., cutaneous marginal zone lymphoma or cutaneous follicle center lymphomas)
- Small lymphocytic lymphoma (SLL)
- Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma
- Hodgkin lymphoma, nodular lymphocyte-predominant

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Prior to initiating therapy, all members must receive at least one full dose of a rituximab product by intravenous infusion without experiencing severe adverse reactions.

Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)

Authorization of 12 months may be granted for treatment of CD20 positive CLL or SLL.

Hairy cell leukemia (HCL)

Authorization of 12 months may be granted for treatment of CD20 positive HCL.

B-cell lymphomas

Authorization of 12 months may be granted for treatment of any of the following oncologic disorders that are CD20-positive as confirmed by testing or analysis:

- Castleman's disease (CD)

- Diffuse large B-cell lymphoma (DLBCL)
- Follicular lymphoma
- High grade B-cell lymphoma (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)
- Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
- Mantle cell lymphoma
- Nodal marginal zone lymphoma
- Post-transplant lymphoproliferative disorder (PTLD)
- Marginal zone lymphomas
    - Nodal marginal zone lymphoma
    - Extranodal Marginal Zone Lymphoma (Gastric and Nongastric MALT lymphoma)
    - Splenic marginal zone lymphoma

Primary cutaneous B-cell lymphoma

Authorization of 12 months may be granted for treatment of CD20 positive primary cutaneous B-cell lymphoma (e.g., cutaneous marginal zone lymphoma or cutaneous follicle center lymphomas).

Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

Authorization of 12 months may be granted for treatment of CD20 positive Waldenström macroglobulinemia/ lymphoplasmacytic lymphoma.

Hodgkin lymphoma, nodular lymphocyte-predominant

Authorization of 12 months may be granted for treatment of CD20 positive Hodgkin lymphoma, nodular lymphocyte-predominant.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy. Benefit is defined as no unacceptable toxicity while on the current regimen.

Reference number(s)
4475-A

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Rituxan Hycela.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Hairy cell leukemia
- NCCN Guideline: Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma
- NCCN Guideline: Hodgkin lymphoma
- NCCN Guideline: Primary cutaneous lymphomas
- NCCN Guideline: Chronic lymphocytic leukemia/small lymphocytic lymphoma
- NCCN Guideline: B-cell lymphomas

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Rituxan Hycela are covered in addition to the following:

- B-cell lymphomas:
    - Castleman's disease (CD)
    - High grade B-cell lymphoma (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)
    - Histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma
    - Marginal zone lymphomas
        - Nodal marginal zone lymphoma
        - Extranodal Marginal Zone Lymphoma (Gastric and Nongastric mucosa associated lymphoid tissue {MALT} lymphoma)
        - Splenic marginal zone lymphoma
    - Mantle cell lymphoma
- Post-transplant lymphoproliferative disorder (PTLD)
- Hairy cell leukemia
- Primary cutaneous B-cell lymphoma (e.g., cutaneous marginal zone lymphoma or cutaneous follicle center lymphomas)
- Small lymphocytic lymphoma (SLL)
- Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma
- Hodgkin lymphoma, nodular lymphocyte-predominant.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Rituxan Hycela for the compendial uses listed in section IV can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

References

1. Rituxan Hycela [package insert]. South San Francisco, CA: Genentech, Inc.; June 2021.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed April 11, 2024.

Reference number(s)
2501-A

Standard Medicare Part B Management Rituxan - Ruxience - Truxima - Riabni

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Rituxan	rituximab
Ruxience	rituximab-pvvr
Truxima	rituximab-abbs
Riabni	rituximab-arrx

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Rituxan is indicated for the treatment of pediatric patients aged 6 months and older with previously untreated, advanced stage, CD20-positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL) or mature B-cell acute leukemia (B-AL) in combination with chemotherapy.

Rituxan, Ruxience, Truxima, and Riabni are indicated for:

- Non-Hodgkin's Lymphoma (NHL) in adult patients with:
  - Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
  - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy
  - Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent after first-line CVP (cyclophosphamide, vincristine, and prednisone) chemotherapy
  - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens

- Chronic lymphocytic leukemia (CLL), in combination with fludarabine and cyclophosphamide (FC), for the treatment of adult patients with previously untreated and previously treated CD20-positive CLL.
- Granulomatosis with Polyangiitis (Wegener's Granulomatosis) and Microscopic Polyangiitis, in combination with glucocorticoids.
- Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies.

Rituxan is also indicated for:

Pemphigus Vulgaris (PV):

Rituxan is indicated for the treatment of adult patients with moderate to severe pemphigus vulgaris.

Compendial Uses

- B-cell lymphoma
    - Human Immunodeficiency Virus (HIV) related B-cell lymphoma[3]
    - Burkitt lymphoma
    - Castleman's disease
    - Diffuse large B-cell lymphoma
    - High grade B-cell lymphoma (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)
    - Histological transformation of indolent lymphomas to diffuse large B-cell lymphoma
    - Histological transformation of indolent lymphomas to high-grade B-cell lymphoma with MYC and BCL6 without BCL2 rearrangements
    - Follicular lymphoma
    - Mantle cell lymphoma
    - Marginal zone lymphoma (nodal, extranodal [gastric and non-gastric mucosa associated lymphoid tissue (MALT) lymphoma], splenic)
    - Post-transplant lymphoproliferative disorder (PTLD)
    - Pediatric aggressive mature B-cell lymphomas
    - B-cell lymphoblastic lymphoma
    - Primary Mediastinal Large B-Cell Lymphoma
- Malignant ascites, in advanced low-grade non-Hodgkin lymphoma
- B-cell acute lymphoblastic leukemia (ALL)
- CLL/small lymphocytic lymphoma (SLL)
- Hairy cell leukemia
- Rosai-Dorfman disease
- Hodgkin's lymphoma, nodular lymphocyte-predominant
- Hodgkin's lymphoma, CD20-positive, relapsed or progressive
- Primary cutaneous B-cell lymphoma
- Central nervous system (CNS) cancers
    - Leptomeningeal metastases from lymphomas
    - Primary CNS lymphoma
- Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma/Bing-Neel syndrome

- Rheumatoid arthritis, moderate or high disease activity despite disease-modifying anti-rheumatic drug (DMARD) monotherapy
- Autoimmune hemolytic anemia
- Immune or idiopathic thrombocytopenic purpura (ITP), as initial therapy
- Immune or idiopathic thrombocytopenic purpura (ITP), relapsed/refractory to standard therapy (e.g., corticosteroids, immune globulin)
- Thrombotic thrombocytopenic purpura
- Relapsing-remitting multiple sclerosis
- Primary progressive multiple sclerosis
- Myasthenia gravis, refractory to standard therapy (e.g., corticosteroids, immunosuppressants)
- Systemic lupus erythematosus, refractory to standard therapy (e.g., corticosteroids, immunosuppressants)
- Sjögren's syndrome
- Chronic graft-versus-host disease (GVHD)
- Prevention of Epstein-Barr virus (EBV)-related PTLD in hematopoietic stem cell transplant in (HSCT) recipients
- Evans syndrome
- Nephrotic syndrome, refractory to standard therapy (e.g., corticosteroids, immunosuppressants)
- Acquired factor VIII deficiency (acquired hemophilia A)
- Idiopathic inflammatory myopathy, refractory
- Immune checkpoint inhibitor-related toxicities
- Allogeneic transplant conditioning
- Lung disease with systemic sclerosis
- Thyroid eye disease (moderate to severe)
- Neuromyelitis optica (i.e., neuromyelitis optica spectrum disorder, NMOSD, Devic disease)
- Solid organ transplant
- Severe, refractory polyarteritis nodosa
- Membranous nephropathy

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Rheumatoid arthritis

Authorization of 12 months may be granted for treatment of rheumatoid arthritis when either of the following criteria are met.

- The member has previously received treatment with a biologic or targeted synthetic DMARD (e.g., TNF inhibitor, JAK inhibitor) indicated for the treatment of rheumatoid arthritis.
- The member has had an inadequate response to methotrexate or leflunomide or there is a clinical reason to avoid treatment with methotrexate or leflunomide (e.g., renal or hepatic impairment).

Oncologic indications

Oncologic disorders must be CD20-positive as confirmed by testing or analysis to identify the CD20 protein on the surface of the B-cell.

B-cell lymphoma

Authorization of 12 months may be granted for treatment of any of the following indications:

- HIV-related B-cell lymphoma
- Burkitt lymphoma
- Castleman's disease
- Diffuse large B-cell lymphoma
- High grade B-cell lymphoma (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)
- Histological transformation of indolent lymphomas to diffuse large B-cell lymphoma
- Histological transformation of indolent lymphomas to high-grade B-cell lymphoma with MYC and BCL6 without BCL2 rearrangements
- Follicular lymphoma
- Mantle cell lymphoma
- Marginal zone lymphoma (nodal, extranodal [gastric and non-gastric MALT], splenic)
- Post-transplant lymphoproliferative disorder
- Pediatric aggressive mature B-cell lymphomas
- B-cell lymphoblastic lymphoma
- Primary Mediastinal Large B-Cell Lymphoma

Malignant ascites

Authorization of 12 months may be granted for treatment of malignant ascites in patients with advanced low-grade non-Hodgkin lymphoma

B-cell acute lymphoblastic leukemia (ALL)

Authorization of 12 months may be granted for treatment of B-cell ALL.

Chronic lymphocytic leukemia/Small lymphocytic lymphoma

Authorization of 12 months may be granted for treatment of CLL/SLL.

Hairy cell leukemia

Authorization of 12 months may be granted for treatment of hairy cell leukemia.

Hodgkin's lymphoma

Authorization of 12 months may be granted for treatment of any of the following indications:

- Nodular lymphocyte-predominant Hodgkin's lymphoma
- CD20-positive relapsed or progressive Hodgkin's lymphoma

Primary cutaneous B-cell lymphoma

Authorization of 12 months may be granted for treatment of primary cutaneous B-cell lymphoma.

Central nervous system (CNS) cancers

Authorization of 12 months may be granted for treatment of any of the following indications:

- Leptomeningeal metastases from lymphomas
- Primary CNS lymphoma

Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma/Bing-Neel syndrome

Authorization of 12 months may be granted for treatment of Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma or Bing-Neel syndrome.

Rosai-Dorfman disease

Authorization of 12 months may be granted for the treatment of Rosai-Dorfman disease.

Hematologic indications

Authorization of 12 months may be granted for treatment of any of the following indications:

- Autoimmune hemolytic anemia
- Immune or idiopathic thrombocytopenic purpura
- Thrombotic thrombocytopenic purpura
- Evans syndrome
- Acquired factor VIII deficiency (acquired hemophilia A)

Multiple sclerosis

Authorization of 12 months may be granted for treatment of relapsing-remitting multiple sclerosis and primary progressive multiple sclerosis.

Myasthenia gravis

Authorization of 12 months may be granted for treatment of myasthenia gravis that is refractory to standard therapy (e.g., corticosteroids, immunosuppressants) or if there is a clinical reason to avoid standard therapy.

Systemic lupus erythematosus

Authorization of 12 months may be granted for treatment of systemic lupus erythematosus that is refractory to standard therapy (e.g., corticosteroids, immunosuppressants) or if there is a clinical reason to avoid standard therapy.

Granulomatosis with polyangiitis (Wegener's granulomatosis) and microscopic polyangiitis

Authorization of 12 months may be granted for treatment of granulomatosis with polyangiitis and microscopic polyangiitis.

Sjögren's syndrome

Authorization of 12 months may be granted for treatment of Sjögren's syndrome.

Nephrotic syndrome

Authorization of 12 months may be granted for treatment of nephrotic syndrome (e.g., minimal change disease) that is refractory to standard therapy (e.g., corticosteroids, immunosuppressants) or if there is a clinical reason to avoid standard therapy.

Idiopathic inflammatory myopathy

Authorization of 12 months may be granted for treatment of refractory idiopathic inflammatory myopathy.

Immune checkpoint inhibitor-related toxicities

Authorization of 3 months may be granted for treatment of immune checkpoint inhibitor-related toxicities.

Lung disease with systemic sclerosis

Authorization of 12 months may be granted for the treatment of lung disease with systemic sclerosis that is refractory to standard therapy (e.g., cyclophosphamide, mycophenolate) or if there is a clinical reason to avoid standard therapy.

Thyroid eye disease (moderate to severe)

Authorization of 12 months may be granted for the treatment of moderate to severe thyroid eye disease (excluding patients with risk for dysthyroid optic neuropathy) that is refractory to standard therapy (e.g., IV glucocorticoids) or if there is a clinical reason to avoid standard therapy.

Solid organ transplant

Authorization of 12 months may be granted for prevention and treatment of antibody mediated rejection in solid organ transplant.

Membranous nephropathy

Authorization of 12 months may be granted for treatment of membranous nephropathy when the member is at moderate to high risk for disease progression.

Other indications

Authorization of 12 months may be granted for treatment of any of the following indications:

- Chronic GVHD
- Prevention of EBV-related PTLD in HSCT recipients

- Pemphigus vulgaris
- As part of a non-myeloablative conditioning regimen for allogeneic transplant
- Neuromyelitis optica (i.e., neuromyelitis optica spectrum disorder, NMOSD, Devic disease)
- Severe, refractory polyarteritis nodosa

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 3 months may be granted for the diagnosis of immune checkpoint inhibitor-related toxicities when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy.

Authorization for 12 months may be granted for all diagnoses (except immune checkpoint inhibitor-related toxicities) when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Rituxan, Ruxience, Truxima, and Riabni.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Histiocytic neoplasms
- NCCN Guideline: Hairy cell leukemia
- NCCN Guideline: Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma
- NCCN Guideline: Hodgkin lymphoma
- NCCN Guideline: Hematopoietic cell transplantation
- NCCN Guideline: B-cell lymphoma
- Diagnosis and management of acquired coagulation inhibitors: a guideline from UKHCDO
- Guidelines on the management of drug-induced immune and secondary autoimmune, haemolytic anemia
- Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial
- American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia

- American Society of Hematology 2019 guidelines for immune thrombocytopenia
- French recommendations for the management of systemic sclerosis
- Is rituximab effective for systemic sclerosis? A systematic review and meta-analysis
- Kidney Disease Improving Global Outcomes (KDIGO) Glomerular Diseases Working Group: KDIGO clinical practice guideline for the management of glomerular diseases
- Myasthenia gravis: Association of British Neurologists' management guidelines
- Canadian Cardiovascular Society/Canadian Cardiac Transplant Network position statement on heart transplantation: patient eligibility, selection, and post-transplantation care
- Rituximab effectiveness and safety for treating primary Sjogren's syndrome (pSS): systematic review and meta-analysis
- Efficacy and safety of rituximab in relapsing-remitting multiple sclerosis: a systematic review and metanalysis
- Efficacy and safety of different doses and retreatment of rituximab: a randomized, placebo-controlled trial in patients who are biological naïve with active rheumatoid arthritis in an inadequate response to methotrexate (SERENE)
- Efficacy and safety of various repeat treatment dosing regimens of rituximab in patients with active rheumatoid arthritis: results of a phase III randomized study (MIRROR)
- Efficacy and safety of rituximab in the treatment of non-renal systemic lupus erythematosus
- 2019 update of EULAR recommendations for the management of systemic lupus erythematosus
- A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura
- Efficacy and safety of first-line rituximab in severe, acquired thrombotic thrombocytopenic purpura with suboptimal response to plasma exchange: experience of the French Thrombotic Microangiopathic Reference Center
- 2021 European Group on Grave's orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Grave's orbitopathy
- Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Rituxan, Ruxience, Truxima and Riabni are covered in addition to the following:

- B-cell lymphoma
    - Human Immunodeficiency Virus (HIV) related B-cell lymphoma
    - Burkitt lymphoma
    - Castleman's disease
    - Diffuse large B-cell lymphoma
    - High grade B-cell lymphoma (including high-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma], high-grade B-cell lymphoma, not otherwise specified)
    - Histological transformation of indolent lymphomas to diffuse large B-cell lymphoma
    - Histological transformation of indolent lymphomas to high-grade B-cell lymphoma with MYC and BCL6 without BCL2 rearrangements
    - Follicular lymphoma
    - Mantle cell lymphoma
    - Marginal zone lymphoma (nodal, extranodal {gastric and non-gastric mucosa associated lymphoid

tissue (MALT) lymphoma}, splenic)
    - Post-transplant lymphoproliferative disorder (PTLD)
    - Pediatric aggressive mature B-cell lymphomas
    - B-cell lymphoblastic lymphoma
    - Primary Mediastinal Large B-Cell Lymphoma
- Malignant ascites in advanced low-grade non-Hodgkin lymphoma
- B-cell acute lymphoblastic leukemia (ALL)
- CLL/small lymphocytic lymphoma (SLL)
- Hairy cell leukemia
- Rosai-Dorfman disease
- Hodgkin's lymphoma, lymphocyte-predominant
- Hodgkin's lymphoma, CD20-positive, relapsed or progressive
- Primary cutaneous B-cell lymphoma
- Central nervous system (CNS) cancers
    - Leptomeningeal metastases from lymphomas
    - Primary CNS lymphoma
- Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma/Bing-Neel syndrome
- Rheumatoid arthritis, moderate or high disease activity despite disease-modifying anti-rheumatic drug (DMARD) monotherapy
- Autoimmune hemolytic anemia
- Immune or idiopathic thrombocytopenic purpura (ITP), as initial therapy
- Immune or idiopathic thrombocytopenic purpura (ITP), relapsed/refractory to standard therapy (e.g., corticosteroids, immune globulin)
- Thrombotic thrombocytopenic purpura
- Relapsing-remitting multiple sclerosis
- Primary progressive multiple sclerosis
- Myasthenia gravis, refractory to standard therapy (e.g., corticosteroids, immunosuppressants)
- Systemic lupus erythematosus, refractory to standard therapy (e.g., corticosteroids, immunosuppressants)
- Sjögren's syndrome
- Chronic graft-versus-host disease (GVHD)
- Prevention of Epstein-Barr virus (EBV)-related PTLD in hematopoietic stem cell transplant in (HSCT) recipients
- Evans syndrome
- Nephrotic syndrome, refractory to standard therapy (e.g., corticosteroids, immunosuppressants)
- Acquired factor VIII deficiency (acquired hemophilia A)
- Idiopathic inflammatory myopathy, refractory
- Immune checkpoint inhibitor-related toxicities
- Allogeneic transplant conditioning
- Lung disease with systemic sclerosis
- Thyroid eye disease (moderate to severe)
- Neuromyelitis optica (i.e., neuromyelitis optica spectrum disorder, NMOSD, Devic disease)
- Solid organ transplant
- Severe, refractory polyarteritis nodosa
- Membranous nephropathy

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the below indications can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

- B-cell lymphomas (human immunodeficiency virus (HIV)-related B-cell lymphoma, Burkitt lymphoma, Castleman's disease, diffuse large B-cell lymphoma, high grade B-cell lymphoma, histological transformation of indolent lymphomas to diffuse large B-cell lymphoma, histological transformation of indolent lymphomas to high-grade B-cell lymphoma with MYC and BCL6 without BCL2 rearrangements, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, post-transplant lymphoproliferative disorder, pediatric aggressive mature B-cell lymphomas, B-cell lymphoblastic lymphoma, primary mediastinal large B-cell lymphoma)
- B-cell acute lymphoblastic leukemia
- CLL/SLL
- Hairy cell leukemia
- Rosai-Dorfman disease
- Hodgkin's lymphoma, lymphocyte-predominant
- Hodgkin's lymphoma, CD20-positive, relapsed or progressive
- Primary cutaneous B-cell lymphoma
- Leptomeningeal metastases from lymphomas
- CNS lymphomas
- Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma/Bing-Neel syndrome

Support for using rituximab to treat malignant ascites in patients with advanced low-grade non-Hodgkin lymphoma can be found in a case report by Ng, Pagliuca and Mufti (2002). The 59-year-old man had achieved partial remission with modified CHOP (cyclophosphamide, doxorubicin, vinblastine, and prednisolone) chemotherapy every 3 weeks for 6 cycles followed by weekly IV rituximab for 4 weeks. Regular drainage of abdominal ascites was still required 8 weeks after IV rituximab. Intraperitoneal rituximab (375 mg/m2 in 250 mL of 5% dextrose over 4 hours) was administered every 3 days for 4 doses. The treatment was well tolerated, with no reported adverse events or significant changes in blood parameters. An abdominal computed tomography scan 3 weeks after intraperitoneal rituximab showed a marked regression of ascites. No ascites was detected with clinical examination and no additional drainage of ascites was required during the 8-month follow-up period.

Support for using rituximab to treat rheumatoid arthritis that continues to be of moderate or high disease activity despite DMARD monotherapy can be found in two studies. The addition of rituximab to methotrexate in patients with active rheumatoid arthritis (RA) despite methotrexate treatment significantly improved American College of Rheumatology (ACR)20 and ACR50 response rates at week 24 in the Study Evaluating Rituximab's Efficacy in MTX Inadequate Responders (SERENE), a multicenter, randomized, double-blind, placebo-controlled, phase 3 study (n=509). Eligible patients were 18 to 80 years old, had active RA for at least 6 months despite methotrexate treatment (10 to 25 mg/week) for at least 12 weeks, and had not previously received biological treatment for RA. After a 2-week or longer washout of disease modifying antirheumatic drugs, during which patients continued stable dose methotrexate (10 to 25 mg/week) and folic acid (5 mg/week or greater), patients were randomized to IV therapy on days 1 and 15 with rituximab 500 mg (2 x500 group; n=167), rituximab 1000 mg (2 x 1000 group; n=170), or placebo (n=172); premedication

for all 3 groups was methylprednisolone 100 mg IV. NSAIDs and stable dose corticosteroids (prednisolone less than or equal to 10 mg/day orally [or equivalent]) were allowed. Patients who were not in remission at week 24 (Disease Activity Score [28 joints]-erythrocyte sedimentation rate [DAS28-ESR] less than 2.6) and met safety criteria were eligible for open-label rituximab treatment with the randomized dose (or 2 doses of 500 mg for initial placebo assignment). Initiation of 1 non-biologic DMARD was allowed if a less than 20% improvement in tender joint count (JC) and swollen (JC) versus baseline was noted between weeks 16 and 23. At week 24, significantly more patients in the rituximab 2 x500 mg and rituximab 2 x 1000 mg groups than in the placebo group, respectively, achieved an ACR20 response (primary outcome; 54.5% and 50.6% vs 23.3%) and an ACR 50 response (26.3% and 25.9% vs 9.3%). In the rituximab 2 x 500 mg and rituximab 2 x 1000 mg groups compared with the placebo group, respectively, there were also significant improvements in clinical remission (9.6% and 9.4% vs 2.3%), European League Against Rheumatism (EULAR) good response (17.4% and 11.8% vs 4.7%), and EULAR moderate response (49.1% and 51.2% vs 29.1%). By week 48, 93.5% of the rituximab 2 x 500 mg group, 91.3% of the rituximab 2 x 1000 mg group, and 89.5% of the placebo group had received a second course of treatment. At week 48, levels of disease activity were maintained or improved, with ACR20 response rates at 55.7% for rituximab 2 x 500 mg and 57.6% for rituximab 2 x 1000 mg and ACR50 response rates at 32.9% and 34.1%, respectively. Adverse effects to week 24 were reported in 77% of the rituximab 2 x 500 mg group, 76% of the rituximab 2 x 1000 mg group, and 74% of the placebo group, and included infusion-related reactions with the day 1 infusion (19%, 25%, and 14%) and with the day 15 infusion (7%, 6%, and 8%). The overall infection rate per 100 patient-years was 138.13 in the rituximab 500 mg group, 120.45 in the rituximab 1000 mg group, and 159 in the placebo group with a serious infection rate of 1.26, 2.46, and 8.83, respectively. Adverse effects to 48 weeks with rituximab 2 x 500 mg and rituximab 2 x 1000 mg were similar to the rates at 24 weeks.

An American College of Rheumatology (ACR)20 response was achieved in 64% to 72% of patients with rheumatoid arthritis (RA) at 48 weeks after treatment with 1 of 3 rituximab regimens administered initially and at 24 weeks plus methotrexate, in the multicenter, randomized, double-blind, phase 3 MIRROR trial (n=346). Eligible patients had a diagnosis of RA for at least 6 months, had active disease despite methotrexate therapy (10 to 25 mg/week) for at least 12 weeks (stable dose for at least 4 weeks), and had previously received no more than 1 biological agent for RA. Patients continued stable methotrexate doses of 10 to 25 mg/week during the study and were randomized to 1 of 3 rituximab regimens: 2 x 500 mg group, who received two 500 mg doses initially and at week 24 (n=134; mean age, 53.6 years); dose escalation group, who received two 500 mg doses initially and two 1000 mg doses at week 24 (n=119; mean age, 52.3 years); and 2 x 1000 mg group, who received two 1000 mg doses initially and at week 24 (n=93; mean age 51.3 years). Methylprednisolone 100 mg IV was administered before all rituximab infusions. Folic acid (5 mg/week), NSAIDs, oral glucocorticoids (10 mg/day or less), and intra-articular glucocorticoid injections of no more than 1 joint per 24 weeks were allowed; additional nonbiological and biological disease modifying antirheumatic drugs were not allowed. ACR20 response rates at 48 weeks were not significantly different between the rituximab 2 x 500 mg group and the dose escalation group (primary outcome; 64% for both groups) or between the rituximab 2 x 500 mg group and the rituximab 2 x 1000 mg group (64% vs 72%). ACR20 response rates at 48 weeks were similar in patients who had received a previous biological agent and patients who had not (65% and 67%, respectively). There were no significant differences among the 2 x 500 mg group, the dose escalation group, and the 2 x 1000 mg group, respectively, at 48 weeks in ACR50 response rates (39%, 39%, and 48%) or ACR70 response rates (20%, 19%, 23%). A moderate or good European League Against Rheumatism (EULAR) response was achieved by significantly more patients in the rituximab 2 x 1000 mg group than in the rituximab 2 x 500 mg group (89% vs 73%) or the dose escalation group (89% vs 72%). Disease Activity Score (28 joints)-erythrocyte sedimentation rate (DAS28-ESR) remission (DAS28-ESR less than 2.6) was achieved by 9% in the rituximab 2 x 500 mg group, by 13% in the dose escalation group, and by 19% in the rituximab 2 x 1000 mg group. Adverse effects were similar in all 3 treatment groups, occurred in 89% to 91% of patients, and included infusion-related reactions (30% to 39%) and infections (56% to 65%).

Jager et al supports using rituximab in the treatment of autoimmune hemolytic anemia. In patients with symptomatic, primary cold agglutinin disease, first-line treatment consists of rituximab alone, or rituximab plus bendamustine in fit patients. Rituximab plus bendamustine should be given if not previously used, or in patients who responded to it as first-line therapy and at least 2 years have passed since treatment. Rituximab monotherapy may be repeated in patients who previously responded for at least 1 year. Rituximab plus fludarabine is an option for fit, elderly patients. Corticosteroids remain first-line therapy for warm-AIHA, while the addition of rituximab should be considered early in severe cases and if no prompt response to steroids is achieved.

A systematic review by Liu et al identified 2 randomized studies of rituximab in patients with newly-diagnosed warm autoimmune hemolytic anemia. The addition of rituximab to a glucocorticoid significantly increased the likelihood of a complete hematological response at 12 months compared with glucocorticoid alone, but there were no significant improvements on the likelihood of a complete response at 6 months, partial responses at 6 or 12 months, or red blood cell requirement at 2, 6, or 12 months.

Support for using rituximab to treat immune thrombocytopenia is supported in treatment guidelines. The American Society of Hematology has published guidelines on the treatment of immune thrombocytopenia (Neunert et al). Rituximab may be considered in patients who have failed first-line therapy with conventional doses of corticosteroids, IV immune globulin, or splenectomy and who are at risk of bleeding. In 19 reports, the pooled estimate of overall platelet count response in 313 patients was 62.5%; however, durability of response varied. In 1 study of 306 patients, severe or life-threatening complications associated with rituximab occurred in 3.3%. Rituximab may be considered in patients with ITP who continue to have significant bleeding despite first-line therapy with corticosteroids or IV immune globulin.

As initial treatment of newly diagnosed ITP, corticosteroids alone rather than corticosteroids with rituximab is suggested (evidence with very low certainty). An initial course of corticosteroids with rituximab may be preferred if the potential for remission is valued higher than the potential for adverse events with rituximab.

Rituximab may also be considered as an alternative to splenectomy in patients with chronic ITP and in those who respond poorly to splenectomy. In 1 study, only 8 of 36 patients maintained platelet counts greater than 50 x 109/L at the 1-year follow-up after weekly doses of rituximab; however, other studies have demonstrated higher response rates, particularly when the rituximab dose was doubled after lack of response. Serum sickness was reported in some patients.

Froissart et al for the French Thrombotic Microangiopathies Reference Center, supports using rituximab for thrombotic thrombocytopenic purpura. The time to a durable remission was significantly shorter in patients with thrombotic thrombocytopenic purpura (TTP) who had a suboptimal response to therapeutic plasma exchange (TPE) and received rituximab compared with historical controls who did not receive rituximab; however, the mean plasma volume required to achieve durable remission did not differ significantly between the 2 groups in a prospective cohort study (n=74). Patients with thrombotic microangiopathy (Coombs-negative microangiopathic hemolytic anemia, acute peripheral thrombocytopenia [platelet count less than 150 x 109/L], and absence of identifiable cause for thrombocytopenia and microangiopathic hemolytic anemia) and mild renal involvement (less than 2.26 mg/dL) were diagnosed with TTP, with a definitive diagnosis confirmed by ADAMTS13 activity of less than 10%. Patients with hemolytic uremic syndrome, rituximab therapy for a previous TTP episode, or detectable ADAMTS13 activity after rituximab therapy were excluded. Patients with a suboptimal response to daily TPE (plasma volume, 1.5 predicted plasma volume for first procedure, 1 times predicted plasma volume thereafter until remission, followed by maintenance TPE tapered over 3 weeks) received rituximab 375 mg/m2 on the day of diagnosis of suboptimal response (day 0), day 3, day 7, and day 14 with premedication of dexchlorpheniramine 10 mg IV and acetaminophen 1 g IV. Patients without active infection received glucocorticoid therapy (1 mg/kg/day) for 3 weeks; patients not receiving glucocorticoids received methylprednisolone 30 mg IV. Suboptimal response was defined as an exacerbation (worsening neurologic manifestations, platelet count of less than 100 x 109/L for at least 2 days, or platelet count decrease of more than one-third the highest count for at least 2

days) or TTP refractory to TPE (platelet count after 4 days of TPE less than 2 times baseline with LDH persistently greater than ULN). Durable remission was defined as complete response (resolution of neurologic manifestations and platelet count greater than 150 x 109/L for at least 2 days) with no thrombocytopenia or clinical worsening during at least 30 days after first day of platelet recovery (including time on maintenance TPE). In the rituximab group (n=21; mean age, 36.8 +/- 11 years; glucocorticoid therapy, 71%; cytotoxic therapy, 0%; mean follow-up, 33 +/- 17.4 months) compared with historical controls (n=53; mean age, 41.7 +/- 16 years; glucocorticoid therapy, 79%; vincristine, n=17; vincristine and cyclophosphamide, n=3; mean follow-up, 35.3 +/- 28.5 months), platelet count recovery time (coprimary outcome) was significantly shorter (p=0.03). At day 35, significantly more patients (100% vs 78%; p less than 0.02) had achieved a durable remission; durable remission was achieved at a mean of 12 +/- 6.7 days after rituximab initiation. There were no significant differences between the rituximab group and the historical controls in mean plasma volume required to achieve a durable remission (coprimary outcome; 891 +/- 402 vs 999 +/- 583 mL/kg; p=0.67), exacerbation rate (2 of 21 vs 16 of 53; p less than 0.08), or relapse rate (within first year, 0% vs 9.4% [p=0.34]; after first year, 15.8% vs not reported [p=0.68]). In the rituximab group, mean peripheral B-cell counts were decreased by 80% compared with baseline on day 4; decreased to 1% of baseline by day 8; undetectable at month 3; less than 5% of baseline after 3 and 6 months; and greater than 10% of baseline after 12 months. In an analysis of the rituximab group (n=21) compared with historical controls with available data (n=19), ADAMTS13 activity was significantly higher after 1, 3, 6, and 9 months, but was similar at 12 months, and ADAMTS13 antibody titers were significantly lower at 3, 6, and 9 months and similar at 12 months. No severe adverse effects, hypogammaglobulinemia, or clinically relevant infections were reported with rituximab.

Support for using rituximab to treat multiple sclerosis can be found in two randomized trials.

A randomized, controlled trial and systematic review support using rituximab to treat relapsing-remitting multiple sclerosis. Svenningsson et al found rituximab therapy significantly reduced risk of relapse at 24 months compared with dimethyl fumarate in adults with treatment-naive relapsing remitting multiple sclerosis in the randomized, phase 3 RIFUND-MS trial. Toxicity was consistent with known safety profiles of each agent.

In a systematic review and meta-analysis by Tian et al in patients with relapsing-remitting multiple sclerosis, rituximab significantly reduced both the annualized relapse rate and the functional burden of disease, as measured by the mean Expanded Disability Status Scale score. Relapse rates declined over duration of rituximab use but remained at less than 15% through 96 weeks. This compilation of studies is inclusive, down to reports of 10 or more patients, but methodological quality and overall heterogeneity of the studies may limit these findings.

Support for using rituximab for primary progressive multiple sclerosis can be found in a randomized trial of patients with a disease duration of at least one year (N=439) by Hawker et al. There was no significant difference in rate of confirmed disease progression (CDP) between rituximab (30.2%) and placebo (38.5%) at 96 weeks. However, patients receiving rituximab did experience significantly smaller increases in median T2 lesion volume compared with those receiving placebo (301.95 mm3 vs 809.5 mm3). Subgroup analyses demonstrated that time to CDP was significantly delayed with the administration of rituximab in patients younger than 51 years of age (HR, 0.52) and in those with gadolinium brain lesions at baseline (HR, 0.41). Additionally, patients less than 51 years of age with baseline gadolinium lesions experienced a 61.6% relative reduction in total T2 lesion volume accumulation with rituximab compared with 50.7% for patients 51 years or older with baseline gadolinium lesions. In an exploratory analysis the median increase from baseline to week 96 in the Multiple Sclerosis Functional Composite (MSFC) timed 25-foot walk was 0.9 seconds with rituximab versus 1.48 seconds with placebo. Safety follow-up through 122 weeks demonstrated that the incidence of adverse events was similar between treatment groups; mild to moderate infusion-related reactions were more common with rituximab but the incidence decreased with successive infusions.

Support for using rituximab to treat myasthenia gravis (MG) can be found in one published guideline and a large meta-analysis. According to the Association of British Neurologists, rituximab has a role in managing poorly responsive myasthenia gravis when treatment with azathioprine has failed or the patient cannot tolerate it.

Zhao and colleagues (2021) noted that MG is an autoimmune neuromuscular disease. Nearly 10 to 30% of patients with MG are refractory to conventional therapy; rituximab is increasingly used in autoimmune disorders. In a systematic review and meta-analysis, these researchers examined the safety and effectiveness of rituximab for the treatment of refractory MG. Studies published between January 1, 2000 and January 17, 2021 were searched in PubMed, Embase, Cochrane Library, and ClincalTrails.gov. Primary outcomes included proportion of patients achieving minimal manifestation status (MMS) or better and quantitative MG (QMG) score change from baseline. Secondary outcomes were glucocorticoids (GC) doses change from baseline and proportion of patients discontinuing oral immunosuppressants. A total of 24 studies involving 417 patients were included in the meta-analysis. An overall 64 % (95 % CI: 49 % to 77 %) of patients achieved MMS or better. The estimated reduction of QMG score was 1.55 (95 % CI: 0.88 to 2.22). The mean reduction of GC doses was 1.46 (95 % CI: 1.10 to 1.82). The proportion of patients discontinuing oral immunosuppressants was 81 % (95 % CI: 66 % to 93 %). Subgroup analyses showed that the proportion of patients achieving MMS or better and discontinuing oral immunosuppressants was higher in MuSK-MG group than those in AChR-MG group. Improvement was more pronounced in patients with mild-to-moderate MG compared to those with severe MG. Moreover, the effectiveness appeared to be independent of the dose of rituximab. A total of 19.6% of patients experienced AEs, most of which were mild-to-moderate. Only 1 patient developed PML. The authors concluded that this systemic review and meta-analysis suggested that rituximab therapy could improve the PIS of a considerable number of patients with refractory MG to reach MMS or better with a good safety profile. It also exhibited a steroid-sparing effect. Furthermore, rituximab reduced QMG scores and the use of conventional oral immunosuppressants. The effectiveness was related to the patient's serotype and disease severity, but not to the doses of rituximab. These researchers stated that randomized controlled trials are needed to examine the effectiveness of rituximab in the treatment of refractory MG and to identify the characteristics of patients who might respond well to rituximab.

The authors stated that this study had several drawbacks. First, most of the studies included in the meta-analysis were observational studies, which might over-estimate the effectiveness of treatments compared with controlled trials. Second, these researchers could not compare the effectiveness of rituximab with other drugs since most of the included studies were single-arm. Third, the number of patients in each study was relatively small. In subgroup analysis, the number of cases in some studies was no more than 5, which resulted in great randomness of research results. Finally, the heterogeneity between studies was remarkable. There were many reasons for the high heterogeneity. Myasthenia gravis is a rare disease with high heterogeneity. Moreover, the rituximab regimen, follow-up duration and baseline characteristics of patients differed among studies. These investigators could not carry out meta-regression because some information was inaccessible in studies.

Support for using rituximab for systemic lupus erythematosus can be found in treatment guidelines. The European League Against Rheumatism (EULAR) recommendations for the management of systemic lupus erythematosus recommend rituximab as a treatment option for patients with organ-threatening SLE that is refractory to, or in patients with intolerance or contraindications to immunosuppressive agents. Additionally, a systematic review by Cobo-Ibanez et al found rituximab was safe and effective in patients with non-renal systemic lupus erythematosus, specifically disease activity, arthritis, thrombocytopenia, anti-dsDNA, and steroids-paring effect; long-term studies are needed.

Support for using rituximab for primary Sjogren’s syndrome can be found in a published systematic review. Souza et al completed a systematic review and meta-analysis to review the literature available addressing using rituximab for primary Sjogren’s syndrome. Four 24-week randomized trials in 276 adults with primary Sjogren syndrome, a single course of rituximab 1 g IV on days 1 and 15 compared with placebo significantly improved lacrimal gland function using

the lissamine green test (1 study), but no significant between-group difference using the Schirmer test (2 studies). Rituximab was associated with significant improvement in the salivary flow rate (low-quality evidence, 3 studies), but no significant difference in a 30% improvement in fatigue (3 studies), quality of life improvement (3 studies), or disease activity (2 studies). There was no significant between-group difference in serious adverse events.

Support for using rituximab for prophylaxis against Epstein-Barr virus disease in patients who have received a hematopoietic stem cell transplant can be found in a guideline published by Tomblyn et al. To prevent EBV-associated PTLD, high-risk patients (e.g., after T cell depletion, use of anti-T cell antibodies, umbilical cord blood transplants, and haplo identical transplants) should be assessed for EBV DNA load using a EBV PCR assay. Monitoring allows for preemptive immunosuppression reduction if feasible. If no response occurs with immunosuppression reduction, preemptive therapy with rituximab is recommended to prevent PTLD. Infusion of donor-derived, EBV-specific cytotoxic T-lymphocytes has shown some efficacy in the prophylaxis of EBV-lymphoma among recipients of T cell-depleted unrelated or mismatched allogeneic recipients. Other treatments that have been used include expanded donor-derived EBV-specific T cells to control blood EBV DNA levels and use of B cell depletion to decrease the risk of EBV PTLD. Due to lack of efficacy, prophylaxis or preemptive treatment with currently available antiviral agents is not recommended.

Support for using rituximab for Evan syndrome can be found in a guideline, small trials and a case report. The British Society for Haematology supports using rituximab as second-line therapy for primary Evans syndrome. Other second-line therapies include immunosuppressive drugs, danazol, splenectomy or vincristine.

Rituximab appears to effectively treat pediatric patients with refractory Evans syndrome based upon small, prospective, single-arm trials and case reports; however, long-term, randomized, controlled, clinical trials are not available to confirm safety in this population. Two prospective studies, one of severe immune thrombocytopenic purpura and one of autoimmune hemolytic anemia, contained subgroups of Evans patients who responded to treatment with rituximab based upon hematologic results from the entire cohort. Three Evans patients relapsed and were successfully retreated with rituximab. Safety data are inconclusive since adverse events (i.e., infusion reactions, bleeding, and serum sickness) were reported for the entire cohort, and it is unclear which of these occurred in the Evans subpopulation. Varicella infection requiring hospitalization was reported in one Evans syndrome patient after rituximab treatment. During post marketing surveillance, it has been reported that two adult patients died from progressive multifocal leukoencephalopathy (PML) while receiving rituximab for another autoimmune disease, systemic lupus erythematosus. PML was caused by reactivation of JC virus, and risk in the pediatric population is unknown.

Support for using rituximab for the treatment of nephrotic syndrome can be found in the KDIGO glomerular disease working group. In patients with frequently relapsing steroid-dependent minimal change disease, treatment with cyclophosphamide, rituximab, calcineurin inhibitors (cyclosporine, tacrolimus), or mycophenolic acid analogues (mycophenolate mofetil, sodium mycophenolate) is recommended rather than prednisone alone or no treatment. Rituximab has been associated with inducing remission in 65% to 100% of patients and has reduced the number of relapses, and the number of immunosuppressive drugs. However, the long-term efficacy and risks are unknown.

Support for using rituximab for acquired factor VIII deficiency (acquired hemophilia A) can be found in guidelines from UKHCDO. Rituximab can be considered as first-line therapy if standard immunosuppression is contraindicated but may have limited efficacy if used as a single agent. If there is no response within 3–5 weeks, second-line therapies should be considered. The most common second-line treatment is with rituximab combined with other agents. Alternative options are calcineurin inhibitors, multiple immunosuppressive agents and immune tolerance protocols.

Support for using rituximab for idiopathic inflammatory myopathy can be found in a randomized trial. Treatment with rituximab resulted in an 83% total rate of improvement and provided steroid-sparing effects after 44 weeks, despite not showing a difference between the randomized groups of "early" versus "late" rituximab administration in 195 evaluable

patients with muscle weakness due to refractory polymyositis (n=76), dermatomyositis (n=76), or juvenile dermatomyositis (n=48) in the Rituximab in Myositis (RIM) trial. Improvement was defined as at least a 20% improvement in 3 of any 6 core set measures (CSM) plus no more than 2 CSMs worsening by more than 25% (excluding muscle manual testing [MMT]). The 6 CSMs consisted of MMT using the MMT-8 measure, patient global visual analog scale (VAS), physician global VAS, Health Assessment Questionnaire disability index, muscle enzymes, and global extramuscular disease activity score. The time to achieve the preliminary International Myositis Assessment and Clinical Studies Group definition of improvement was 20 weeks in patients who received "early" rituximab (at weeks 0 and 1, followed by placebo at weeks 8 and 9) compared with 20.2 weeks in patients who received "late" rituximab (at weeks 8 and 9, with placebo at weeks 0 and 1). At 8 weeks, 15% of the rituximab group and 20.6% of the placebo group had met the definition of improvement. In 160 patients receiving a mean of 20.8 mg/day of prednisone at baseline, the mean dosage significantly decreased to 14.4 mg/day at the end of the trial. Of the 17 patients with worsening disease after initial improvement, 9 were retreated with rituximab and 8 of these met the definition of improvement after 19.9 weeks. Infections were the most common serious adverse event, particularly pneumonia (n=6) and cellulitis (n=6). Infusion reactions were significantly more common with rituximab than placebo (15.4% vs 5.3%), with 4 severe reactions and 2 hospitalizations. Glucocorticoids were not administered as premedications. Rituximab was administered in adults at a dosage of 750 mg/m2/dose up to 1000 mg/dose IV for 2 doses given 1 week apart. Patients were also receiving stables doses of glucocorticoids and at least one other immunosuppressant.

Support for rituximab as a treatment for systemic sclerosis-associated interstitial lung disease can be found in a guideline and meta-analysis. Hachulla et al indicated rituximab may be considered as a third-line treatment option in patients with systemic sclerosis-associated interstitial lung disease who have failed cyclophosphamide and/or mycophenolate. A meta-analysis by de Figueriredo Caldas et al found rituximab significantly improved lung function, but not skin fibrosis, in adults with systemic sclerosis. A systematic review that included the 3 studies from the meta-analysis (90 patients) plus 7 nonrandomized studies (128 patients) reported mixed results.

Support for using rituximab to treat thyroid eye disease is supported by a European guideline. The European Group on Grave’s orbitopathy (EUGOGO) indicate rituximab may be used as a second-line treatment for moderate to severe and active Graves' orbitopathy of recent onset (less than 12 months) if refractory to IV glucocorticoids, excluding patients with risk for dysthyroid optic neuropathy. This recommendation is based on two small, randomized double-blind, conflicting trials that differ in final treatment dosage.

Support for using rituximab for chronic graft versus host disease (cGVHD) can be found in the National Comprehensive Cancer Network’s guideline for hematopoietic cell transplantation. The NCCN Guideline for hematopoietic cell transplantation supports the use of rituximab as additional therapy in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options.

Support for using rituximab as conditioning for allogenic transplant can be found in the National Comprehensive Cancer Network’s guideline for hematopoietic cell transplantation. The NCCN Guideline for hematopoietic cell transplantation supports the use of rituximab as conditioning for allogenic transplant as part of a non-myeloablative regimen in combination with cyclophosphamide and fludarabine.

Support for using rituximab for the management of immunotherapy-related toxicities can be found in the National Comprehensive Cancer Network’s guideline for the management of immunotherapy-related toxicities. The NCCN Guideline for hematopoietic cell transplantation supports the use of rituximab as additional therapy for moderate (G2), severe (G3), or life-threatening (G4) immunotherapy-related bullous dermatitis. The guideline also supports the use of rituximab for moderate, severe, or life-threatening steroid-refractory myositis (proximal muscle weakness, neck flexor weakness, with or without myalgias) for significant dysphagia, life-threatening situations, or cases refractory to corticosteroids. Additionally, rituximab may be used as additional therapy for severe (G3-4) myasthenia gravis in

patients refractory to plasmapheresis or intravenous immune globulin (IVIG). Finally, rituximab can be used for encephalitis in patients positive for autoimmune encephalopathy antibody, or who have limited or no improvement after 7 to 14 days on high-dose corticosteroids with or without IVIG.

Support for rituximab as a treatment for neuromyelitis optica spectrum disorder can be found in a randomized trial. Tahara et al found that rituximab compared with placebo significantly reduced the relapse rate in adults with neuromyelitis optica spectrum disorder (NMOSD) who were or had been anti-aquaporin-4 antibody positive (AQP4+). In the 20-month, open-label RIN-2 extension study, relapses were greatly reduced and nearly all patients were completely withdrawn from oral steroids. Rituximab significantly reduced relapses compared with azathioprine in adults (about half AQP4+) in a 12-month randomized trial; more patients discontinued for adverse effects with azathioprine.

Support for rituximab as a treatment for solid organ transplant can be found in guidelines, retrospective studies, and case series. Costanzo et al recommended immune globulin (IVIG) infusion, plasmapheresis, either alone or combined, rituximab, and in very select cases, splenectomy as desensitization therapies for heart transplant. Rituximab may be added to initial therapy (may include immunoadsorption and corticosteroid or plasmapheresis/low dose of IV immunoglobulin and corticosteroid) to reduce the risk of recurrent rejection in heart transplant patients. Chih et all found that rituximab and plasma cell therapies (bortezomib) are the basis of desensitization treatment for heart transplant evidenced by increasing transplantation rates, reduced wait-list time, and graft outcomes similar to non-sensitized patients. Short-term outcomes in patients desensitized with various combinations of rituximab, IVIG, bortezomib, plasmapheresis, and immunoadsorption have been similar to those in patients not receiving desensitization agents. Since rituximab is a human monoclonal antibody and activates complement, it may create false positive crossmatch results. Rituximab and plasma cell depleting therapies (bortezomib) have been used in the treatment of antibody-mediated heart rejection but success rates have been variable. Adjunctive treatment with rituximab and/or bortezomib may be considered. Ravichandran et al found that the addition of rituximab to standard treatment (steroids and plasmapheresis with or without IV immunoglobulin (IVIG)) significantly decreased all-cause mortality and increased survival for 1 week or longer and at 3 years in a small retrospective study in patients with clinical suspicion of rejection following heart transplant. Baradaran et al found that in a case series of patients who underwent liver transplant and developed acute antibody-mediated rejection (AMR) all 4 treated with rituximab survived and had adequate liver function. Sakamoto et al found that in a case series of patients who underwent liver transplant and developed AMR, half of adult patients treated with rituximab had improvement of liver function without progression of fibrosis while the other half of adults died due to graft failure complicated with sepsis or progression of fibrosis or hepatic necrosis. In a case series case series of patients who underwent liver transplant and developed antibody-mediated rejection (AMR) less than half of pediatric patients treated with rituximab had improvement of liver function and pathological findings, while the remainder of patients had progression of fibrosis, and there was a death due to graft failure. Dhanasekaran et al found that in a case series of patients who underwent liver transplant and developed AMR, half of adult patients treated with rituximab had improvement of liver function without progression of fibrosis while the other half of adults died due to graft failure complicated with sepsis or progression of fibrosis or hepatic necrosis. Anti-B-cell agents (eg, rituximab), IV immunoglobulin, and bortezomib (antiproteasome antibody that depletes plasma cells) have been used in treatment of antibody-mediated liver transplant rejection. Charlton et al found that treatment of moderate to severe antibody-mediated liver transplant rejection may include plasmapheresis and IV immunoglobulin with or without anti-B cell or plasma cell drugs (e.g., rituximab, bortezomib, or eculizumab) Available data are based on case reports or inferred from the strategies used in non-hepatic transplants. Neuhaus et al, Vacha et al, Otani et al, and Witt et al found that Rituximab has been used for the treatment of antibody-mediated rejection (AMR) in adult lung transplant recipients. Vianna et al found that in intestine transplants induction with rabbit antithymocyte globulin plus rituximab compared with less intensive induction significantly reduced the risk of acute cellular rejection (ACR) and severe ACR during the first 24 days posttransplant but not after 24 days and significantly reduced the risk of graft loss due to rejection during

the first 6 months posttransplant but not after 6 months. Kubal et al and Vianna et al found that in intestine transplant patients induction with rabbit antithymocyte globulin and rituximab followed by maintenance with tacrolimus and steroids with or without an anti-IL-2 receptor antibody was associated with acute rejection in about a quarter to half of the patients.

Support for rituximab as a treatment for polyarteritis nodosa can be found in a guideline and some case reports. Chung et al indicated that rituximab may be considered in newly diagnosed, active, severe polyarteritis nodosa (defined as vasculitis with life-or organ-threatening disease [e.g., renal disease, mononeuritis multiplex, muscle disease, mesenteric ischemia, coronary involvement, limb/digit ischemia]). Treatment should be initiated with cyclophosphamide and glucocorticoids over rituximab and glucocorticoids. Efficacy remains uncertain. In some case reports, rituximab was successful in the treatment of severe, refractory polyarteritis nodosa but is role remains uncertain due to the lack of comparative or larger single-arm trials.

Support for rituximab as a treatment for membranous nephropathy can be found in guidelines from KDIGO. Rituximab can be considered in those with membranous nephropathy and at least one risk factor for disease progression.

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Reference number(s)
4824-A

Standard Medicare Part B Management
Rylaze

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Rylaze	asparaginase erwinia chrysanthemi (recombinant)-rywn

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Rylaze is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adult and pediatric patients 1 month or older who have developed hypersensitivity to E. coli-derived asparaginase.

Compendial Uses

Extranodal Natural Killer/T-cell lymphoma/ Aggressive NK-cell Leukemia (ANKL)

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Reference number(s)
4824-A

Coverage Criteria

Acute Lymphoblastic Leukemia (ALL) and Lymphoblastic Lymphoma (LBL)

Authorization of 12 months may be granted for treatment of ALL or LBL in members 1 month or older who have developed hypersensitivity to E. coli-derived asparaginase (e.g., pegaspargase) and the requested medication will be used in conjunction with multi-agent chemotherapy.

Extranodal Natural Killer/T-cell Lymphoma / Aggressive NK-cell Leukemia (ANKL)

Authorization of 12 months may be granted for treatment of ENKL or ANKL when both of the following criteria are met:

- The member has previously received and developed hypersensitivity to an E. coli-derived asparaginase (e.g., pegaspargase).
- The requested medication is used in conjunction with multi-agent chemotherapy.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat an indication listed in the coverage criteria section.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen and
    - No evidence of disease progression while on the current regimen.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Rylaze.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Acute lymphoblastic leukemia
- NCCN Guideline: T-cell lymphomas
- NCCN Guideline: Pediatric acute lymphoblastic leukemia

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Rylaze are covered in addition to extranodal Natural Killer/T-cell lymphoma/ Aggressive NK-cell Leukemia (ANKL).

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Rylaze to treat ALL, LBL, and extranodal natural killer/T-cell lymphoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Rylaze to treat extranodal natural killer/T-cell lymphoma can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

References

1. Rylaze [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; April 2024.
2. The NCCN Drugs & Biologics Compendium® ©2024 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed May 28, 2024.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: T-Cell Lymphomas. Version 4.2024. https:// www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf. Accessed May 28, 2024.
4. Rylaze. Micromedex® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com. Accessed May 28, 2024.

Reference number(s)
6041-A

Standard Medicare Part B Management
Rystiggo

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Rystiggo	rozanolixizumab-noli

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Rystiggo is indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- For initial requests: chart notes, medical records, or claims history documenting:
  - Positive anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody test
  - Myasthenia Gravis Foundation of America (MGFA) clinical classification
  - MG activities of daily living score
  - Previous medications tried, including response to therapy. If therapy is not advisable, documentation of clinical reasons to avoid therapy.

- For continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

Exclusions

The requested medication will not be used in combination with another neonatal Fc receptor blocker (e.g., Vyvgart, Vyvgart Hytrulo) or complement inhibitor (e.g., Soliris, Ultomiris, Zilbrysq).

Coverage Criteria

Generalized myasthenia gravis (gMG)

Authorization of 6 months may be granted for treatment of generalized myasthenia gravis (gMG) when all of the following criteria are met:

- Anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive
- Myasthenia Gravis Foundation of America (MGFA) clinical classification II to IV
- MG activities of daily living (MG-ADL) total score of greater than or equal to 5
- Meets one of the following:
    - Member has had an inadequate response or intolerable adverse event to at least two immunosuppressive therapies over the course of at least 12 months (e.g., azathioprine, corticosteroids, cyclosporine, methotrexate, mycophenolate, tacrolimus)
    - Member has had an inadequate response or intolerable adverse event to at least one immunosuppressive therapy and intravenous immunoglobulin (IVIG) over the course of at least 12 months
    - Member has a documented clinical reason to avoid therapy with immunosuppressive agents and IVIG

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication enumerated in the coverage criteria section.
- The member is receiving benefit from therapy (e.g., improvement in MG-ADL score, MG Manual Muscle Test (MMT), MG Composite).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Rystiggo.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- International consensus guidance for management of myasthenia gravis

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Rystiggo are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for Myasthenia Gravis Activities of Daily Living (MG-ADL) total score of greater than or equal to 5 can be found in the trials associated with Vyvgart and Vyvgart Hytrulo. Most clinical trials of myasthenia gravis agents required a MG-ADL of greater than or equal to 6, however, to align myasthenia gravis programs the baseline requirement will be greater than or equal to 5. MG-ADL is a scale that assesses the impact of myasthenia gravis on daily functions. This scale was used as an assessment tool to evaluate response to myasthenia gravis treatment from baseline in the clinical trials.

Support for the trial of immunosuppressive agents and IVIG before initiating therapy with Rystiggo can be found in the 2020 update to the international consensus guidance for management of myasthenia gravis. The update was completed prior to the approval of several new myasthenia gravis agents; however, the guidance includes recommendations for initiating treatment with a complement inhibitor (eculizumab [Soliris]). The recommendations indicate that eculizumab should be considered in the treatment of severe, refractory myasthenia gravis (after trials of other immunotherapies have been unsuccessful in meeting treatment goals).

Currently there are no treatment guidelines or literature supporting the concomitant use of complement inhibitors (e.g., Soliris, Ultomiris, Zilbrysq) or neonatal Fc receptor blockers (e.g., Vyvgart, Vyvgart Hytrulo, Rystiggo).

References

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2. Sanders D, Wolfe G, Benatar M et al. International consensus guidance for management of myasthenia gravis. Neurology. 2021; 96 (3) 114-122.
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Reference number(s)
6523-A

Standard Medicare Part B Management
Rytelo

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Rytelo	imetelstat

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Rytelo is indicated for adult patients with low- to intermediate-1 risk myelodysplastic syndromes (MDS) with transfusion-dependent anemia requiring 4 or more red blood cell units over 8 weeks who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESAs).

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Myelodysplastic Syndromes (MDS)[1]

Authorization of 24 weeks may be granted for treatment of low or intermediate-1 risk myelodysplastic syndromes (MDS) with transfusion-dependent anemia when both of the following criteria are met:

- The member has not responded to, has lost response to, or is ineligible for erythropoiesis-stimulating agents (ESAs).

- The member has been receiving regular red blood cell (RBC) transfusions as defined by greater than or equal to 4 units per 8 weeks.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 6 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Rytelo
- Rytelo is being used to treat an indication listed in the coverage criteria section
- The member is receiving benefit from therapy. Benefit is defined as:
    - Achieving or maintaining red blood cell transfusion burden reduction
    - No evidence of unacceptable toxicity from Rytelo.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Rytelo.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer’s prescribing information.

References

1. Rytelo [package insert]. Forest City, CA: Geron Corporation; June 2024.

Reference number(s)
4878-A

Standard Medicare Part B Management Saphnelo

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Saphnelo	anifrolumab-fnia

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Saphnelo is indicated for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), who are receiving standard therapy.

Limitations of Use: The efficacy of Saphnelo has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. Use of Saphnelo is not recommended in these situations.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Initial requests

Medical records (e.g., chart notes, lab reports) documenting the presence of autoantibodies relevant to SLE (e.g., ANA, anti-ds DNA, anti-Sm, antiphospholipid antibodies, complement proteins).

Continuation requests

Medical records (e.g., chart notes, lab reports) documenting disease stability or improvement.

Exclusions

Coverage will not be provided for members with any of the following exclusions:

- Severe active lupus nephritis in a member initiating therapy with Saphnelo.
- Severe active central nervous system (CNS) lupus (including seizures that are attributed to CNS lupus, psychosis, organic brain syndrome, cerebritis, or CNS vasculitis requiring therapeutic intervention within 60 days before initiation of anifrolumab) in a member initiating therapy with Saphnelo.
- Member is using Saphnelo in combination with other biologics.

Coverage Criteria

Systemic lupus erythematosus (SLE)

Authorization of 12 months may be granted for treatment of active SLE when all of the following criteria are met:

- Prior to initiating therapy, the member is positive for autoantibodies relevant to SLE (e.g., ANA, anti-ds DNA, anti-Sm, antiphospholipid antibodies, complement proteins).
- The member meets either of the following criteria:
  - The member is receiving a stable standard treatment for SLE with any of the following (alone or in combination):
    - Glucocorticoids (e.g., prednisone, methylprednisolone, dexamethasone)
    - Antimalarials (e.g., hydroxychloroquine)
    - Immunosuppressants (e.g., azathioprine, methotrexate, mycophenolate, cyclosporine, cyclophosphamide)
  - The member has a clinical reason to avoid treatment with a standard treatment regimen.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication enumerated in Section IV.
- The member is receiving benefit from therapy. Benefit is defined as disease stability or improvement.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Saphnelo.
- The available compendium
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)
  - Lexi-Drugs
  - Clinical Pharmacology
- 2019 Update of the EULAR Recommendations for the Management of Systemic Lupus Erythematosus
- 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus
- The British Society for Rheumatology guideline for the management of systemic lupus erythematosus
- Derivation and Validation of Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Saphnelo are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

The content of the exclusions can be found in the prescribing information.

The British Society for Rheumatology report that ANAs are present in about 95% of SLE patients. If the test for ANAs is negative, there is a low clinical probability of a member having SLE. The presence of anti-dsDNA antibodies, low complement levels or anti-Smith (Sm) antibodies are highly predictive of a diagnosis of SLE in patients with relevant clinical features. Anti-Ro/La and anti-RNP antibodies are less-specific markers of SLE as they are found in other autoimmune rheumatic disorders as well as SLE.

The SLICC group devised evidence-based classification criteria for lupus. These criteria introduced a requirement for at least one clinical and one immunological criterion and two others from an expanded list of items compared with the ACR criteria. These classification criteria may be used to aid diagnosis.

THE EULAR/ACR classification criteria for SLE require ANA antibodies ≥ 1:80 on HEp-2 cells or an equivalent positive test and a classification threshold score of ≥ 10. The classification criteria should not be used as diagnostic criteria. Testing by immunofluorescence on HEp-2 cells or a solid-phase ANA screening immunoassay with at least equivalent performance is highly recommended.

References

1. Saphnelo [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; December 2023.

2. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2023 Update of the EULAR Recommendations for the Management of Systemic Lupus Erythematosus. Ann Rheum Dis. 2024;83:15-29.
3. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis. 2019;78:1151-1159.
4. Gordon C, Amissah-Arthru MB, Gayed M, et al. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. Rheumatology (Oxford). 2018; 57(1):e1-e45.
5. Petri M, Orbai A-M, Alarcon GS, et al. Derivation and Validation of Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheum. 2012; 64:2677-2686. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3409311/. Accessed January 10, 2024.

Reference number(s)
4695-A

Standard Medicare Part B Management Sevenfact

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Sevenfact	coagulation factor VIIa [recombinant]-jncw

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication[1]

Sevenfact [coagulation factor VIIa (recombinant)-jncw] is indicated for the treatment and control of bleeding episodes occurring in adults and adolescents (12 years of age and older) with hemophilia A or B with inhibitors.

Limitations of Use

Sevenfact is not indicated for the treatment of patients with congenital Factor VII deficiency.

All other indications will be assessed on an individual basis.Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Hemophilia A with Inhibitors[1,3]

Authorization of 12 months may be granted for members 12 years of age or older for treatment of hemophilia A with inhibitors (see Appendix) when the inhibitor titer is ≥ 5 Bethesda units per milliliter (BU/mL) or the member has a history of an inhibitor titer ≥ 5 BU.

Hemophilia B with Inhibitors[1,3]

Authorization of 12 months may be granted for members 12 years of age or older for treatment of hemophilia B with inhibitors (see Appendix) when the inhibitor titer is ≥ 5 Bethesda units per milliliter (BU/mL) or the member has a history of an inhibitor titer ≥ 5 BU.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Hemophilia A or B with Inhibitors

Authorization for 12 months may be granted for members 12 years of age or older when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat Hemophilia A or B with inhibitors.
- The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

Appendix

Inhibitors - Bethesda Units (BU)[3]

The presence of inhibitors is confirmed by a specific blood test called the Bethesda inhibitor assay.

- High-titer inhibitors:
  - ≥ 5 BU/mL
  - Inhibitors act strongly and quickly neutralize factor
- Low-titer inhibitors:
  - < 5 BU/mL
  - Inhibitors act weakly and slowly neutralize factor

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Sevenfact.
- The available compendium
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)

  - Lexi-Drugs
  - Clinical Pharmacology
- WFH Guidelines for the Management of Hemophilia, 3rd edition.
- MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Sevenfact are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Sevenfact [package insert]. Puteaux , France: Laboratoire Francais du Fractionnement et des Biotechnologies S.A. (LFB S.A.); June 2024.
2. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020;26 Suppl 6:1-158. doi:10.1111/hae.14046.
3. National Hemophilia Foundation. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised October 2024. MASAC Document #290. https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed December 11, 2024.

Reference number(s)
2749-A

Standard Medicare Part B Management Signifor LAR

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Signifor LAR	pasireotide

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

- Treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option.
- Treatment of patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

Compendial Uses[2]

- Carcinoid syndrome.
- Metastatic neuroendocrine tumors (NETs) of the gastrointestinal (GI) tract (carcinoid tumors).

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Acromegaly:

- For initial approval: Laboratory report indicating high pretreatment insulin-like growth factor-1 (IGF-1) level and chart notes indicating an inadequate or partial response to surgery or a clinical reason for not having surgery.
- For continuation: Laboratory report indicating normal current IGF-1 levels or chart notes indicating that the member's IGF-1 level has decreased or normalized since initiation of therapy.

Cushing's Disease:

- For initial requests, pretreatment cortisol level as measured by one of the following tests:
  - Urinary free cortisol (UFC)
  - Late-night salivary cortisol
  - 1 mg overnight dexamethasone suppression test (DST)
  - Longer, low dose DST (2 mg per day for 48 hours)
- For continuation of therapy (if applicable), laboratory report indicating current cortisol level has decreased from baseline as measured by one of the following tests:
  - Urinary free cortisol (UFC)
  - Late-night salivary cortisol
  - 1 mg overnight dexamethasone suppression test (DST)
  - Longer, low dose DST (2 mg per day for 48 hours)

Coverage Criteria

Acromegaly[1,3,4]

Authorization of 12 months may be granted for treatment of acromegaly when all of the following criteria are met:

- Member has a high pretreatment insulin-like growth factor-1 (IGF-1) level for age and/or gender based on the laboratory reference range.
- Member has had an inadequate or partial response to surgery OR there is a clinical reason why the member has not had surgery.

Cushing's Disease[1,5]

Authorization of 12 months may be granted for treatment of Cushing's disease when the member has had surgery that was not curative OR the member is not a candidate for surgery.

Neuroendocrine Tumors (NETs) of the Gastrointestinal (GI) Tract (Carcinoid Tumors)[2]

Authorization of 12 months may be granted for treatment of metastatic NETs of the GI tract (carcinoid tumors).

Carcinoid Syndrome[2]

Authorization of 12 months may be granted for treatment of carcinoid syndrome.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy. Benefit is defined as:
    - Acromegaly: decreased or normalized IGF-1 level since initiation of therapy.
    - Cushing's disease (any of the following):
        - Lower cortisol levels since the start of therapy per one of the following tests:
            - Urinary free cortisol (UFC)
            - Late-night salivary cortisol
            - 1 mg overnight dexamethasone suppression test (DST)
            - Longer, low dose DST (2 mg per day for 48 hours)
        - Improvement in signs and symptoms of the disease
    - All other indications: improvement or stabilization of clinical signs and symptoms since initiation of therapy.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Signifor LAR.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Acromegaly: an endocrine society clinical practice guideline.
- American Association of Clinical Endocrinologists Acromegaly Guidelines Task Force. Medical guidelines for clinical practice for the diagnosis and treatment of acromegaly – 2011 update.
- Treatment of Cushing's syndrome: An Endocrine Society Clinical Practice Guideline.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Signifor LAR are covered in addition to the following:

- Carcinoid syndrome

- Metastatic neuroendocrine tumors (NETs) of the gastrointestinal (GI) tract (carcinoid tumors)

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Signifor LAR to treat carcinoid syndrome and metastatic neuroendocrine tumors (NETs) of the gastrointestinal tract can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for utilizing a high pretreatment insulin-like growth factor-1 (IGF-1) as a diagnostic requirement and targeting IGF-1 in patients with acromegaly is supported by two professional guidelines.

According to Katznelson et al, the biochemical target goal is an age-normalized IGF-1. An age-normalized IGF-1 signifies control of acromegaly.

According to the Endocrine Society, IGF-1 should be measured and patients with elevated or equivocal serum IGF-1 levels should have the diagnosis confirmed by finding lack of suppression of growth hormone to less than 1 microgram/L following documented hyperglycemia during an oral glucose load. The Endocrine Society also supports the normalization of IGF-1 as the biochemical target goal of therapy with Signifor LAR.

References

1. Signifor LAR [package insert]. Bridgewater, NJ: Recordati Rare Diseases Inc; July 2024.
2. IBM Micromedex® DRUGDEX® (electronic version). Micromedex Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com [available with subscription]. Accessed November 8, 2024.
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4. American Association of Clinical Endocrinologists Acromegaly Guidelines Task Force. Medical guidelines for clinical practice for the diagnosis and treatment of acromegaly – 2011 update. Endocr Pract. 2011;17(suppl 4):1-44.
5. Nieman LK, Biller BM, Findling JW, et al. Treatment of Cushing's syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015;100(8):2807-31.
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7. Colao A, Bronstein MD, Freda P, et al. Pasireotide versus octreotide in acromegaly: a head-to-head superiority study. J Clin Endocrinol Metab. 2014;99:791–799.

Reference number(s)
2394-A

Standard Medicare Part B Management
Simponi Aria

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Simponi Aria	golimumab

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

- Treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) in combination with methotrexate
- Treatment of active psoriatic arthritis (PsA) in patients 2 years of age and older
- Treatment of adult patients with active ankylosing spondylitis (AS)
- Treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older

Compendial Uses

- Non-radiographic axial spondyloarthritis
- Oligoarticular juvenile idiopathic arthritis
- Immune checkpoint inhibitor-related toxicities – inflammatory arthritis

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Rheumatoid Arthritis (RA)

For Initial Requests

Chart notes, medical record documentation, or claims history supporting previous medications tried (if applicable), including response to therapy. If therapy is not advisable, documentation of clinical reason to avoid therapy.

For Continuation Requests

Chart notes or medical record documentation supporting benefit from therapy.

Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Non-Radiographic Axial Spondyloarthritis (nr-axSpA), and Articular Juvenile Idiopathic Arthritis (JIA)

For Continuation Requests

Chart notes or medical record documentation supporting benefit from therapy.

Immune Checkpoint Inhibitor-Related Toxicity

For Initial Requests

Chart notes, medical record documentation, or claims history supporting previous medications tried (if applicable), including response to therapy. If therapy is not advisable, documentation of clinical reason to avoid therapy.

For Continuation Requests

Chart notes or medical record documentation supporting benefit from therapy.

Coverage Criteria

Rheumatoid Arthritis (RA)

Authorization of 12 months may be granted for treatment of moderately to severely active rheumatoid arthritis when either of the following criteria is met:

- Simponi Aria will be used in combination with methotrexate.
- The member has a clinical reason to avoid methotrexate (e.g., breastfeeding, pregnancy or currently planning pregnancy, renal or hepatic impairment, previous intolerance to methotrexate).

Psoriatic Arthritis (PsA)

Authorization of 12 months may be granted for treatment of active psoriatic arthritis.

Ankylosing Spondylitis (AS) and Non-Radiographic Axial Spondyloarthritis (nr-axSpA)

Authorization of 12 months may be granted for treatment of active ankylosing spondylitis or active non-radiographic axial spondyloarthritis.

Articular Juvenile Idiopathic Arthritis (JIA)

Authorization of 12 months may be granted for treatment of active articular juvenile idiopathic arthritis.

Immune Checkpoint Inhibitor-Related Toxicity

Authorization of 12 months may be granted for treatment of immune checkpoint inhibitor-related toxicity when the member has moderate or severe immunotherapy-related inflammatory arthritis and either of the following is met:

- Member has had an inadequate response to corticosteroids or a conventional synthetic drug (e.g., methotrexate, sulfasalazine, leflunomide, hydroxychloroquine).
- Member has an intolerance or contraindication to corticosteroids and a conventional synthetic drug (e.g., methotrexate, sulfasalazine, leflunomide, hydroxychloroquine).

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

All Indications

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Simponi Aria.
- Simponi Aria is being used to treat an indication listed in the coverage criteria section.
- The member is receiving benefit from therapy.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Simponi Aria.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs

- EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update.
- 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis.
- 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the treatment of psoriatic arthritis.
- EULAR recommendations for management of psoriatic arthritis with pharmacological therapies: 2019 update.
- 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 Non radiographic axial spondyloarthritis.
- 2016 update of the international ASAS-EULAR management recommendations for axial spondyloarthritis.
- 2019 American College of Rheumatology/Arthritis Foundation guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis.
- 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis.
- NCCN guideline: Management of immunotherapy-related toxicities.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Simponi Aria are covered in addition to the following:

- Non-radiographic axial spondyloarthritis
- Oligoarticular juvenile idiopathic arthritis
- Immune checkpoint inhibitor-related toxicity – inflammatory arthritis

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

According to the 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis, in patients who are DMARD-naïve (disease-modifying antirheumatic drug) methotrexate is strongly recommended over hydroxychloroquine or sulfasalazine in patients with moderate-to-high disease activity. Methotrexate is conditionally recommended over leflunomide.

Non-radiographic axial spondyloarthritis is listed as an approvable indication along with ankylosing spondylitis. The 2016 update of the ASAS-EULAR recommendations for the treatment of non-radiographic axial spondyloarthritis support golimumab along with other TNF inhibitors. Support for including non-radiographic axial spondyloarthritis can be found in the 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network guidelines. In adults with active ankylosing spondylitis or active non-radiographic axial spondyloarthritis despite treatment with NSAIDs, tumor necrosis factor inhibitors (TNFs) are strongly recommended over no treatment with TNFs.

Support for using Simponi Aria for oligoarticular juvenile idiopathic arthritis can be found in the 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis. For patients who have had an inadequate

response or intolerance to non-biologic DMARDs, the next step is a biologic DMARD such as golimumab. The guideline indicates there is no preferred agent.

Support for using Simponi Aria to manage immune checkpoint inhibitor-related toxicity can be found in the National Comprehensive Cancer Network's guideline for the management of immunotherapy-related toxicities. The NCCN Guideline for the management of immunotherapy-related toxicities supports the use of adding Simponi Aria for moderate or severe inflammatory arthritis as additional disease modifying antirheumatic drug (DMARD) therapy if no improvement after holding immunotherapy and treating with oral corticosteroids or if unable to taper corticosteroids, or no response to conventional synthetic DMARDs.

References

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4. Singh JA, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. Arthritis Rheum. 2018;71:5-32.
5. Gossec L, Baraliakos X, Kerschbaumer A. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis. 2020;79(6):700-712.
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Reference number(s)
6325-A

Standard Medicare Part B Management
Skyrizi

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Skyrizi	risankizumab-rzaa

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met, the member has no exclusions to the prescribed therapy, and the drug or biological is usually not self-administered. The criteria outlined in this policy is only applicable to drugs not usually self-administered and are furnished incident to a physician's service. Requests for drugs on a region's self-administered drug list are not covered. Members enrolled in Medicare Part D may seek coverage under their Medicare Part D plan.

FDA-Approved Indications[1]

- For the treatment of moderately to severely active Crohn's disease (CD) in adults.
- For the treatment of moderately to severely active ulcerative colitis (UC) in adults.

The following indications are FDA-approved but the drug approved to treat the indication is usually self-administered and thus not covered by this policy.

- For the treatment of moderate to severe plaque psoriasis (PsO) in adults who are candidates for phototherapy or systemic therapy.
- For the treatment of active psoriatic arthritis (PsA) in adults.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Crohn's Disease (CD) and Ulcerative Colitis (UC)

For continuation requests: Chart notes or medical record documentation supporting benefit of therapy.

Coverage Criteria

Crohn's Disease (CD)[1,2]

Authorization of 12 months may be granted for treatment of moderately to severely active Crohn's disease.

Ulcerative Colitis (UC)[1,2]

Authorization of 12 months may be granted for treatment of moderately to severely active ulcerative colitis.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Crohn's Disease (CD) and Ulcerative Colitis (UC)

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Skyrizi.
- Skyrizi is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Skyrizi.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service-Drug Information (AHFS-DI)

  - Lexi-Drugs
  - Clinical Pharmacology
- ACG Clinical Guideline: Management of Crohn's Disease in Adults
- AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease.
- 2019 ACG Clinical Guideline: Ulcerative Colitis in Adults
- AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Skyrizi are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Skyrizi [package insert]. North Chicago, IL: AbbVie Inc.; June 2024.
2. 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: 2496- 2508.
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5. Self-Administered Drug Exclusion List: (A53032). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.
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9. Self-Administered Drug Exclusion List: (A53127). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.
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11. Self-Administered Drug Exclusion List: Medical Policy Article (A53022). Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 10, 2024.

Reference number(s)
1632-A

Standard Medicare Part B Management Soliris and Biosimilars

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Soliris	eculizumab
Bkemv	eculizumab-aeeb
Epysqli	eculizumab-aagh

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Soliris is indicated for the treatment of:

- Paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis
- Atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy
- Generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive
- Neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

Bkemv and Epysqli are indicated for the treatment of:

- Paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis
- Atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy

Compendial Uses

- Antibody mediated renal transplant rejection

Limitation of Use:

Soliris, Bkemy, and Epysqli are not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- For initial requests:
  - Paroxysmal nocturnal hemoglobinuria: flow cytometry used to show results of glycosylphosphatidylinositol-anchored proteins (GPI-APs) deficiency
  - Generalized myasthenia gravis:
    - Positive anti-acetylcholine receptor (AChR) antibody test
    - Myasthenia Gravis Foundation of America (MGFA) clinical classification
    - MG activities of daily living score
    - Previous medications tried, including response to therapy. If therapy is not advisable, documentation of clinical reasons to avoid therapy.
  - Neuromyelitis optica spectrum disorder: Immunoassay used to confirm anti-aquaporin-4 (AQP4) antibody is present
- For continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

Coverage Criteria

Paroxysmal nocturnal hemoglobinuria (PNH)

Authorization of 6 months may be granted for treatment of paroxysmal nocturnal hemoglobinuria (PNH) when all of the following criteria are met:

- The diagnosis of PNH was confirmed by detecting a deficiency of glycosylphosphatidylinositol-anchored proteins (GPI-APs) (e.g., at least 5% PNH cells, at least 51% of GPI-AP deficient poly-morphonuclear cells)
- Flow cytometry is used to demonstrate GPI-APs deficiency
- Member has and exhibits clinical manifestations of disease (e.g., LDH > 1.5 ULN, thrombosis, renal dysfunction, pulmonary hypertension, dysphagia)
- The requested medication will not be used in combination with another complement inhibitor (e.g., Empaveli, Fabhalta, Piasky, Ultomiris) for the treatment of PNH (concomitant use with Voydeya is allowed).

Atypical hemolytic uremic syndrome (aHUS)

Authorization of 6 months may be granted for treatment of atypical hemolytic uremic syndrome (aHUS) that is not caused by Shiga toxin when all of the following criteria are met:

- Absence of Shiga toxin
- The requested medication will not be used in combination with another complement inhibitor (e.g., Ultomiris) for the treatment of aHUS.

Generalized myasthenia gravis

Authorization of 6 months may be granted for treatment of generalized myasthenia gravis (gMG) when all of the following criteria are met:

- The member is anti-acetylcholine receptor (AchR) antibody positive
- Myasthenia Gravis Foundation of America (MGFA) clinical classification II to IV
- MG activities of daily living (MG-ADL) total score of greater than or equal to 5
- Meets one of the following:
    - Member has had an inadequate response or intolerable adverse event to at least two immunosuppressive therapies over the course of at least 12 months (e.g., azathioprine, corticosteroids, cyclosporine, methotrexate, mycophenolate, tacrolimus)
    - Member has had an inadequate response or intolerable adverse event to at least one immunosuppressive therapy and intravenous immunoglobulin (IVIG) over the course of at least 12 months
    - Member has a documented clinical reason to avoid therapy with immunosuppressive agents and IVIG
- The requested medication will not be used in combination with another complement inhibitor (e.g., Ultomiris, Zilbrysq) or neonatal Fc receptor blocker (e.g., Vyvgart, Vyvgart Hytrulo, Rystiggo).

Neuromyelitis optica spectrum disorder

Authorization of 6 months may be granted for treatment of neuromyelitis optica spectrum disorder (NMOSD) when all of the following criteria are met:

- The member is anti-aquaporin-4 (AQP4) antibody positive.
- The member exhibits one of the following core clinical characteristics of NMOSD:
    - Optic neuritis
    - Acute myelitis
    - Area postrema syndrome (episode of otherwise unexplained hiccups or nausea and vomiting)
    - Acute brainstem syndrome
    - Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
    - Symptomatic cerebral syndrome with NMOSD-typical brain lesions
- The member will not receive the requested medication concomitantly with other biologics for the treatment of NMOSD.

Antibody mediated renal transplant rejection

Authorization of 6 months may be granted for treatment of antibody mediated renal transplant rejection.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Paroxysmal nocturnal hemoglobinuria

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy (e.g., improvement in hemoglobin levels, normalization of lactate dehydrogenase [LDH] levels).
- The requested medication will not be used in combination with another complement inhibitor (e.g., Empaveli, Fabhalta, Piasky, Ultomiris) for the treatment of PNH (concomitant use with Voydeya is allowed).

Atypical hemolytic uremic syndrome

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with requested medication.
- The member is receiving benefit from therapy (e.g., normalization of lactate dehydrogenase [LDH] levels, platelet counts).
- The requested medication will not be used in combination with another complement inhibitor (e.g., Ultomiris) for the treatment of aHUS.

Neuromyelitis optica spectrum disorder

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy (e.g., reduction in number of relapses as compared to baseline).
- The member will not receive the requested medication concomitantly with other biologics for the treatment of NMOSD.

Generalized myasthenia gravis

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy (e.g., improvement in MG-ADL score, MG Manual Muscle Test (MMT), MG Composite).
- The requested medication will not be used in combination with another complement inhibitor (e.g., Ultomiris, Zilbrysq) or neonatal Fc receptor blocker (e.g., Vyvgart, Vyvgart Hytrulo, Rystiggo).

Antibody mediated renal transplant rejection

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy.

Dosage And Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Soliris and Bkemy.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Management of paroxysmal nocturnal hemoglobinuria in the era of complement inhibitory therapy.
- Guidelines for the Diagnosis and Monitoring of Paroxysmal Nocturnal Hemoglobinuria and Related Disorders by Flow Cytometry.
- International consensus guidance for management of myasthenia gravis.
- An international consensus approach to the management of atypical hemolytic uremic syndrome in children.
- International consensus guidance for management of myasthenia gravis: 2020 update.
- International consensus diagnostic criteria for neuromyelitis optica spectrum disorders.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Soliris and Bkemy are covered in addition to antibody mediated renal transplant rejection.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using percentage of PNH cells or percentage of GPI-AP deficiency poly-morphonuclear cells can be found in the guidelines for diagnosis of PNH (Borowitz et al and Preis et al). Flow cytometry is the gold standard for assessing the percentage of GPI-AP deficient poly-morphonuclear cells. Classic PNH is defined as greater than 50% of GPI-AP deficient PMNs. It is also possible to diagnose PNH by assessing the percentage of PNH cells. Most clinical trials for the

complement inhibitors required at least 10% PNH cells, but the trials associated with Ultomiris only required 5% PNH cells. Therefore, the baseline requirement for all complement inhibitor programs will be at least 5%.

Currently there are no treatment guidelines or literature supporting the concomitant use of complement inhibitors (e.g., Empaveli, Fabhalta, Piasky, Ultomiris) for the treatment of PNH.

Currently there are no treatment guidelines or literature supporting the concomitant use of complement inhibitors (e.g., Ultomiris) for the treatment of aHUS

Support for Myasthenia Gravis Activities of Daily Living (MG-ADL) total score of greater than or equal to 5 can be found in the trials associated with Vyvgart and Vyvgart Hytrulo. Most clinical trials of myasthenia gravis agents required a MG-ADL of greater than or equal to 6, however, to align myasthenia gravis programs the baseline requirement will be greater than or equal to 5. MG-ADL is a scale that assesses the impact of myasthenia gravis on daily functions. This scale was used as an assessment tool to evaluate response to myasthenia gravis treatment from baseline in the clinical trials.

Support for the trial of immunosuppressive agents and IVIG before initiating therapy with eculizumab (Soliris) can be found in the 2020 update to the international consensus guidance for management of myasthenia gravis. The recommendations indicate that eculizumab should be considered in the treatment of severe, refractory myasthenia gravis (after trials of other immunotherapies have been unsuccessful in meeting treatment goals).

Currently there are no treatment guidelines or literature supporting the concomitant use of complement inhibitors (e.g., Soliris, Ultomiris, Zilbrysq) or neonatal Fc receptor blockers (e.g., Vyvgart, Vyvgart Hytrulo, Rystiggo).

Support for the list of core clinical characteristics of NMOSD can be found in the International Consensus Diagnostic Criteria for Neuromyelitis Optica Spectrum Disorder (Wingerchuk et al). There are six clinical characteristics cited in the diagnostic criteria:

- Optic neuritis
- Acute myelitis
- Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
- Acute brainstem syndrome
- Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
- Symptomatic cerebral syndrome with NMOSD-typical brain lesions

Currently there are no treatment guidelines or literature supporting the concomitant use with other biologics for the treatment of NMOSD.

Support for antibody mediated renal transplant rejection can be found in several small studies. In a study by Tan et al, eculizumab treatment alone or in combination with plasmapheresis and/or IV immune globulin improved graft function and histologic factors in a case series of solitary kidney transplant recipients with active antibody-mediated rejection (AMR) within the first 30 days posttransplant, and no graft losses occurred during the median follow up of 13 months. Eculizumab alone compared with plasmapheresis and IV immune globulin (standard of care) did not prevent progression to chronic AMR or transplant glomerulopathy in a small, open-label, randomized trial (Heo et al) in kidney transplant recipients with biopsy-proven AMR; however, no patient lost their graft and DSA titers were reduced in both groups. In a study (Norville et al) of electronic health records of kidney transplant recipients, treatment with eculizumab improved graft survival and patient survival rates compared with published reported incidences in a cohort of patients with AMR also receiving plasmapheresis and IV immunoglobulin. When evaluated with regard to splenectomy, treatment with eculizumab plus splenectomy improved outcomes compared with eculizumab or splenectomy alone in a retrospective

study (Orandi et al) of incompatible live donor kidney transplant recipients with early severe AMR; all patients also received plasmapheresis and IV immune globulin.

References

1. Soliris [package insert]. Boston, MA: Alexion Pharmaceuticals, Inc.; March 2024.
2. Parker CJ. Management of paroxysmal nocturnal hemoglobinuria in the era of complement inhibitory therapy. Hematology. 2011; 21-29.
3. Loirat C, Fakhouri F, Ariceta G, et al. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. Pediatr Nephrol. Published online: January 1, 2016.
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5. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85:177-189.
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7. Preis M, Lowrey CH. Laboratory tests for paroxysmal nocturnal hemoglobinuria (PNH). Am J Hematol. 2014;89(3):339-341.
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9. Dezern AE, Borowitz MJ. ICCS/ESCCA consensus guidelines to detect GPI-deficient cells in paroxysmal nocturnal hemoglobinuria (PNH) and related disorders part 1 - clinical utility. Cytometry B Clin Cytom. 2018 Jan;94(1):16-22.
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13. Epysqli [package insert]. Republic of Korea: Samsung Bioepis Co., Ltd.; July 2024.

Reference number(s)
5582-A

Standard Medicare Part B Management
Spevigo

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Spevigo	spesolimab-sbzo

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

For the treatment of generalized pustular psoriasis (GPP) in adults and pediatric patients 12 years of age and older and weighing at least 40 kg.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Generalized pustular psoriasis (GPP) flare

Chart notes or medical record documentation of affected area(s) must be available, upon request, for all submissions.

Generalized pustular psoriasis (GPP) when not experiencing a flare

For continuation requests: Chart notes or medical record documentation supporting benefit of therapy.

Coverage Criteria

Generalized pustular psoriasis (GPP) flare[1-3]

Authorization of 1 month may be granted for treatment of generalized pustular psoriasis flares in members 12 years of age or older when all of the following criteria are met:

- Member has a known documented history of GPP (either relapsing [greater than 1 episode] or persistent [greater than 3 months]).
- Member is presenting with primary, sterile, macroscopically visible pustules (new or worsening) on an erythematous base (excluding cases where pustulation is restricted to psoriatic plaques).
- At least 5% body surface area (BSA) is covered with erythema and the presence of pustules.

Generalized pustular psoriasis (GPP) when not experiencing a flare

Authorization of 12 months may be granted for treatment of generalized pustular psoriasis in members 12 years of age or older when all of the following criteria are met:

- Member has a known documented history of GPP (either relapsing [greater than 1 episode] or persistent [greater than 3 months]).
- Member meets either of the following:
  - Member has had a history of at least two moderate-to-severe GPP flares (e.g., at least 5% body surface area is covered with erythema and the presence of pustules; Generalized Pustular Psoriasis Physician Global Assessment [GPPPGA] total score of greater or equal to 3).
  - Member has a history of flaring while on concomitant treatment (e.g., retinoids, methotrexate, cyclosporine).
- Member currently has clear to almost clear skin.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Generalized pustular psoriasis (GPP) flare

All members 12 years of age or older requesting authorization for continuation of therapy must meet all requirements in the coverage criteria section.

Generalized pustular psoriasis (GPP) when not experiencing a flare

Authorization of 12 months may be granted for members 12 years of age or older when both of the following criteria are met:

- The member is currently receiving therapy with Spevigo.
- The member is receiving benefit from therapy.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Spevigo.
- The available compendium
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)
  - Lexi-Drugs
  - Clinical Pharmacology

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Spevigo [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; March 2024.
2. Bachelez H, Choon SE, Marrakchi S, et al. Trial of Spesolimab for Generalized Pustular Psoriasis. N Engl J Med. 2021;385(26):2431-2440.
3. Navarini AA, Burden AD, Capon F, et al. European consensus statement on phenotypes of pustular psoriasis. J Eur Acad Dermatol Venereol. 2017;31(11):1792-1799.
4. Morita A, Choon SE, Bachelez H, et al. Design of Effisayil™ 2: A Randomized, Double-Blind, Placebo-Controlled Study of Spesolimab in Preventing Flares in Patients with Generalized Pustular Psoriasis. Dermatol Ther (Heidelb). 2023;13(1):347-359.
5. Armstrong AW, Elston CA, Elewski BE, et al. Generalized pustular psoriasis: A consensus statement from the National Psoriasis Foundation. J Am Acad Dermatol. 2024 Apr;90(4):727-730.

Reference number(s)
2133-A

Standard Medicare Part B Management Spinraza

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Spinraza	nusinersen

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Spinraza is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all initial submissions: Deletion or mutation at the SMN1 allele confirmed by genetic testing.

Coverage Criteria

Spinal muscular atrophy (SMA)

Authorization of 12 months may be granted for treatment of SMA when all of the following criteria are met:

- Member has a diagnosis of SMA confirmed by genetic testing showing deletion or mutation at the SMN1 allele.
- Member has Type 1, Type 2 or Type 3 SMA.
- Member will not use Spinraza and Evrysdi concomitantly.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Spinraza.
- Spinraza is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy.
- Member will not use Spinraza and Evrysdi concomitantly.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Spinraza.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Spinal muscular atrophy: diagnosis and management in a new therapeutic era.
- EFNS guidelines for the molecular diagnosis of neurogenetic disorders: motoneuron, peripheral nerve and muscle disorders.
- Consensus statement for standard care in spinal muscular atrophy.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Spinraza are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using genetic testing as a requirement for diagnosis is supported by a guideline by Arnold and colleagues. Molecular genetic testing is the standard tool for the diagnosis of SMA. Patients with SMA have homozygous loss of function of both SMN1 copies. Genetic testing for homozygous deletion will confirm the disease in 95% of patients

irrespective of disease severity. All other patients with SMN-related SMA will be compound heterozygotes with a single SMN1 deletion and a frameshift, nonsense, or missense mutation in the other SMN1 copy. If homozygous SMN1 deletion is not evident in a patient with suspected SMA, SMN1 dosage analysis and sequencing of the remaining SMN1 gene should be performed.

The traditional classification strategy divides patients into four groups. Type 1 is the most common and severe form. Patients experience an onset in the first six months of life and are never able to sit upright. Patients with Type 2 SMA are usually diagnosed in the first eighteen months of life. The ability to sit is typically achieved by 9 months and patients will never stand or walk independently, but some patients will be able to stand with assistance of bracing or a standing frame. Patients with Type 3 SMA typically exhibit symptoms after 18 months. The patient is able to stand or walk without support, but many patients lose these abilities when the disease progresses. Patients with type 4 SMA experience symptoms starting in adulthood and are ambulatory. The studies cited in the prescribing information included patients with type 1, 2 and 3 SMA.

References

1. Spinraza [package insert]. Cambridge, MA: Biogen Inc.; February 2023.
2. Arnold WD, Kassar D, Kissel JT, et al. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. Muscle & Nerve. 2015;51(2):157-167.
3. Burgunder JM, Schols L, Baets J, et al. EFNS guidelines for the molecular diagnosis of neurogenetic disorders: motoneuron, peripheral nerve and muscle disorders. European J Neurol. 2011;18:207-217.
4. Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Lancet. 2016;388:3017-26.
5. Ionis Pharmaceuticals, Inc. A Study to Assess the Efficacy and Safety of IONIS-SMN Rx in Infants with Spinal Muscular Atrophy. In: ClinicalTrials.gov [internet]. Bethesda (MD): National Library of Medicine (US). 2000- [2016 Feb 14]. Available from: https://clinicaltrials.gov/ct2/show/NCT02193074.
6. Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med. 2018; 378:625-635.
7. Wang CH, Finkel RS, Bertini ES, et al. Consensus statement for standard care in spinal muscular atrophy. J Child Neurol. 2007;22(8):1027-1049.

Reference number(s)
4213-A

Standard Medicare Part B Management Spravato (esketamine) nasal spray

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name	Dosage form
Spravato	esketamine	nasal spray

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

Spravato is indicated for the treatment of:

- Treatment-resistant depression (TRD) in adults as monotherapy or in conjunction with an oral antidepressant
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior in conjunction with an oral antidepressant

Limitations 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.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

For Initial Requests

- Pretreatment depression severity score(s) from standardized rating scale(s) that reliably measure depressive symptoms (e.g., Beck Depression Inventory [BDI], Hamilton Depression Rating Scale [HDRS], Montgomery-Asberg Depression Rating Scale [MADRS], etc.)
- Medical records documenting inadequate response with antidepressants for the current depressive episode (if applicable)

For Continuation of Therapy

Current depression severity score(s) from standardized rating scale(s) that reliably measure depressive symptoms (if applicable)

Coverage Criteria

Treatment-Resistant Depression (TRD)/Major Depressive Disorder (MDD) with Acute Suicidal Ideation or Behavior[1]

Authorization of 3 months may be granted for the treatment of TRD or 1 month for the treatment of MDD with acute suicidal ideation or behavior when all of the following criteria are met:

- Member has a confirmed diagnosis of severe major depressive disorder (single or recurrent episode), documented by standardized rating scales that reliably measure depressive symptoms (e.g., Beck Depression Inventory [BDI], Hamilton Depression Rating Scale [HDRS], Montgomery-Asberg Depression Rating Scale [MADRS], etc.).
- The requested drug will be administered under the direct supervision of a healthcare provider.
- Member meets either of the following criteria:
    - For treatment resistant depression, member has experienced an inadequate response during the current depressive episode with two antidepressants (e.g., selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor [SNRI], tricyclic antidepressant [TCA], bupropion, mirtazapine).
    - For major depressive disorder with acute suicidal ideation or behavior, member meets both of the following:
        - Member has current suicidal ideation with intent defined as both of the following:
            - Member has thoughts, even momentarily, of self-harm with at least some intent or awareness that they may die as a result, or member thinks about suicide.
            - Member intends to act on thoughts of killing themselves.

- The requested drug will be used in combination with an oral antidepressant (e.g., duloxetine, escitalopram, sertraline, venlafaxine).

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Treatment-Resistant Depression (TRD)

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Spravato
- Spravato is being used to treat treatment-resistant depression
- The member is receiving benefit from therapy. Benefit is defined as:
    - An improvement or sustained improvement from baseline in depressive symptoms documented by standardized rating scales that reliably measure depressive symptoms (e.g., Beck Depression Inventory [BDI], Hamilton Depression Rating Scale [HDRS], Montgomery-Asberg Depression Rating Scale [MADRS], etc.).

Major Depressive Disorder (MDD) with Acute Suicidal Ideation or Behavior

- If the member has not received 1 full month of therapy, then authorization for up to 1 month to complete a treatment course may be granted when all the following criteria are met:
    - The member is currently receiving therapy with Spravato
    - Spravato is being used to treat major depressive disorder with acute suicidal ideation or behavior
- If the member has completed one full month of therapy, then member must meet all initial criteria for approval. The use of Spravato beyond 4 weeks has not been systematically evaluated in the treatment of depressive symptoms in members with MDD with acute suicidal ideation or behavior.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Spravato.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Spravato are covered.

Reference number(s)
4213-A

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Spravato [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; January 2025.

Reference number(s)
2393-A

Standard Medicare Part B Management Stelara and Biosimilars Intravenous (IV)

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name	Dosage Form
Stelara	ustekinumab	intravenous (IV)
Imuldosa	ustekinumab-srlf	intravenous (IV)
Otulfi	ustekinumab-aauz	intravenous (IV)
Pyzchiva	ustekinumab-ttwe	intravenous (IV)
Selarsdi	ustekinumab-aekn	intravenous (IV)
Steqeyma	ustekinumab-stba	intravenous (IV)
Wezlana	ustekinumab-auub	intravenous (IV)
Yesintek	ustekinumab-kfce	intravenous (IV)
ustekinumab-aekn (unbranded Selarsdi)	ustekinumab-aekn	intravenous (IV)
ustekinumab-ttwe (unbranded Pyzchiva)	ustekinumab-ttwe	intravenous (IV)

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met, the member has no exclusions to the prescribed therapy, and the drug or biological is usually not self-administered. The criteria outlined in this policy is only applicable to drugs not usually self-administered and are furnished incident to a physician's service. Requests for drugs on a region's self-administered drug list are not covered. Members enrolled in Medicare Part D may seek coverage under their Medicare Part D plan.

FDA-approved Indications[1-10]

- For the treatment of adult patients with moderately to severely active Crohn's disease (CD).
- For the treatment of adult patients with moderately to severely active ulcerative colitis (UC).

The following indications are FDA-approved but the drug approved to treat the indication is usually self-administered and thus not covered by this policy.

- For the treatment of patients 6 years or older with moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy.
- For the treatment of patients 6 years or older with active psoriatic arthritis (PsA).

Compendial Uses[15,16]

Immune checkpoint inhibitor-related toxicity

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Ulcerative colitis (UC) and Crohn's disease (CD)

Continuation requests

Chart notes or medical record documentation supporting benefit of therapy.

Immune checkpoint inhibitor-related toxicity

Chart notes, medical record documentation, or claims history supporting previous medications tried (if applicable), including response to therapy. If therapy is not advisable, documentation of clinical reason to avoid therapy.

Coverage Criteria

Crohn's disease (CD)[1-10]

Authorization of 12 months may be granted for treatment of moderately to severely active Crohn's disease.

Ulcerative colitis (UC)[1-10]

Authorization of 12 months may be granted for treatment of moderately to severely active ulcerative colitis.

Immune checkpoint inhibitor-related toxicity[15,16]

Authorization of 6 months may be granted for treatment of immune checkpoint inhibitor-related diarrhea or colitis when the member has had an inadequate response, intolerance, or has a contraindication to infliximab or vedolizumab.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Immune checkpoint inhibitor-related toxicity

All members (including new members) requesting authorization for continuation of therapy must meet all requirements in the coverage criteria.

All other indications

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with an ustekinumab product.
- The requested medication is being used to treat an indication listed in the coverage criteria.
- The member is receiving benefit from therapy.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Stelara and its biosimilars.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Management of immunotherapy-related toxicities
- An evidence-based systematic review on medical therapies for inflammatory bowel disease
- ACG Clinical Guideline: Management of Crohn's Disease in Adults
- 2019 ACG Clinical Guideline: Ulcerative Colitis in Adults
- AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis
- AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Stelara and its biosimilars are covered in addition to immune checkpoint inhibitor-related toxicity.

Reference number(s)
2393-A

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using ustekinumab to manage immune checkpoint inhibitor-related toxicity can be found in the National Comprehensive Cancer Network's guideline for the management of immunotherapy-related toxicities. The NCCN Guideline for the management of immunotherapy-related toxicities supports the use of adding ustekinumab for mild (G1) diarrhea or colitis if persistent or progressive symptoms and positive lactoferrin/calprotectin. Additionally, consider ustekinumab for infliximab- and/or vedolizumab-refractory moderate (G2) or severe (G3-4) diarrhea or colitis.

References

1. Stelara [package insert]. Horsham, PA: Janssen Biotech, Inc.; November 2024.
2. Imuldosa [package insert]. Raleigh, NC: Accord BioPharma Inc.; October 2024.
3. Otulfi [package insert]. Lake Zurich, IL: Fresenius Kabi USA, LLC; September 2024.
4. Pyzchiva [package insert]. Princeton, NJ: Sandoz Inc.; December 2024.
5. Selarsdi [package insert]. Leesburg, VA: Alvotech USA Inc.; October 2024.
6. Steqeyma [package insert]. Jersey City, NJ: Celltrion USA, Inc.; December 2024.
7. ustekinumab-aekn [package insert]. Leesburg, VA: Alvotech USA Inc.; October 2024.
8. ustekinumab-ttwe [package insert]. Grand Cayman, Cayman Islands: Quallent Pharmaceuticals Health LLC; March 2025.
9. Wezlana [package insert]. Thousand Oaks, CA: Amgen Inc.; December 2024.
10. Yesintek [package insert]. Cambridge, MA: Biocon Biologics Inc.; November 2024.
11. Talley NJ, Abreu MT, Achkar J, et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. Am J Gastroenterol. 2011;106(Suppl 1):S2-S25.
12. Lichtenstein GR, Loftus Jr EV, Isaacs KI, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2018;113:481-517.
13. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. 2019 ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019;114:384-413.
14. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. Gastroenterology. 2020; 158:1450.
15. The NCCN Drugs & Biologics Compendium® © 2025 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed January 21, 2025.
16. NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®). Management of Immunotherapy-Related Toxicities. Version 1.2025. Available at: www.nccn.org. Accessed January 21, 2025.
17. 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: 2496- 2508.
18. Self-Administered Drug Exclusion List: and Biologicals Excluded from Coverage- Medical Policy Article (A52527) Version R57. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 22, 2025.
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20. Self-Administered Drug Exclusion List: (A53032) Version R40. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 22, 2025.

21. Self-Administered Drug Exclusion List: (A53033) Version R41. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 22, 2025.
22. Self-Administered Drug Exclusion List: Medical Policy Article (A53021) Version R40. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 22, 2025.
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25. Self-Administered Drug Exclusion List: (A53066) Version R46. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed January 22, 2025.
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Reference number(s)
5046-A

Standard Medicare Part B Management Susvimo

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name	Dosage Form
Susvimo	ranibizumab	injection

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

Neovvascular (wet) Age-related Macular Degeneration (AMD)

Susvimo is indicated for the treatment of patients with Neovascular (wet) Age-related Macular Degeneration (AMD) who have previously responded to at least two intravitreal injections of a Vascular Endothelial Growth Factor (VEGF) inhibitor medication.

Diabetic Macular Edema (DME)

Susvimo is indicated for the treatment of patients with Diabetic Macular Edema (DME) who have previously responded to at least two intravitreal injections of a Vascular Endothelial Growth Factor (VEGF) inhibitor medication.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Neovascular (Wet) Age-Related Macular Degeneration (AMD)[1,2]

Authorization of 6 months may be granted for treatment of neovascular (wet) age-related macular degeneration when all of the following criteria are met:

- Member has a diagnosis of neovascular (wet) age-related macular degeneration.
- Member has previously responded to at least two intravitreal injections of a Vascular Endothelial Growth Factor (VEGF) inhibitor (e.g., Avastin, Eylea) within the past 6 months.
- Must be used in conjunction with the Susvimo ocular implant.

Diabetic Macular Edema (DME)[1]

Authorization of 6 months may be granted for the treatment of diabetic macular edema when all of the following criteria are met:

- Member has a diagnosis of diabetic macular edema .
- Member has previously responded to at least two intravitreal injections of a Vascular Endothelial Growth Factor (VEGF) inhibitor (e.g., Avastin, Eylea).
- Must be used in conjunction with the Susvimo ocular implant.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication listed in the coverage criteria section.
- The member demonstrated a positive clinical response to therapy (e.g., improvement or maintenance in best corrected visual acuity [BCVA] or vision field, or a reduction in the rate of vision decline or the risk of more severe vision loss).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Susvimo.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Age-Related Macular Degeneration.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Susvimo are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Susvimo. [package insert]. San Francisco, CA: Genentech, Inc.; Feburary 2025.
2. American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Age-Related Macular Degeneration. San Francisco, CA: American Academy of Ophthalmology; 2019. Available at: https://www.aao.org/education/preferred-practice-pattern/age-related-macular-degeneration-ppp

Reference number(s)
5794-A

Standard Medicare Part B Management Syfovre

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Syfovre	pegcetacoplan

Indications

FDA-approved Indications[1]

Syfovre is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions.

Initial Requests

Chart notes or medical records confirming the diagnosis of geographic atrophy (GA) secondary to AMD.

Continuation Requests

Chart notes or medical records confirming a positive clinical response to therapy.

Exclusions

Coverage will not be provided for the treatment of geographic atrophy (GA) secondary to a condition other than AMD (such as Stargardt disease, cone rod dystrophy, toxic maculopathies).

Coverage Criteria

Geographic atrophy (GA) secondary to age-related macular degeneration[1,2]

Authorization of 12 months may be granted for treatment of geographic atrophy when the member has a diagnosis of geographic atrophy secondary to age-related macular degeneration.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested product.
- The requested product is being used to treat an indication listed in the coverage criteria.
- The medication has been effective for treating the diagnosis or condition (e.g., a reduction or stabilization in the rate of vision decline or the risk of more severe vision loss, stabilization or reduction in total area of GA lesions).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Syfovre.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Age-Related Macular Degeneration Preferred Practice Pattern 2019

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Syfovre are covered.

Reference number(s)
5794-A

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Syfovre [package insert]. Waltham, MA: Apellis Pharmaceuticals Inc; November 2023.
2. Age-Related Macular Degeneration PPP 2019. American Academy of Ophthalmology. Published October 2019. Accessed December 11, 2023. https://www.aao.org/education/preferred-practice-pattern/age-related-macular-degeneration-ppp.

Reference number(s)
2670-A

Standard Medicare Part B Management Takhzyro

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Takhzyro	lanadelumab-flyo

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Takhzyro is indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients aged 2 years and older.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- For initial authorization:
  - C1 inhibitor functional and antigenic protein levels
  - F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation testing, if applicable
  - Chart notes confirming family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy, if applicable
- For continuation of therapy, chart notes demonstrating a reduction in frequency of attacks

Reference number(s)
2670-A

Coverage Criteria

Hereditary angioedema (HAE)[1-4]

Authorization of 12 months may be granted for prevention of HAE attacks when either of the following criteria is met at the time of diagnosis:

- Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
  - C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test, or
  - Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test).
- Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
  - Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
  - Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy (i.e., cetirizine at 40 mg per day or the equivalent) for at least one month.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for prevention of HAE attacks when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy. Benefit is defined as:
  - A significant reduction in frequency of attacks (e.g., ≥ 50%) since starting treatment, and
  - A reduction in the use of medications to treat acute attacks since starting treatment.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Takhzyro.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema.
- Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Takhzyro are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the above diagnostic criteria can be found in the US HAEA Medical Advisory Board Guidelines for the Management of Hereditary Angioedema. When HAE is suspected based on the clinical presentation, the provider should test serum C4, C1INH antigenic level, and C1INH functional level. Low C4 and low C1INH antigenic or functional levels are consistent with a diagnosis of HAE with an abnormal C1INH.

When a diagnosis of HAE with normal C1INH is suspected, additional genetic tests for factor XII, plasminogen, angiopoietin-1, and kininogen mutations should be performed. If the genetic testing is unable to be performed or a known mutation is not found, the US HAEA guidelines indicate a positive family history of recurrent angioedema and a documented lack of efficacy of high-dose antihistamine therapy for at least 1 month or an interval expected to be associated with three or more attacks of angioedema, whichever is longer, can be used as clinical criteria to support the diagnosis. The understanding of the genetic mutations associated with HAE is evolving. Veronez et al have identified additional genetic mutations not mentioned in the US HAEA guidelines. There are five new genes associated with HAE and a normal C1-INH: ANGPT1 (angiopoietin-1), PLG (plasminogen), KNG1 (kininogen), MYOF (myoferlin), and HS3ST6 (heparan sulfate-glucosamine 3-O-sulfotransferase 6).

References

1. Takhzyro [package insert]. Lexington, MA: Dyax Corp., a Takeda company; February 2023.
2. Zuraw BL, Bork K, Binkley KE, et al. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel. Allergy Asthma Proc. 2012; 33(6):S145-S156.
3. 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.
4. Veronez CL, Csuka D, Sheik FR, et al. The expanding spectrum of mutations in hereditary angioedema. J Allergy Clin Immunol Pract. 2021;S2213-2198(21)00312-3.

Reference number(s)
6123-A

Standard Medicare Part B Management Talvey

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Talvey	talquetamab-tgvs

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Multiple Myeloma

Authorization of 12 months may be granted for treatment of relapsed or refractory multiple myeloma in members who have received at least 4 prior therapies, including at least one drug from each of the following categories:

- Proteasome inhibitor (e.g., bortezomib, ixazomib, carfilzomib)
- Immunomodulatory agent (e.g., lenalidomide, pomalidomide, thalidomide)
- Anti-CD38 monoclonal antibody (e.g., daratumumab, isatuximab)

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat an indication listed in the coverage criteria section
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen, and
    - No evidence of disease progression while on the current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Talvey.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Talvey [package insert]. Horsham, PA: Janssen Biotech, Inc.; August 2023.

Reference number(s)
2132-A

CVS caremark

Standard Medicare Part B Management Tecentriq (atezolizumab)

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Tecentriq	atezolizumab

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Non-small cell lung cancer (NSCLC)

Tecentriq, as a single-agent, is indicated as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage II to IIIA non-small cell lung cancer (NSCLC) whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test

Tecentriq, as a single-agent, is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

Tecentriq, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment, of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.

Tecentriq, in combination with paclitaxel protein-bound and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.

Tecentriq, as a single agent is, indicated for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving the requested medication.

Small cell lung cancer (SCLC)

Tecentriq, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

Hepatocellular Carcinoma (HCC)

Tecentriq, in combination with bevacizumab, is indicated for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy.

Melanoma

Tecentriq, in combination with cobimetinib and vemurafenib, is indicated for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Alveolar Soft Part Sarcoma (ASPS)

Tecentriq, as a single agent, is indicated for the treatment of adult and pediatric patients 2 years of age and older with unresectable or metastatic ASPS.

Compendial Uses

- Urothelial carcinoma
- Non-small cell lung cancer (NSCLC)
- Mesothelioma
- Cervical cancer
- Hepatocellular carcinoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Criteria for Initial Approval

Urothelial carcinoma

Authorization of 12 months may be granted for treatment of urothelial carcinoma when any of the following criteria is met:

- Member is not eligible for cisplatin-containing chemotherapy, and the member's tumor expresses PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering $\geq$5% of the tumor area).
- Member is not eligible for any platinum containing chemotherapy.
- The requested medication will be used for the first-line treatment of locally advanced or metastatic urothelial carcinoma in combination with gemcitabine and cisplatin or gemcitabine and carboplatin.
- The requested medication will be used for the treatment of locally advanced or metastatic urothelial carcinoma in members with disease that has progressed during or following chemotherapy.

Non-small cell lung cancer (NSCLC)

- Authorization of 12 months may be granted for treatment of recurrent, advanced or metastatic non-small cell lung cancer when there are no EGFR exon 19 deletions or L858R mutations or ALK rearrangements (unless testing is not feasible due to insufficient tissue) and any of the following criteria are met:
    - The requested medication will be used as continued maintenance therapy as a single agent or in combination with bevacizumab.
    - The requested medication will be used as first line or subsequent therapy in combination with chemotherapy with or without bevacizumab.
    - The requested medication will be used as first line therapy for PD-L1 expression positive (≥50%) tumors as a single agent.
- Authorization of 6 months may be granted for treatment of stage II to III non-small cell lung cancer that is PD-L1 positive as single agent adjuvant therapy.
- Authorization of 12 months may be granted for treatment of recurrent, advanced or metastatic non-small cell lung cancer as single agent subsequent therapy.

Small cell lung cancer (SCLC)

Authorization of 12 months may be granted for treatment of small cell lung cancer when the requested medication will be used as initial treatment in combination with etoposide and carboplatin (followed by single agent maintenance) for extensive-stage disease.

Hepatocellular carcinoma (HCC)

- Authorization of 12 months may be granted for treatment of unresectable, inoperable, metastatic, or disease with extensive liver tumor burden hepatocellular carcinoma when the requested medication will be used as initial treatment in combination with bevacizumab.
- Authorization of 12 months may be granted in combination with bevacizumab for adjuvant treatment following resection or ablation.

Melanoma

Authorization of 12 months may be granted for treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma when the requested medication is used in combination with cobimetinib (Cotellic) and vemurafenib (Zelboraf).

Mesothelioma

Authorization of 12 months may be granted for subsequent treatment of peritoneal mesothelioma, pericardial mesothelioma, or tunica vaginalis testis mesothelioma when used in combination with bevacizumab.

Alveolar Soft Part Sarcoma (ASPS)

Authorization of 12 months may be granted for the treatment of patients with unresectable or metastatic alveolar soft part sarcoma when used as a single agent.

Cervical Cancer

Authorization of 12 months may be granted for the treatment of persistent, recurrent or metastatic small cell neuroendocrine carcinoma of the cervix (NECC) when used in combination with etoposide and either cisplatin or carboplatin.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months (12 months total for adjuvant treatment of HCC and NSCLC) may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication enumerated in the Coverage Criteria section.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Tecentriq.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Small cell lung cancer
- NCCN Guideline: Peritoneal mesothelioma
- NCCN Guideline: Cutaneous melanoma
- NCCN Guideline: Non-small cell lung cancer
- NCCN Guideline: Hepatocellular carcinoma
- NCCN Guideline: Soft tissue sarcoma

- NCCN Guideline: Bladder cancer
- NCCN Guideline: Cervical cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Tecentriq are covered in addition to the following:

- Urothelial carcinoma
- Non-small cell lung cancer (NSCLC)
- Mesothelioma
- Cervical Cancer
- Hepatocellular carcinoma

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Tecentriq to treat urothelial carcinoma, non-small cell lung cancer , hepatocellular carcinoma, cervical cancer, and peritoneal mesothelioma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using Tecentriq to treat urothelial carcinoma can be found in the Clinical Pharmacology database. Use of information in the Clinical Pharmacology database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen). The Clinical Pharmacology database supports the use of Tecentriq as treatment of locally advanced or metastatic urothelial carcinoma.

References

1. Tecentriq [package insert]. South San Francisco, CA: Genentech, Inc.; April 2024.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. https://www.nccn.org. September 30, 2024.
3. Clinical Pharmacology powered by ClinicalKey. Tampa (FL): Elsevier. 2023- [cited August 9, 2023]. Available from: http://www.clinicalkey.com.

Reference number(s)
5658-A

Standard Medicare Part B Management Tecvayli

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Tecvayli	teclistamab-cqyv

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Tecvayli is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Multiple Myeloma

Authorization of 12 months may be granted for treatment of relapsed or refractory multiple myeloma in members who have received at least 4 prior therapies, including at least one drug from each of the following categories:

- Anti-CD38 monoclonal antibody (e.g., daratumumab, isatuximab)
- Proteasome inhibitor (e.g., bortezomib, ixazomib, carfilzomib)

- Immunomodulatory agent (e.g., lenalidomide, pomalidomide, thalidomide)

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat an indication listed in the coverage criteria
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Tecvayli.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Multiple Myeloma

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Tecvayli [package insert]. Horsham, PA: Janssen Biotech, Inc.; February 2024.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed May 2, 2024.

Reference number(s)
4701-A

Standard Medicare Part B Management
Tepezza

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Tepezza	teprotumumab-trbw

Indications

FDA-approved Indications[1]

Tepezza is indicated for the treatment of thyroid eye disease regardless of Thyroid Eye Disease activity or duration.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions: Supporting chart notes or medical record indicating moderate-to-severe disease as applicable to the coverage criteria section.

Exclusions

Coverage will not be provided for repeat series of Tepezza infusions.

Reference number(s)
4701-A

Coverage Criteria

Thyroid eye disease (TED)[1-5]

Authorization of 6 months may be granted for treatment of TED when all of the following criteria are met:

- Member is 18 years of age or older.
- Member has moderate-to-severe (active and inactive) disease (see Appendix A).
- Member will not exceed a one-time treatment course consisting of 8 infusions given once every 3 weeks (10mg/kg on first infusion, followed by 20mg/kg every 3 weeks for 7 additional infusions).

Appendix

Appendix A: Disease Severity Assessment[2]

Mild disease, at least one of the following:

- Minor lid retraction (<2 mm)
- Mild soft-tissue involvement
- Exophthalmos <3 mm above normal for race and gender
- No or intermittent diplopia
- Corneal exposure responsive to lubricants

Moderate-to-severe disease, at least one of the following:

- Lid retraction ≥2 mm
- Moderate or severe soft-tissue involvement
- Exophthalmos ≥3 mm above normal for race and gender
- Inconstant or constant diplopia

Sight-threatening disease, at least one of the following:

- Dysthyroid optic neuropathy (DON)
- Corneal breakdown

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Tepezza.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs

    - Clinical Pharmacology
- 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis.
- Management of Thyroid Eye Disease: A Consensus Statement by the American Thyroid Association and the European Thyroid Association.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Tepezza are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Tepezza [package insert]. Deerfield Lake, IL: Horizon Therapeutics USA Inc; July 2023.
2. Bartalena L, Kahaly L, Baldeschi L, et al. The 2021 European Thyroid Association/European Group on Graves' Orbitopathy guidelines for the management of Graves' orbitopathy. Eur J Endocrinol. 2021;185(4):G43-G67.
3. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;26(10):1343-1421.
4. Burch HB, Perros P, Bednarczuk T, Cooper DS, et al. Management of Thyroid Eye Disease: A Consensus Statement by the American Thyroid Association and the European Thyroid Association. Thyroid. 2022 Dec;32(12):1439-1470.
5. ClinicalTrials.gov [Internet]. Bethesda, MD: National Library of Medicine. 2023 March 16 NCT04583735, A Study Evaluating TEPEZZA® Treatment in Patients with Chronic (Inactive) Thyroid Eye Disease; Accessed December 11, 2023.

Reference number(s)
3361-A

Standard Medicare Part B Management teriparatide-Forteo

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Forteo	teriparatide
Teriparatide (branded generic)	teriparatide

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1-4]

Indicated for:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture (defined herein as having a history of osteoporotic fracture or multiple risk factors for fracture) or who have failed or are intolerant to other available osteoporosis therapy.
- Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture or who have failed or are intolerant to other available osteoporosis therapy.
- Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture or who have failed or are intolerant to other available osteoporosis therapy.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this coverage criteria section should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Osteoporosis Treatment[1-4]

Authorization of 12 months may be granted for the treatment of osteoporosis in men or postmenopausal women at high risk for fracture.

Glucocorticoid-Induced Osteoporosis[1-4]

Authorization of 12 months may be granted for the treatment of glucocorticoid-induced osteoporosis in members who are at high risk for fracture.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested drug.
- The requested drug is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy. Benefit is defined as:
    - Disease stability, or
    - Disease improvement

Other

The cumulative duration of parathyroid hormone analogs (teriparatide and abaloparatide) will not exceed a total of 24 months in the member's lifetime unless the member remains at or has returned to having a high risk for fracture.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Forteo and teriparatide.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Forteo and teriparatide are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Forteo [package insert]. Indianapolis, IN: Eli Lilly and Company; July 2024.
2. Teriparatide [package insert]. Parsippany, NJ: Teva Pharmaceuticals USA, Inc.; November 2021.
3. Teriparatide [package insert]. Morristown, NJ: Alvogen, Inc.; November 2023.
4. Teriparatide [package insert]. Weston, FL: Apotex Corp.; December 2023.

Reference number(s)
6423-A

Standard Medicare Part B Management Tevimbra

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Tevimbra	tislelizumab-jsgr

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Esophageal Cancer

- Tevimbra, in combination with platinum-containing chemotherapy, is indicated for the first-line treatment of adults with unresectable or metastatic esophageal squamous cell carcinoma (ESCC) whose tumors express PD-L1 (≥1).
- Tevimbra as a single agent, is indicated for the treatment of adults with unresectable or metastatic esophageal squamous cell carcinoma after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor.

Gastric Cancer

Tevimbra, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of adults with unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma (G/GEJ) whose tumors express PD-L1 (≥1).

Compendial Uses[2]

- Esophageal cancer/esophagogastric junction cancer
- Hepatocellular carcinoma
- Histologic (Richter) transformation to diffuse large B-cell lymphoma

- Gastric cancer
- Small bowel adenocarcinoma
- Anal carcinoma
- Head and neck cancer
- Colon cancer
- Appendiceal cancer
- Rectal cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- Documentation of programmed death ligand 1 (PD-L1) tumor expression, where applicable.
- Documentation of laboratory report confirming MSI-H, mismatch repair deficient (dMMR) or polymerase epsilon/delta (POLE/POLD1) tumor status, where applicable.
- Documentation of human epidermal growth factor receptor 2 (HER2) status, where applicable.

Exclusions

Coverage will not be provided for members who have experienced progression while on PD-1 or PD-L1 therapy.

Coverage Criteria

Esophageal Cancer[1,2]

Authorization of 12 months may be granted for the treatment of esophageal and esophagogastric junction cancer in members who are not surgical candidates or have unresectable, recurrent, or metastatic disease when the requested medication will be used for any of the following:

- First-line therapy for members with PD-L1 ≥1 and squamous cell carcinoma or HER2-negative adenocarcima in combination with platinum-containing chemotherapy
- Subsequent therapy for esophageal squamous cell carcinoma as a single agent

Authorization of 12 months may be granted for induction therapy for relieving dysphagia in combination with platinum-containing chemotherapy for members with PD-L1 ≥1 planned for esophagectomy.

Hepatocellular Carcinoma[2]

Authorization of 12 months may be granted as a single agent for the first line treatment of hepatocellular carcinoma when the member is deemed ineligible for resection, transplant, or locoregional therapy.

Histologic (Richter) transformation to diffuse large B-cell lymphoma[2]

Authorization of 12 months may be granted for treatment of Histologic (Richter) transformation to diffuse large B-cell lymphoma in combination with zanubrutinib.

Gastric Cancer[1]

Authorization of 12 months may be granted for the treatment of HER2-negative gastric adenocarcinoma in members who are not surgical candidates or have unresectable, recurrent, or metastatic disease in combination with platinum and fluoropyrimidine-based chemotherapy for first-line treatment of tumors expressing PD-L1 (≥1).

Small Bowel Adenocarcinoma[2]

Authorization of 12 months may be granted as a single agent for treatment of unresectable, inoperable, advanced or metastatic small bowel adenocarcinoma for microsatellite instability-high (MSI-H), or mismatch repair deficient (dMMR), or polymerase epsilon/delta (POLE/POLD1) tumors with ultra-hypermutated phenotype (e.g., tumor mutational burden (TMB) > 50 mut/Mb).

Anal Carcinoma[2]

Authorization of 12 months may be granted as a single agent for treatment of locally recurrent, progressive, or metastatic anal carcinoma.

Head and Neck Cancer[2]

Authorization of 12 months may be granted in combination with cisplatin and gemcitabine or as a single agent for treatment of unresectable or metastatic nasopharyngeal cancer.

Colon Cancer[2]

Authorization of 12 months may be granted as a single agent for neoadjuvant therapy or treatment of unresectable, inoperable, or metastatic colon adenocarcinoma for microsatellite instability-high (MSI-H), or mismatch repair deficient (dMMR), or polymerase epsilon/delta (POLE/POLD1) tumors with ultra-hypermutated phenotype (e.g., tumor mutational burden (TMB) > 50 mut/Mb).

Appendiceal Cancer[2]

Authorization of 12 months may be granted as a single agent for treatment of advanced or metastatic appendiceal adenocarcinoma for microsatellite instability-high (MSI-H), or mismatch repair deficient (dMMR), or polymerase epsilon/delta (POLE/POLD1) tumors with ultra-hypermutated phenotype (e.g., tumor mutational burden (TMB) > 50 mut/Mb).

Rectal Cancer[2]

Authorization of 12 months may be granted as a single agent for neoadjuvant therapy or treatment of recurrent or metastatic rectal adenocarcinoma for microsatellite instability-high (MSI-H), or mismatch repair deficient (dMMR), or polymerase epsilon/delta (POLE/POLD1) tumors with ultra-hypermutated phenotype (e.g., tumor mutational burden (TMB) > 50 mut/Mb).

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat an indication listed in the coverage criteria section
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen, and
    - No evidence of disease progression while on the current regimen

Summary of Evidence

The contents of this document were created after examining the following resources:

- The prescribing information for Tevimbra.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Esophageal and esophagogastric junction cancer
- NCCN Guideline: Gastric cancer
- NCCN Guideline: Hepatocellular carcinoma
- NCCN Guideline: Chronic lymphocytic leukemia/Small lymphocytic lymphoma
- NCCN Guideline: Small bowel adenocarcinoma
- NCCN Guideline: Anal carcinoma
- NCCN Guideline: Head and neck cancers
- NCCN Guideline: Colon cancer
- NCCN Guideline: Rectal cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Tevimbra are covered in addition to the following:

- Hepatocellular carcinoma

- Histologic (Richter) transformation to diffuse large B-cell lymphoma
- Small bowel adenocarcinoma
- Anal carcinoma
- Head and neck cancer
- Colon cancer
- Appendiceal cancer
- Rectal cancer

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Tevimbra to treat the indications in coverage criteria section can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

References

1. Tevimbra [package insert]. San Mateo, CA: BeiGene USA, Inc; March 2025.
2. The NCCN Drugs & Biologics Compendium® © 2025 National Comprehensive Cancer Network, Inc. https://www.nccn.org. Accessed March 7, 2025.

Reference number(s)
5106-A

Standard Medicare Part B Management
Tezspire

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Tezspire	tezepelumab-ekko

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

Tezspire is indicated for add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma.

Limitations of Use

Not for relief of acute bronchospasm or status asthmaticus.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- Initial requests: Chart notes, medical record documentation, or claims history supporting previous medications tried including drug, dose, frequency, and duration.
- Continuation requests: Chart notes or medical record documentation supporting improvement in asthma control.

Coverage Criteria[1-3]

Authorization of 12 months may be granted for treatment of severe asthma when all of the following criteria are met:

- Member is 12 years of age or older.
- Member has a history of severe asthma despite current treatment with both of the following medications at optimized doses, unless the member has a clinical reason to avoid these therapies:
    - Inhaled corticosteroid
    - Additional controller (i.e., long-acting beta2-agonist, long-acting muscarinic antagonist, leukotriene modifier, or sustained-release theophylline)
- Member will not use the requested medication concomitantly with other biologics indicated for asthma (e.g., Cinqair, Dupixent, Fasenra, Nucala, Xolair).

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication.

Authorization of 12 months may be granted for when all of the following criteria are met:

- Member is 12 years of age or older.
- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication listed in the coverage criteria section.
- The member is receiving benefit from therapy as defined by a reduction in the frequency and/or severity of symptoms and exacerbations.
- Member will not use the requested medication concomitantly with other biologics indicated for asthma (e.g., Cinqair, Dupixent, Fasenra, Nucala, Xolair).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Tezspire.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2023 update.
- Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Tezspire are covered.

Reference number(s)
5106-A

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Tezspire to treat severe asthma can be found in the Global Initiative for Asthma (GINA) guidelines. For adults and adolescents 12 years of age and older, thymic stromal lymphopoietin (TSLP) blockers (anti-TSLP) can be a drug used when either medium dose maintenance inhaled corticosteroids with formoterol or medium to high dose maintenance inhaled corticosteroids with long-acting beta2-agonists are not controlling the patient's asthma.

References

1. Tezspire [package insert]. Thousand Oaks, CA: Amgen Inc.; February 2023
2. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2023 update. Available at: https://ginasthma.org/wp-content/uploads/2023/07/GINA-Full-Report-23_07_06-WMS.pdf. Accessed March 8, 2024.
3. Cloutier MM, Dixon AE, Krishnan JA, et al. Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program. JAMA. 2020;324(22): 2301-2317.

Reference number(s)
4371-A

Standard Medicare Part B Management Thrombate III

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Thrombate III	antithrombin III [human]

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

- Indicated in patients with hereditary antithrombin deficiency for treatment and prevention of thromboembolism
- Indicated in patients with hereditary antithrombin deficiency for prevention of peri-operative and peri-partum thromboembolism

Compendial Uses[2,3]

- Acquired antithrombin III deficiency
- Heparin resistance prior to and during cardiopulmonary bypass (CPB)
- Sickle cell-thalassemia, treatment of chronic leg ulcers

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Reference number(s)
4371-A

Coverage Criteria

Hereditary Antithrombin Deficiency[1]

Authorization of 12 months may be granted for treatment of hereditary antithrombin deficiency when the requested medication will be used for any of the following indications:

- Treatment of thromboembolism
- Prevention of thromboembolism

Authorization of 1 month may be granted for the treatment of hereditary antithrombin deficiency when the requested medication will be used for any of the following indications:

- Prevention of peri-operative (i.e., surgical procedures) thromboembolism
- Prevention of peri-partum (i.e., obstetrical procedures) thromboembolism

Acquired Antithrombin Deficiency[2,3]

Authorization of 6 months may be granted for treatment of acquired antithrombin deficiency when both of the following criteria is met:

- The member has a condition associated with low levels of antithrombin III (e.g., disseminated intravascular coagulation (DIC) associated with sepsis or trauma, liver failure, asparaginase-induced antithrombin deficiency)
- The requested medication will be used for the treatment or prophylaxis of thromboembolism

Heparin Resistance[2]

Authorization of 1 month may be granted for treatment of heparin resistance prior to and during cardiopulmonary bypass (CPB).

Sickle Cell Beta Thalassemia[2]

Authorization of 3 months may be granted for treatment of chronic leg ulcers in patients with sickle cell beta thalassemia

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Thrombate III

- Thrombate III is being used to treat hereditary antithrombin deficiency (excluding prevention of peri-operative and peri-partum thromboembolism), acquired antithrombin deficiency, or sickle cell beta thalassemia
- The member is receiving benefit from therapy.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Thrombate III.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Thrombate III are covered in addition to the following:

- Acquired antithrombin III deficiency
- Heparin resistance prior to and during cardiopulmonary bypass (CPB)
- Sickle cell-thalassemia, treatment of chronic leg ulcers

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Thrombate III to treat acquired antithrombin III deficiency be found in a study of by Eisele et al. Antithrombin III (AT III) therapy was safe and well tolerated in 42 patients with severe SEPSIS who were receiving standard supportive care and antimicrobial therapy. The endpoints, safety and 30-day all-cause mortality relative to placebo established in this double-blind, phase II, multicenter, multinational clinical trial showed a positive trend for the group that received AT III with the following results: AT III was safe and well tolerated; an overall 39% reduction in 30-day all-cause mortality (41% mortality in the placebo group (9 out of 22) compared to only 25% mortality (5 out of 20) in AT III patients); shorter stay in the ICU; and improved APACHE (Acute Physiology and Chronic Health Evaluation II, multiple organ failure, organ system failure) scores. Patients were randomized to receive an intravenous loading dose of 3000 International Units (IU) AT III, or placebo, administered over approximately 1 hour, followed by a maintenance dose of 1500 IU every 12 hours for 5 days. An author conducted meta-analysis of two other double-blind, placebo-controlled trials involving 122 patients (62 placebo, 60 AT III) with severe sepsis showed a similar 22.9% reduction in 30-day all-cause mortality.

Additionally, antithrombin III (ATIII) was safe and effective in a 40-year-old burn patient with a high incidence of hypercoagulability and thrombosis (Kowal-Vern, et al). The patient presented with third degree burns covering over 68% of his body. He also had a comminuted femoral fracture and C5-C6 subluxation as a result of a motor vehicle accident and a baseline ATIII level of 45%. He was treated with standard burn wound care and received a total of nine ATIII

concentrate infusions within the first four days. The plasma level of ATIII was maintained at 175% or higher, with a dose determined by the following formula: [(desired ATIII level %-patient ATIII level %) x (admission weight, kg)] divided by 1.4. The patient tolerated ATIII treatment with no excessive bleeding and no drop in blood pressure. The authors concluded that ATIII treatment in burn patients is beneficial and may be crucial to increase vascularization of subcutaneous tissue, as well as inhibit anti-inflammatory protease. They also state that ATIII therapy should be initiated as early as possible within the first 24 hours, during the time of low plasma ATIII levels.

Support for using Thrombate III to treat heparin resistance prior to and during cardiopulmonary bypass can be found in a study of 22 patients by Rossi and colleagues. In a study of 22 patients with unstable angina, antithrombin III (ATIII) allowed for adequate anticoagulation during elective coronary artery bypass surgery. It also avoided the activation of the coagulation cascade. Patients were randomly divided into group A and received ATIII 3000 IU and heparin 300 units/kilogram (U/kg), or group B, and received only heparin 300 U/kg. Heparin 10000 units was included in the bypass circuit of all patients. Activated coagulation time (ACT) was monitored throughout the surgery and maintained at 480 seconds or greater. Prothrombin time (PT) activated prothrombin time (aPTT), and fibrinogen and platelets were monitored. Whole blood samples were also obtained to monitor ATIII, thrombin-antithrombin complexes (TAT), fragment 1.2 of prothrombin (F 1.2), and split products of the cross-linked fibrin (D-dimers). Additional heparin was required in group B to maintain ACT values, but not in group A (p less than 0.05). The need for protamine sulfate to neutralize heparin was significantly lower in group A (p less than 0.05). Both groups had similar results in PT, aPTT, fibrinogen values, and platelet levels. TAT and F 1.2 increased significantly in group B (p less than 0.01), however differences in D-dimers were not significant. The authors concluded that patients who received ATIII showed a better intraoperative and postoperative coagulation pattern and expression of a more correct functioning of the hemostatic balance. The high cost of ATIII should be considered, as should the costs associated with blood transfusions and surgical reexploration.

Support for using Thrombate III to treat chronic leg ulcers associated with sickle cell thalassemia can be found in a study by Cacciola and colleagues. The combination of antithrombin III concentrate as 1000 units intravenously every 48 hours for 2 weeks, followed by the same dose every 72 hours for 4 further weeks plus calcium heparin 150 units/kg subcutaneously once daily for 6 weeks was effective in increasing antithrombin III levels and producing clinical improvement of chronic leg ulcers in patients with sickle cell beta-thalassemia in an uncontrolled study. The reduced levels of antithrombin III in plasma, as well as elevated levels of fibrinopeptide A, observed prior to treatment were suggestive of hypercoagulation via chronic thrombin activation in these patients. Antithrombin III concentrate was administered due to suspected acquired antithrombin III deficiency. All patients in this study had been refractory either to conventional therapy or anticoagulants. Controlled clinical studies are needed to further assess the efficacy of antithrombin III concentrate in treating refractory leg ulcers in patients with sickle cell beta-thalassemia.

References

1. Thrombate III [package insert]. Research Triangle Park, NC: Grifols Therapeutics LLC; December 2023.
2. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com (cited: October 9, 2024).
3. Hunault-Berger M, Chevallier P, Delain M, et al. Changes in antithrombin and fibrinogen levels during induction chemotherapy with L-asparaginase in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma. Use of supportive coagulation therapy and clinical outcome: the CAPELAL study. Haematologica. 2008;93(10):1488-1494.

4. Eisele B, Lamy M, Thijs LG et al: Antithrombin III in patients with severe sepsis: a randomized, placebo-controlled, double-blind multicenter trial plus a meta-analysis on all randomized, placebo-controlled, double-blind trials with antithrombin III in severe sepsis. Intensive Care Med (1998); 24:663-672, (1998).
5. Kowal-Vern A, McGill V, Walenga JM, et al: Antithrombin III concentrate in the acute phase of thermal injury. Burns 2000; 26:97-101.
6. Rossi M, Martinelli L, Storti S, et al: The role of antithrombin III in the perioperative management of the patient with unstable angina. Ann Thorac Surg 1999; 68:2231-2236.
7. Cacciola E, Giustolisi R, Musso R, et al: Antithrombin III concentrate for treatment of chronic leg ulcers in sickle-cell-beta thalassemia: a pilot study. Ann Intern Med 1989; 111:534-536.

Reference number(s)
4821-A

Standard Medicare Part B Management treprostinil-Remodulin

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Remodulin	treprostinil injection
treprostinil injection (all other brands)	treprostinil injection

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

- Treatment of pulmonary arterial hypertension (PAH; World Health Organization [WHO] Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with New York Heart Association (NYHA) Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH, PAH associated with congenital systemic-to-pulmonary shunts, or PAH associated with connective tissue diseases.
- In patients with PAH requiring transition from epoprostenol, to diminish the rate of clinical deterioration. Consider the risks and benefits of each drug prior to transition.

Compendial Uses

Severe peripheral ischemia

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Reference number(s)
4821-A

Coverage Criteria

Pulmonary hypertension (PH)

Indefinite authorization may be granted for treatment of pulmonary hypertension when ALL of the following criteria are met:

- The pulmonary hypertension is not secondary to pulmonary venous hypertension (e.g., left-sided atrial or ventricular disease, left-sided valvular heart disease, etc.) or disorders of the respiratory system (e.g., chronic obstructive pulmonary disease, interstitial lung disease, obstructive sleep apnea, or other sleep disordered breathing, alveolar hypoventilation disorders, etc.).
- The member has primary pulmonary hypertension or pulmonary hypertension, which is secondary to one of the following conditions: connective tissue disease, thromboembolic disease of the pulmonary arteries, human immunodeficiency virus (HIV) infection, cirrhosis, diet drugs, congenital left to right shunts, etc. If these conditions are present, all of the following criteria must be met:
    - The pulmonary hypertension has progressed despite maximal medical and/or surgical treatment of the identified condition.
    - The mean pulmonary artery pressure is greater than 25 mmHg at rest or greater than 30 mmHg with exertion.
    - The member has significant symptoms from the pulmonary hypertension (i.e., severe dyspnea on exertion, and either fatigability, angina, or syncope).
    - Treatment with oral calcium channel blocking agents has been tried and failed or has been considered and ruled out.

Severe peripheral ischemia

Authorization of 12 months may be granted for treatment of severe peripheral ischemia.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication through a paid pharmacy or medical benefit.

Pulmonary hypertension (PAH)

Authorization for members who are requesting authorization for continuation of therapy must meet all requirements in the coverage criteria section.

Severe peripheral ischemia

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat severe peripheral ischemia.

- The member is receiving benefit from therapy. Benefit is defined as either:
    - Disease stability
    - Disease improvement

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Remodulin and generic treprostinil.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- External Infusion Pumps Local Coverage Determination (L33794)

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Remodulin and generic treprostinil are covered in addition to severe peripheral ischemia.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information and the External Infusion Pumps Local Coverage Determination (L33794).

Support for using Remodulin or generic treprostinil to treat severe peripheral ischemia can be found in two small studies. Berman et al. (2006) conducted an open-label study of 10 patients with at least 1 ischemic wound who received treprostinil via an ambulatory subcutaneous infusion pump. The mean worst ischemic rest pain score decreased from baseline to week 12 by 62% and the mean average ischemic rest pain score decreased from baseline to week 12 by 57%. Three patients with small wounds (0.2 to 2 cm2) had complete wound healing and no new wounds developed in any patient during the study period. Within 2 months following the end of the study, 3 patients had below the knee amputations as a result of wound progression.

Additionally, Mohler and colleagues conducted a sequential dose-escalation trial where 8 patients received an initial infusion rate of treprostinil 10 nanograms/kg/min followed by doubling of the infusion rate every 60 minutes until dose-limiting side effects (i.e., severe flushing, headache, nausea, or diarrhea) occurred. The maximum tolerated dose was determined to be 10 to 20 nanograms/kg/min. Blood flow in the common femoral artery was increased by 35% over baseline at the end of the maximum dosage, 29% over baseline at the end of the maintenance dosage, and 28% over baseline at the end of the washout phase.

References

1. Remodulin [package insert]. Research Triangle Park, NC: United Therapeutics Corp.; October 2023.

2. Treprostinil [package insert]. Princeton, NJ: Sandoz, Inc.; April 2023.
3. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/ (cited: 04/10/2024).
4. Berman S, Quick R, Yoder P, et al. Treprostinil sodium (Remodulin), a prostacyclin analog, in the treatment of critical limb ischemia: open-label study. Vascular. 2006;14(3):142-148.
5. Mohler ER, Klugherz B, Goldman R, et al. Trial of a novel prostacyclin analog, UT-15, in patients with severe intermittent claudication. Vasc Med. 2000;5:231-237.
6. External Infusion Pumps (L33794) Version R30. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed April 10, 2024.
7. External Infusion Pumps - Policy Article (A52507) Version R33. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed April 10, 2024.

Reference number(s)
5002-A

Standard Medicare Part B Management
Tretten

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Tretten	coagulation Factor XIII A-subunit [recombinant]

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

Tretten is indicated in patients with congenital factor XIII A-subunit deficiency for routine prophylaxis for bleeding.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Congenital Factor XIII A-Subunit Deficiency[1-2]

Authorization of 12 months may be granted for prophylactic treatment of congenital factor XIII A-subunit deficiency.

Reference number(s)
5002-A

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- Tretten is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Tretten.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service-Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- MASAC recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Tretten are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Tretten [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; June 2020.
2. National Hemophilia Foundation. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised April 2024. MASAC Document #284. https://www.bleeding.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed October 16, 2024.

Reference number(s)
2195-A

Standard Medicare Part B Management Tymlos

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Tymlos	abaloparatide

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

Indicated for:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture (defined as history of osteoporotic fracture or multiple risk factors for fracture) or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment to increase bone density in men with osteoporosis 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.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Osteoporosis treatment[1-3]

Authorization of 12 months may be granted for the treatment of osteoporosis in men or postmenopausal women at high risk for fracture.

Reference number(s)
2195-A

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Tymlos.
- Tymlos is being used to treat an indication listed in the coverage criteria section.
- The member is receiving benefit from therapy. Benefit is defined as:
    - Disease stability, or
    - Disease improvement

Other

The cumulative duration of parathyroid hormone analogs (teriparatide and abaloparatide) will not exceed a total of 24 months in the member's lifetime.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Tymlos.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Tymlos are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Reference number(s)
2195-A

References

1. Tymlos [package insert]. Boston, MA: Radius Health, Inc. February 2024.
2. Miller PD, Hattersley G, Riis BJ, et al. Effect of Abaloparatide Vs Placebo on New Vertebral Fractures in Postmenopausal Women with Osteoporosis: A Randomized Clinical Trial. JAMA. 2016; 316 (7): 722:733.
3. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis-2020 update. Endocr Pract. 2020;26 (Suppl 1):1-46.

Reference number(s)
4822- A

Standard Medicare Part B Management Tyvaso

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Tyvaso	treprostinil inhalation solution

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

- Treatment of pulmonary arterial hypertension (PAH; World Health Organization [WHO] Group 1) to improve exercise ability. Studies establishing effectiveness predominately included patients with New York Heart Association (NYHA) Functional Class III symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.
- Treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE), and WHO Group 3 connective tissue disease.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Reference number(s)
4822- A

Coverage Criteria

Pulmonary arterial hypertension (PAH)

Authorization of 12 months may be granted for treatment of pulmonary arterial hypertension when ALL of the following criteria are met:

- The pulmonary hypertension is not secondary to pulmonary venous hypertension (e.g., left sided atrial or ventricular disease, left sided valvular heart disease) or disorders of the respiratory system other than interstitial lung disease (e.g., chronic obstructive pulmonary disease, obstructive sleep apnea or other sleep disordered breathing, alveolar hypoventilation disorders).
- The member has primary pulmonary hypertension or pulmonary hypertension which is secondary to one of the following conditions: connective tissue disease, human immunodeficiency virus (HIV) infection, cirrhosis, anorexigens, or congenital left to right shunts. If these conditions are present, then all of the following criteria must be met:
    - The pulmonary hypertension has progressed despite maximal medical and/or surgical treatment of the identified condition.
    - The mean pulmonary artery pressure is greater than 25 mmHg at rest or greater than 30 mmHg with exertion.
    - The member has significant symptoms from the pulmonary hypertension (i.e., severe dyspnea on exertion, and either fatigability, angina, or syncope).
    - Treatment with oral calcium channel blocking agents has been tried and failed or has been considered and ruled out.

Pulmonary hypertension associated with interstitial lung disease (PH-ILD)

Authorization of 12 months may be granted for treatment of pulmonary hypertension associated with interstitial lung disease when ALL of the following criteria are met:

- The presence of interstitial lung disease has been confirmed by a high-resolution computed tomography (CT) scan of the chest.
- The mean pulmonary artery pressure is greater than or equal to 25 mmHg.
- The pulmonary capillary wedge pressure or left ventricular end-diastolic pressure is less than or equal to 15 mmHg.
- The pulmonary vascular resistance is greater than or equal to 3 Wood units at rest.
- The member has significant symptoms of pulmonary hypertension (e.g., dyspnea on exertion, fatigability).

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy for an indication in the coverage criteria section must be currently receiving therapy with the requested medication through a paid pharmacy or medical benefit and must meet all requirements in the coverage criteria section.

Reference number(s)
4822- A

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Tyvaso.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Nebulizers Local Coverage Determination (L33370)

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Tyvaso are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information and Nebulizers Local Coverage Determination (L33370)

References

1. Tyvaso [package insert]. Research Triangle Park, NC: United Therapeutics Corp.; May 2022.
2. Nebulizers (L33370) Version R12. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed April 14, 2024.
3. Nebulizers - Policy Article (A52466) Version R19. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed April 14, 2024.

Reference number(s)
5682-A

Standard Medicare Part B Management Tzield

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Tzield	teplizumab-mzwv

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indication

Tzield is indicated to delay the onset of Stage 3 type 1 diabetes in adults and pediatric patients 8 years of age and older with Stage 2 type 1 diabetes.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- Presence of two or more pancreatic islet cell autoantibodies within the past 6 months
- Abnormal oral glucose tolerance test (OGTT) results within the past 2 months

Reference number(s)
5682- A

Coverage Criteria

Delay of Stage 3 Type 1 Diabetes

Authorization of 1 month may be granted for members with Stage 2 type 1 diabetes to delay the onset of Stage 3 type 1 diabetes when all of the following criteria are met:

- Member is 8 years of age and older
- Member has two or more of the following pancreatic islet cell autoantibodies detected in two samples obtained within the past 6 months:
  - Glutamic acid decarboxylase 65 (GAD) autoantibodies
  - Insulin autoantibody (IAA)
  - Insulinoma-associated antigen 2 autoantibody (IA-2A)
  - Zinc transporter 8 autoantibody (ZnT8A)
  - Islet cell autoantibody (ICA)
- Member has an abnormal oral glucose tolerance test (OGTT) confirming dysglycemia within the past 2 months when any of the following are met:
  - Fasting blood glucose level of 100 to 125 mg/dL (5.6 to 6.9 mmol/L)
  - 2-hour postprandial plasma glucose level of at least 140 mg/dL (7.8 mmol/L) and less than 200 mg/dL (11.1 mmol/L)
  - Intervening postprandial glucose level at 30, 60, or 90 minutes of greater than 200 mg per deciliter (11.1 mmol/L) on two occasions
- Member does not have symptoms associated with type 1 diabetes (e.g., increased urination, excessive thirst, weight loss)
- Member will not exceed a one-time 14-day treatment course consisting of the following dosing schedule:
  - Day 1: 65 mcg/m^2
  - Day 2: 125 mcg/m^2
  - Day 3: 250 mcg/m^2
  - Day 4: 500 mcg/m^2
  - Days 5 through 14: 1,030 mcg/m^2

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Tzield.
- The available compendium
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium

  - Micromedex DrugDex
  - American Hospital Formulary Service- Drug Information (AHFS-DI)
  - Lexi-Drugs
  - Clinical Pharmacology
- American Diabetes Association Professional Practice Committee; 2. Diagnosis and Classification of Diabetes: *Standards of Care in Diabetes—2024*.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Tzield are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for a fasting blood glucose level of 100 to 125 mg/dL can be found in the American Diabetes Association Standards of Care in Diabetes 2024 guidelines.

References

1. Tzield [package insert]. Red Bank, NJ: Provention Bio, Inc.; December 2023.
2. Herold KC, Bundy BN, Long SA, et al. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. N Engl J Med 2019; 381:603-613. https://www.nejm.org/doi/full/10.1056/nejmoa1902226
3. American Diabetes Association Professional Practice Committee; 2. Diagnosis and Classification of Diabetes: *Standards of Care in Diabetes—2024*. *Diabetes Care* 1 January 2024; 47 (Supplement_1): S20–S42.

Reference number(s)
2836-A

Standard Medicare Part B Management
Ultomiris

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Ultomiris	ravulizumab-cwvz

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

- Ultomiris is indicated for the treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH).
- Ultomiris is indicated for the treatment of adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).
- Ultomiris is indicated for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive.
- Ultomiris is indicated for the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive.

Limitations of Use

Ultomiris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Reference number(s)
2836-A

Documentation

The following documentation must be available, upon request, for all submissions:

- For initial requests:
  - Paroxysmal nocturnal hemoglobinuria: Flow cytometry used to show results of glycosylphosphatidylinositol-anchored proteins (GPI-APs) deficiency
  - Generalized myasthenia gravis:
    - Positive anti-acetylcholine receptor (AChR) antibody test
    - Myasthenia Gravis Foundation of America (MGFA) clinical classification
    - MG activities of daily living score
    - Previous medications tried, including response to therapy. If therapy is not advisable, documentation of clinical reasons to avoid therapy.
  - Neuromyelitis optica spectrum disorder: immunoassay used to confirm anti-aquaporin-4 (AQP4) antibody is present.
- For continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

Coverage Criteria

Paroxysmal nocturnal hemoglobinuria (PNH)

Authorization of 6 months may be granted for treatment of paroxysmal nocturnal hemoglobinuria (PNH) when all of the following criteria are met:

- The diagnosis of PNH was confirmed by detecting a deficiency of glycosylphosphatidylinositol-anchored proteins (GPI-APs) (e.g., at least 5% PNH cells, at least 51% of GPI-AP deficient poly-morphonuclear cells)
- Flow cytometry is used to demonstrate GPI-APs deficiency
- Member has and exhibits clinical manifestations of disease (e.g., LDH > 1.5 ULN, thrombosis, renal dysfunction, pulmonary hypertension, dysphagia)
- The requested medication will not be used in combination with another complement inhibitor (e.g., Empaveli, Fabhalta, Piasky, Soliris) for the treatment of PNH (concomitant use with Voydeya is allowed).

Atypical hemolytic uremic syndrome (aHUS)

Authorization of 6 months may be granted for treatment of atypical hemolytic uremic syndrome (aHUS) that is not caused by Shiga toxin when all of the following criteria are met:

- Absence of Shiga toxin
- The requested medication will not be used in combination with another complement inhibitor (e.g., Soliris) for the treatment of aHUS.

Generalized myasthenia gravis (gMG)

Authorization of 6 months may be granted for treatment of generalized myasthenia gravis (gMG) when all of the following criteria are met:

- Anti-acetylcholine receptor (AchR) antibody positive
- Myasthenia Gravis Foundation of America (MGFA) clinical classification II to IV
- MG activities of daily living (MG-ADL) total score of greater than or equal to 5
- Meets one of the following:
    - Member has had an inadequate response or intolerable adverse event to at least two immunosuppressive therapies over the course of at least 12 months (e.g., azathioprine, corticosteroids, cyclosporine, methotrexate, mycophenolate, tacrolimus)
    - Member has had an inadequate response or intolerable adverse event to at least one immunosuppressive therapy and intravenous immunoglobulin (IVIG) over the course of at least 12 months
    - Member has a documented clinical reason to avoid therapy with immunosuppressive agents and IVIG
- The requested medication will not be used in combination with another complement inhibitor (e.g., Soliris, Zilbrysq) or neonatal Fc receptor blocker (e.g., Vyvgart, Vyvgart Hytrulo, Rystiggo).

Neuromyelitis Optica Spectrum Disorder (NMOSD)

Authorization of 6 months may be granted for treatment of neuromyelitis optica spectrum disorder (NMOSD) when all of the following criteria are met:

- Anti-aquaporin-4 (AQP4) antibody positive
- Member exhibits one of the following core clinical characteristics of NMOSD:
    - Optic neuritis
    - Acute myelitis
    - Area postrema syndrome (episode of otherwise unexplained hiccups or nausea and vomiting)
    - Acute brainstem syndrome
    - Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
    - Symptomatic cerebral syndrome with NMOSD-typical brain lesions
- The member will not receive the requested medication concomitantly with other biologics for the treatment of NMOSD.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy (e.g., improvement in hemoglobin levels, normalization of lactate dehydrogenase [LDH] levels).
- The requested medication will not be used in combination with another complement inhibitor (e.g., Empaveli, Fabhalta, Piasky, Soliris) for the treatment of PNH (concomitant use with Voydeya is allowed).

Atypical hemolytic uremic syndrome (aHUS)

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy (e.g., normalization of lactate dehydrogenase [LDH] levels, platelet counts).
- The requested medication will not be used in combination with another complement inhibitor (e.g., Soliris) for the treatment of aHUS.

Generalized myasthenia gravis (gMG)

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy (e.g., improvement in MG-ADL score, MG Manual Muscle Test (MMT), MG Composite).
- The requested medication will not be used in combination with another complement inhibitor (e.g., Soliris, Zilbrysq) or neonatal Fc receptor blocker (e.g., Vyvgart, Vyvgart Hytrulo, Rystiggo).

Neuromyelitis optica spectrum disorder (NMOSD)

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy (e.g., reduction in number of relapses as compared to baseline).
- The member will not receive the requested medication concomitantly with other biologics for the treatment of NMOSD.

Dosage and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Ultomiris.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Management of paroxysmal nocturnal hemoglobinuria in the era of complement inhibitory therapy.
- Guidelines for the Diagnosis and Monitoring of Paroxysmal Nocturnal Hemoglobinuria and Related Disorders by Flow Cytometry.
- International consensus guidance for management of myasthenia gravis.
- International consensus diagnostic criteria for neuromyelitis optica spectrum disorders.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Ultomiris are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using percentage of PNH cells or percentage of GPI-AP deficiency poly-morphonuclear cells can be found in the guidelines for diagnosis of PNH (Borowitz et al and Preis et al). Flow cytometry is the gold standard for assessing the percentage of GPI-AP deficient poly-morphonuclear cells. Classic PNH is defined as greater than 50% of GPI-AP deficient PMNs. It is also possible to diagnose PNH by assessing the percentage of PNH cells. Most clinical trials for the complement inhibitors required at least 10% PNH cells, but the trials associated with Ultomiris only required 5% PNH cells. Therefore, the baseline requirement for all complement inhibitor programs will be at least 5%.

Currently there are no treatment guidelines or literature supporting the concomitant use of complement inhibitors (e.g., Empaveli, Fabhalta, Piasky, Soliris) for the treatment of PNH.

Currently there are no treatment guidelines or literature supporting the concomitant use of complement inhibitors (e.g., Soliris) for the treatment of aHUS.

Support for Myasthenia Gravis Activities of Daily Living (MG-ADL) total score of greater than or equal to 5 can be found in the trials associated with Vyvgart and Vyvgart Hytrulo. Most clinical trials of myasthenia gravis agents required a MG-ADL of greater than or equal to 6, however, to align myasthenia gravis programs the baseline requirement will be greater than or equal to 5. MG-ADL is a scale that assesses the impact of myasthenia gravis on daily functions. This scale was used as an assessment tool to evaluate response to myasthenia gravis treatment from baseline in the clinical trials.

Support for the trial of immunosuppressive agents and IVIG before initiating therapy with Ultomiris can be found in the 2020 update to the international consensus guidance for management of myasthenia gravis. The update was completed

prior to the approval of several new myasthenia gravis agents; however, the guidance includes recommendations for initiating treatment with a complement inhibitor (eculizumab [Soliris]). The recommendations indicate that eculizumab should be considered in the treatment of severe, refractory myasthenia gravis (after trials of other immunotherapies have been unsuccessful in meeting treatment goals).

Currently there are no treatment guidelines or literature supporting the concomitant use of complement inhibitors (e.g., Soliris, Ultomiris, Zilbrysq) or neonatal Fc receptor blockers (e.g., Vyvgart, Vyvgart Hytrulo, Rystiggo).

Support for the list of core clinical characteristics of NMOSD can be found in the International Consensus Diagnostic Criteria for Neuromyelitis Optica Spectrum Disorder (Wingerchuk et al). There are six clinical characteristics cited in the diagnostic criteria:

- Optic neuritis
- Acute myelitis
- Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
- Acute brainstem syndrome
- Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical
- diencephalic MRI lesions
- Symptomatic cerebral syndrome with NMOSD-typical brain lesions

Currently there are no treatment guidelines or literature supporting the concomitant use with other biologics for the treatment of NMOSD.

Dosage and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

References

1. Ultomiris [package insert]. Boston, MA: Alexion Pharmaceuticals, Inc.; March 2024.
2. Parker CJ. Management of paroxysmal nocturnal hemoglobinuria in the era of complement inhibitory therapy. Hematology. 2011; 21-29.
3. Lee JW, Sicre de Fontbrune F, Wong LL, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: The 301 study. Blood. 2019;133(6):530-539. doi:10.1182/blood-2018-09-876136.
4. Borowitz MJ, Craig F, DiGiuseppe JA, et al. Guidelines for the Diagnosis and Monitoring of Paroxysmal Nocturnal Hemoglobinuria and Related Disorders by Flow Cytometry. Cytometry B Clin Cytom. 2010: 78: 211-230.
5. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. Hematology Am Soc Hematol Educ Program. 2016;2016(1):208-216.
6. Sanders D, Wolfe G, Benatar M et al. International consensus guidance for management of myasthenia gravis. Neurology. 2021; 96 (3) 114-122.
7. Tuan Vu, Andreas Meisel, Renato Mantegazza, et al. Terminal Complement Inhibitor Ravulizumab in Generalized Myasthenia Gravis. NEJM Evid 2022; 1 (5).

8. Dezern AE, Borowitz MJ. ICCS/ESCCA consensus guidelines to detect GPI-deficient cells in paroxysmal nocturnal hemoglobinuria (PNH) and related disorders part 1 - clinical utility. Cytometry B Clin Cytom. 2018 Jan;94(1):16-22.
9. Clinical Consult: CVS Caremark Clinical Program Review. Focus on Paroxysmal Nocturnal Hemoglobinuria (PNH). July 2023.
10. Barnett C, Herbelin L, Dimachkie MM, Barohn RJ. Measuring Clinical Treatment Response in Myasthenia Gravis. Neurol Clin. 2018 May;36(2):339-353.
11. Clinical Consult: CVS Caremark Clinical Programs Review. Focus on Neurology – Myasthenia Gravis (MG). November 2023.
12. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015; 85:177-189.

Reference number(s)
6765-A

Standard Medicare Part B Management Unloxcyt

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Unloxcyt	cosibelimab-ipdl

Indication

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication

Cutaneous Squamous Cell Carcinoma (CSCC)

Unloxcyt is indicated for the treatment of adults with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or curative radiation.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this document should be accompanied by supporting evidence from Medicare approved compendia.

Exclusions

Coverage will not be provided for members who have experienced disease progression while on programmed death receptor-1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitor therapy.

Reference number(s)
6765-A

Coverage Criteria

Cutaneous Squamous Cell Carcinoma (CSCC)

Authorization of 12 months may be granted for treatment of metastatic or locally advanced CSCC when member is not a candadidate for curative surgery or radiation.

Continuation of Therapy

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat an indication in the coverage criteria section
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen and
    - No evidence of disease progression while on the current regimen

Summary of Evidence

The contents of this document were created after examining the following resources:

- The prescribing information for Unloxcyt.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Squamous cell skin cancer

Explanation of Rationale

Support for FDA-approved indication can be found in the manufacturer’s prescribing information.

References

1. Unloxcyt [package insert]. Waltham, MA: Checkpoint Therapeutics, Inc.; December 2024.

Reference number(s)
4722-A

Standard Medicare Part B Management Uplizna

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Uplizna	inebilizumab-cdon

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Uplizna is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- For initial requests: Immunoassay used to confirm anti-aquaporin-4 (AQP4) antibody is present.
- For continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

Reference number(s)
4722-A

Coverage Criteria

Neuromyelitis optica spectrum disorder (NMOSD)

Authorization of 12 months may be granted for treatment of neuromyelitis optica spectrum disorder (NMOSD) when all of the following criteria are met:

- The member is anti-aquaporin-4 (AQP4) antibody positive.
- The member exhibits one of the following core clinical characteristics of NMOSD:
    - Optic neuritis
    - Acute myelitis
    - Area postrema syndrome (episode of otherwise unexplained hiccups or nausea and vomiting)
    - Acute brainstem syndrome
    - Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic magnetic resonance imaging (MRI) lesions
    - Symptomatic cerebral syndrome with NMOSD-typical brain lesions
- The member will not receive the requested medication concomitantly with other biologics for the treatment of NMOSD.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy (e.g., reduction in number of relapses).
- The member will not receive the requested medication concomitantly with other biologics for the treatment of NMOSD.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Uplizna.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex

  - American Hospital Formulary Service- Drug Information (AHFS-DI)
  - Lexi-Drugs
  - Clinical Pharmacology
- International consensus diagnostic criteria for neuromyelitis optica spectrum disorders.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Uplizna are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the list of core clinical characteristics of NMOSD can be found in the International Consensus Diagnostic Criteria for Neuromyelitis Optica Spectrum Disorder (Wingerchuk et al). There are six clinical characteristics cited in the diagnostic criteria:

- Optic neuritis
- Acute myelitis
- Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
- Acute brainstem syndrome
- Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
- Symptomatic cerebral syndrome with NMOSD-typical brain lesions

Currently there are no treatment guidelines or literature supporting the concomitant use with other biologics for the treatment of NMOSD.

References

1. Uplizna [package insert]. Deerfield, IL: Horizon Therapeutics USA, Inc.; July 2021.
2. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015; 85:177-189.

Reference number(s)
5160-A

Standard Medicare Part B Management Vabysmo

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Vabysmo	faricimab-svoa

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

- Diabetic macular edema
- Neovascular (wet) age-related macular degeneration
- Macular edema following retinal vein occlusion

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Diabetic Macular Edema[1,2]

Authorization of 12 months may be granted for treatment of diabetic macular edema.

Neovascular (Wet) Age-Related Macular Degeneration[1,3]

Authorization of 12 months may be granted for treatment of neovascular (wet) age-related macular degeneration.

Macular Edema Following Retinal Vein Occlusion[1,4]

Authorization of 12 months may be granted for treatment of macular edema following retinal vein occlusion.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication enumerated in Section II.
- The member demonstrated a positive clinical response to therapy (e.g., improvement or maintenance in best corrected visual acuity [BCVA] or vision field, or a reduction in the rate of vision decline or the risk of more severe vision loss).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Vabysmo.
- The available compendium
    - Natio nal Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Diabetic Retinopathy.
- American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Age-Related Macular Degeneration.
- American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Retinal Vein Occlusion.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Vabysmo are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Vabysmo [package insert]. South San Francisco, CA: Genentech, Inc.; October 2023.
2. American Academy of Ophthalmology Retinal/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.
3. American Academy of Ophthalmology Retinal/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.
4. American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Retinal Vein Occlusions. San Francisco, CA: American Academy of Ophthalmology; 2019. Available at: https://www.aao.org/preferred-practice-pattern/retinal-vein-occlusions-ppp.

Reference number(s)
4823-A

Standard Medicare Part B Management Ventavis

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Ventavis	iloprost inhalation solution

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Ventavis is indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (New York Heart Association [NYHA] Class), and lack of deterioration. Studies establishing effectiveness included predominately patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Pulmonary arterial hypertension (PAH)

Authorization of 12 months may be granted for treatment of pulmonary arterial hypertension when ALL of the following criteria are met:

- The pulmonary hypertension is not secondary to pulmonary venous hypertension (e.g., left sided atrial or ventricular disease, left sided valvular heart disease) or disorders of the respiratory system (e.g., chronic obstructive pulmonary disease, interstitial lung disease, obstructive sleep apnea or other sleep disordered breathing, alveolar hypoventilation disorders).
- The member has primary pulmonary hypertension or pulmonary hypertension which is secondary to one of the following conditions: connective tissue disease, human immunodeficiency virus (HIV) infection, cirrhosis, anorexigens, or congenital left to right shunts. If these conditions are present, then all of the following criteria must be met:
    - The pulmonary hypertension has progressed despite maximal medical and/or surgical treatment of the identified condition.
    - The mean pulmonary artery pressure is greater than 25 mmHg at rest or greater than 30 mmHg with exertion.
    - The beneficiary has significant symptoms from the pulmonary hypertension (i.e., severe dyspnea on exertion, and either fatigability, angina, or syncope).
    - Treatment with oral calcium channel blocking agents has been tried and failed or has been considered and ruled out.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy for an indication in the coverage criteria section must be currently receiving therapy with the requested medication through a paid pharmacy or medical benefit and must meet all requirements in the coverage criteria section.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Ventavis.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Nebulizers Local Coverage Determination (L33370)

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Ventavis are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information and Nebulizers Local Coverage Determination (L33370).

References

1. Ventavis [package insert]. Titusville, NJ: Actelion Pharmaceuticals US, Inc.; March 2022.
2. Nebulizers (L33370) Version R12. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed April 14, 2024.
3. Nebulizers - Policy Article (A52466) Version R19. Available at: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx. Accessed April 14, 2024.

Reference number(s)
6135-A

Standard Medicare Part B Management
Veopoz

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Veopoz	pozelimab-bbfg

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Veopoz is indicated for the treatment of adult and pediatric patients 1 year of age and older with CD55-deficient protein-losing enteropathy (PLE), also known as CHAPLE disease.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- For initial requests: chart notes, medical records and genetic test results documenting:
  - Confirmed biallelic CD55 loss-of-function mutation
  - Hypoalbuminemia (serum albumin concentration of ≤3.2 g/dL)
  - Signs and symptoms of CD-55 PLE (e.g., abdominal pain, diarrhea, peripheral edema, or facial edema)
- For continuation requests: Chart notes or medical record documentation supporting positive clinical response.

Reference number(s)
6135-A

Coverage Criteria

CD55-Deficient Protein-Losing Enteropathy (PLE)

Authorization of 6 months may be granted for treatment of CD55-deficient protein-losing enteropathy (PLE) when all of the following criteria are met:

- The member has a confirmed biallelic CD55 loss-of-function mutation detected by genotype analysis
- The member has hypoalbuminemia (serum albumin concentration of $\leq$3.2 g/dL)
- The member has one or more of the following signs and symptoms of CD-55 PLE within the past 6 months:
    - Abdominal pain
    - Diarrhea
    - Peripheral edema
    - Facial edema

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat an indication listed in the coverage criteria section
- The member is receiving benefit from therapy (e.g., normalization of serum albumin, improvement in signs and symptoms of disease, and/or decrease in number of hospitalizations and infections)

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Veopoz.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Veopoz are covered.

Reference number(s)
6135-A

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Veopoz [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; March 2024.

Reference number(s)
4835-A

Standard Medicare Part B Management
Viltepso

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Viltepso	viltolarsen

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Viltepso 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.

This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with Viltepso. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- Initial requests: laboratory confirmation of Duchenne muscular dystrophy (DMD) diagnosis with a DMD gene mutation that is amenable to exon 53 skipping (refer to examples in Appendix).
- Continuation of therapy requests: documentation (e.g., chart notes) of response to therapy.

Reference number(s)
4835-A

Coverage Criteria

Duchenne Muscular Dystrophy

Authorization of 6 months may be granted for treatment of DMD when all of the following criteria are met:

- Genetic testing was conducted to confirm the diagnosis of DMD and to identify the specific type of DMD gene mutation.
- The DMD gene mutation is amenable to exon 53 skipping (refer to examples in Appendix).
- Treatment with Viltepso is initiated before the age of 10.
- Member is able to walk independently without assistive devices.
- Member will not exceed a dose of 80 mg/kg once weekly.
- The requested medication will not be used concomitantly with golodirsen.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Viltepso.
- Viltepso is being used to treat an indication listed in the coverage criteria section.
- The member is receiving benefit from therapy as evidenced by remaining ambulatory (e.g., not wheelchair dependent).
- The member will not exceed a dose of 80 mg/kg once weekly.
- The requested medication will not be used concomitantly with golodirsen.

Appendix

Examples of DMD gene mutations (exon deletions) amenable to exon 53 skipping (not an all-inclusive list):

- Deletion of exon 52
- Deletion of exon 45-52
- Deletion of exon 47-52
- Deletion of exon 48-52
- Deletion of exon 49-52
- Deletion of exon 50-52

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Viltepso.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Viltepso are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Viltepso [package insert]. Paramus, NJ: NS Pharma, Inc.; March 2021.
2. Watanabe N, Nagata T, Satou Y, et al. NS-065/NCNP-01: An Antisense Oligonucleotide for Potential Treatment of Exon 53 Skipping in Duchenne Muscular Dystrophy. *Mol Ther Nucleic Acids*. 2018;13:442–449. doi:10.1016/j.omtn.2018.09.017

Reference number(s)
1984-A

Standard Medicare Part B Management Visudyne

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Visudyne	verteporfin

Indications

FDA-approved Indications[1]

Predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia, or presumed ocular histoplasmosis.

Compendial Uses[2]

Non-melanoma skin cancer

Nationally Covered Indication[3]

CMS covers Visudyne for age-related macular degeneration in specific circumstances. See Section III for more information.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Exclusions

The following exclusion applies to all requests for Visudyne.

- Use of Visudyne is excluded when it is not used in conjunction with ocular photodynamic therapy or not administered intravenously.

The following exclusions apply to requests for Visudyne for age-related macular degeneration (AMD).

- Treatment of juxtafoveal or extrafoveal CNV lesions (lesions outside the fovea).
- Inability to obtain a fluorescein angiogram.
- Atrophic or "dry" AMD.

Coverage Criteria

Neovascular (wet) age-related macular degeneration[1,3]

Authorization of 12 months may be granted for treatment of neovascular age-related macular degeneration when any of the following criteria are/is met:

- The member has predominately classic subfoveal choroidal neovascularization (CNV) lesions, where the area of classic CNV occupies at least 50% of the area of the entire lesion, at the initial visit as determined by a fluorescein angiogram.
- The member has subfoveal occult with no classic CNV associated with AMD and meets both criteria below:
    - The lesions are small (4 disk areas or less in size) at the time of initial treatment or within the 3 months prior to initial treatment.
    - The lesions have shown evidence of progression within the 3 months prior to initial treatment. Evidence of progression must be documented by deterioration of visual acuity (at least 5 letters on a standard eye examination chart), lesion growth (an increase in at least 1 disk area), or the appearance of blood associated with the lesion.
- The member has subfoveal minimally classic CNV, where the area occupies less than 50% of the area of the entire lesion, associated with AMD and meets both criteria below:
    - The lesions are small (4 disk areas or less in size) at the time of initial treatment or within the 3 months prior to initial treatment.
    - The lesions have shown evidence of progression within the 3 months prior to initial treatment. Evidence of progression must be documented by deterioration of visual acuity (at least 5 letters on a standard eye examination chart), lesion growth (an increase in at least 1 disk area), or the appearance of blood associated with the lesion.

Pathologic myopia associated with classic subfoveal choroidal neovascularization[1]

Authorization of 12 months may be granted for treatment of pathologic myopia associated with classic subfoveal choroidal neovascularization.

Presumed ocular histoplasmosis associated with classic subfoveal choroidal neovascularization[1]

Authorization of 12 months may be granted for the treatment of presumed ocular histoplasmosis associated with classic subfoveal choroidal neovascularization.

Non-melanoma skin cancer[2]

Authorization of 12 months may be granted for the treatment of non-melanoma skin cancer.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with requested medication.
- None of the exclusions delineated in section II are met.
- The requested medication is being used to treat an indication listed in the coverage criteria.
- The medication has been effective for treating the diagnosis or condition.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Visudyne.
- The available compendium.
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- American Academy of Ophthalmology Retinal/Vitreous Panel. Preferred Practice Pattern® Guidelines. Age-Related Macular Degeneration.
- National Coverage Determination: Verteporfin

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Visudyne are covered in addition to non-melanoma skin cancer.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Visudyne to treat non-melanoma skin cancer can be found in the Micromedex DrugDex database. Use of information in the DrugDex database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration is covered according to the conditions outlined in National Coverage Determination Manual section 80.3.1 (Verteporfin).

References

1. Visudyne [package insert]. Charleston, SC: Alcami Carolinas Corporation; February 2023.
2. Micromedex Solutions [database online]. Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com/. Accessed February 14, 2023.
3. National Coverage Determination (NCD) for Verteporfin (80.3.1). Version 2. https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=350&ncdver=2&DocID=80.3.1&SearchType=Advanced&bc=EAAAAAgAAAAA& Accessed December 11, 2023.
4. American Academy of Ophthalmology Retinal/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.

Reference number(s)
4868-A

Standard Medicare Part B Management Vonvendi

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Vonvendi	von Willebrand factor [recombinant]

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

Vonvendi is indicated for use in adults (age 18 and older) diagnosed with von Willebrand disease (VWD) for:

- 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.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Von Willebrand Disease[1-3]

Authorization of 12 months may be granted for members with VWD when any of the following criteria is met:

- Member has type 1, 2A, 2M, or 2N VWD and has had an insufficient response to desmopressin or a documented clinical reason for not using desmopressin (see Appendix).
- Member has type 2B or type 3 VWD.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication listed in the coverage criteria section.
- The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

Appendix

Clinical Reasons for Not Utilizing Desmopressin in Patients with Type 1, 2A, 2M and 2N VWD[2-7]

- Age < 2 years
- Pregnancy
- Fluid/electrolyte imbalance
- High risk for cardiovascular or cerebrovascular disease (especially the elderly)
- Predisposition to thrombus formation
- Trauma requiring surgery
- Life-threatening bleed
- Contraindication or intolerance to desmopressin
- Severe type 1 von Willebrand disease
- Stimate Nasal Spray is unavailable due to backorder/shortage issues (where applicable)

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Vonvendi.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service-Drug Information (AHFS-DI)

    - Lexi-Drugs
    - Clinical Pharmacology
- The diagnosis, evaluation, and management of von Willebrand disease.
- MASAC recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Vonvendi are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Vonvendi to treat von Willebrand disease can be found in the National Institutes of Health publication called the "Diagnosis, Evaluation, and Management of von Willebrand Disease". Type 2B and type 3 VWD do not respond consistently to DDAVP therapy and therefore DDAVP is not considered clinically useful in these patients.

The guideline from the National Bleeding Disorders Foundation (previously the National Hemophilia Foundation) also recommends using Vonvendi in VWD. Vonvendi is used 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 under 2 years of age regardless of VWD type. Vonvendi is approved for use as routine prophylaxis only in individuals with severe type 3 VWD who were previously treated with VWF (recombinant or plasma-derived) on-demand.

References

1. Vonvendi [package insert]. Lexington, MA: Baxalta US Inc.; March 2023.
2. National Hemophilia Foundation. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised April 2024. MASAC Document #284. https://www.bleeding.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed October 16, 2024.
3. National Hemophilia Foundation. MASAC recommendations regarding the treatment of von Willebrand disease. Revised February 2021. MASAC Document #266. https://www.hemophilia.org/sites/default/files/document/files/266.pdf. Accessed October 16, 2024.
4. National Institutes of Health. The diagnosis, evaluation, and management of von Willebrand disease. Bethesda, MD: US Dept of Health and Human Services, National Institutes of Health; 2007. NIH publication No. 08-5832.
5. Stimate [package insert]. King of Prussia, PA: CSL Behring LLC; June 2021.
6. Leissinger C, Carcao M, Gill JC, et al. Desmopressin (DDAVP) in the management of patients with congenital bleeding disorders. Haemophilia. 2014;20:158-167.
7. Clinical Consult. CVS Caremark Clinical Programs Review: Focus on Bleeding Disorders Programs. December 27, 2021.

Reference number(s)
4388-A

Standard Medicare Part B Management Vyepti

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Vyepti	eptinezumab-jjmr

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Vyepti is indicated for the preventive treatment of migraine in adults.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Preventive Treatment of Migraines

Authorization of 6 months may be granted for preventive treatment of migraines for members 18 years of age or older when either of the following criteria are met:

- Member has chronic migraine headache defined as 15 to 26 headache days per month, of which at least 8 are migraine days
- Member has episodic migraine headaches defined as 4 to 14 headache days per month, of which at least 4 are migraine days

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Vyepti
- Vyepti is being used to treat an indication listed in the coverage criteria section
- The member is receiving benefit from therapy. Benefit is defined as a reduction in migraine days per month from baseline

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Vyepti.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- The American Headache Society Consensus Statement: Update on Integrating New Migraine Treatments into Clinical Practice

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Vyepti are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information. The number of headache days and migraine days are supported by the inclusion criteria of the clinical studies listed in the prescribing information.

References

1. Vyepti [package insert]. Bothell, WA: Lundbeck Seattle BioPharmaceuticals, Inc.; October 2022.
2. Ailani J., Burch RC, Robbins MS. The American Headache Society Consensus Statement: Update on Integrating New Migraine Treatments into Clinical Practice. Headache. 2021 Jul;61(7):1021-1039

Reference number(s)
6704-A

Standard Medicare Part B Management
Vyloy

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Vyloy	zolbetuximab-clzb

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Vyloy is indicated in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adults with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors are claudin (CLDN) 18.2 positive as determined by an FDA-approved test.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions: CLDN18.2 and HER2 status.

Reference number(s)
6704-A

Coverage Criteria

Gastric and Gastroesophageal Junction Adenocarcinoma[1]

Authorization of 12 months may be granted for CLDN18.2-positive, HER2-negative locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma as first-line treatment, in combination with fluoropyrimidine- and platinum-containing chemotherapy.

Continuation of Therapy

Authorization of 12 months may be granted for all members (including new members) who are continuing with the requested medication when all of the following criteria are met:

- The member is currently receiving treatment with the requested medication.
- The requested medication is being used to treat a diagnosis or condition listed in the coverage criteria section.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Vyloy.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Vyloy are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Vyloy [package insert]. Northbrook, IL: Astellas Pharma US, Inc.; October 2024.

Reference number(s)
4818-A

Standard Medicare Part B Management
Vyondys 53

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Vyondys 53	golodirsen

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Vyondys 53 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.

This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with Vyondys 53. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- Initial requests: laboratory confirmation of Duchenne muscular dystrophy (DMD) diagnosis with a DMD gene mutation that is amenable to exon 53 skipping (refer to examples in Appendix).
- Continuation of therapy requests: documentation (e.g., chart notes) of response to therapy.

Coverage Criteria

Duchenne Muscular Dystrophy

Authorization of 6 months may be granted for treatment of DMD when all of the following criteria are met:

- Genetic testing was conducted to confirm the diagnosis of DMD and to identify the specific type of DMD gene mutation.
- The DMD gene mutation is amenable to exon 53 skipping (refer to examples in Appendix).
- Treatment with Vyondys 53 is initiated before the age of 16.
- Member is able to achieve an average distance of at least 250 meters while walking independently over 6 minutes.
- Member will not exceed a dose of 30 mg/kg once weekly.
- The requested medication will not be used concomitantly with viltolarsen.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with Vyondys 53.
- Vyondys 53 is being used to treat an indication listed in the coverage criteria section.
- The member is receiving benefit from therapy as evidenced by remaining ambulatory (e.g., able to walk with or without assistance, not wheelchair dependent).
- The member will not exceed a dose of 30 mg/kg once weekly.
- Vyondys 53 will not be used concomitantly with viltolarsen.

Appendix

Examples of DMD gene mutations (exon deletions) amenable to exon 53 skipping (not an all-inclusive list):

- Deletion of exon 52
- Deletion of exon 45-52
- Deletion of exon 47-52
- Deletion of exon 48-52
- Deletion of exon 49-52
- Deletion of exon 50-52

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Vyondys 53.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Vyondys 53 are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Vyondys 53 [package insert]. Cambridge, MA: Sarepta Therapeutics; February 2021.
2. Watanabe N, Nagata T, Satou Y, et al. NS-065/NCNP-01: An Antisense Oligonucleotide for Potential Treatment of Exon 53 Skipping in Duchenne Muscular Dystrophy. *Mol Ther Nucleic Acids*. 2018;13:442–449. doi:10.1016/j.omtn.2018.09.017
3. Vyondys 53™ (golodirsen) eDossier. AMCP Formulary Decisions. AmerisourceBergen Corporation. Conshohocken, PA. Available at: www.formularydecisions.com. Accessed April 15, 2020.

Reference number(s)
5108-A

Standard Medicare Part B Management Vyvgart-Vyvgart Hytrulo

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Vyvgart	efgartigimod alfa-fcab
Vyvgart Hytrulo	efgartigimod alfa and hyaluronidase-qvfc

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Vyvgart

Vyvgart is indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.

Vyvgart Hytrulo

Vyvgart Hytrulo is indicated for the treatment of:

- Generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.
- Adult patients with chronic inflammatory demyelinating polyneuropathy (CIDP).

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- For initial requests: chart notes, medical records, or claims history documenting:
    - Generalized myasthenia gravis:
        - Positive anti-acetylcholine receptor (AChR) antibody test
        - Myasthenia Gravis Foundation of America (MGFA) clinical classification
        - MG activities of daily living score
        - Previous medications tried, including response to therapy. If therapy is not advisable, documentation of clinical reasons to avoid therapy.
    - Chronic inflammatory demyelinating polyneuropathy:
        - Electrodiagnostic testing (e.g., electromyography (EMG), nerve conduction studies (NCS))
        - Previous therapies tried (e.g., immunoglobulins, corticosteroids, or plasma exchange), including response to therapy. If therapy is not advisable, documentation of clinical reasons to avoid therapy.
- For continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

Coverage Criteria

Generalized Myasthenia Gravis (gMG)

Authorization of 6 months may be granted for treatment of generalized myasthenia gravis (gMG) when all of the following criteria are met:

- Anti-acetylcholine receptor (AChR) antibody positive
- Myasthenia Gravis Foundation of America (MGFA) clinical classification II to IV
- MG activities of daily living (MG-ADL) total score of greater than or equal to 5
- Meets one of the following:
    - Member has had an inadequate response or intolerable adverse event to at least two immunosuppressive therapies over the course of at least 12 months (e.g., azathioprine, corticosteroids, cyclosporine, methotrexate, mycophenolate, tacrolimus)
    - Member has had an inadequate response or intolerable adverse event to at least one immunosuppressive therapy and intravenous immunoglobulin (IVIG) over the course of at least 12 months
    - Member has a documented clinical reason to avoid therapy with immunosuppressive agents and IVIG
- The requested medication will not be used in combination with another neonatal Fc receptor blocker (e.g., Rystiggo) or complement inhibitor (e.g., Soliris, Ultomiris, Zilbrysq)

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) (Vyvgart Hytrulo Only)

Authorization of 6 months may be granted for treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) when all of the following criteria are met:

- Disease course is progressive or relapsing/remitting for 2 months or longer
- Diagnosis was confirmed by electrodiagnostic testing (consistent with EFNS/PNS guidelines)
- Meets one of the following:
    - Member has had an inadequate response or intolerable adverse event to immunoglobulins, corticosteroids, or plasma exchange

- Member has a documented clinical reason to avoid therapy with immunoglobulins, corticosteroids, or plasma exchange

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Generalized Myasthenia Gravis (gMG)

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The member is receiving benefit from therapy (e.g., improvement in MG-ADL score, MG Manual Muscle Test (MMT), MG Composite)
- The requested medication will not be used in combination with another neonatal Fc receptor blocker (e.g., Rystiggo) or complement inhibitor (e.g., Soliris, Ultomiris, Zilbrysq)

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) (Vyvgart Hytrulo Only)

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The member is receiving benefit from therapy (e.g., improvement in Inflammatory Rasch-built Overall Disability Scale (I-RODS), Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale, Medical Research Council (MRC) Sum score, grip strength)

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Vyvgart and Vyvgart Hytrulo.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- International consensus guidance for management of myasthenia gravis.
- European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society - second revision.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Vyvgart and Vyvgart Hytrulo are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the trial of immunosuppressive agents and IVIG before initiating therapy with Vyvgart and Vyvgart Hytrulo can be found in the 2020 update to the international consensus guidance for management of myasthenia gravis. The update was completed prior to the approval of several new myasthenia gravis agents; however, the guidance includes recommendations for initiating treatment with a complement inhibitor (eculizumab [Soliris]). The recommendations indicate that eculizumab should be considered in the treatment of severe, refractory myasthenia gravis (after trials of other immunotherapies have been unsuccessful in meeting treatment goals).

Currently there are no treatment guidelines or literature supporting the concomitant use of complement inhibitors (e.g., Soliris, Ultomiris, Zilbrysq) or neonatal Fc receptor blockers (e.g., Vyvgart, Vyvgart Hytrulo, Rystiggo) for the treatment of generalized myasthenia gravis.

Support for the requirement that CIDP disease course be progressive or relapsing/remitting for 2 months or longer can be found in the European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy.

Support for a trial of immunoglobulins, corticosteroids, or plasma exchange can be found in the European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy. The guidelines strongly recommend the use of immunoglobulins, corticosteroids, or plasma exchange as first line treatments for CIDP.

References

1. Vyvgart [package insert]. Boston, MA: Argenx US, Inc.; January 2024.
2. Vyvgart Hytrulo [package insert]. Boston, MA: Argenx US, Inc.: January 2024.
3. Sanders D, Wolfe G, Benatar M et al. International consensus guidance for management of myasthenia gravis. Neurology. 2021; 96 (3) 114-122.
4. Howard JF, Bril V, Vu T, et al. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2021. 20:526-536.
5. Barnett C, Herbelin L, Dimachkie MM, Barohn RJ. Measuring Clinical Treatment Response in Myasthenia Gravis. Neurol Clin. 2018 May;36(2):339-353.
6. Van den Bergh PY, Hadden RD, van Doorn PA, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society - second revision. Eur J Neurol. 2021;28(11):3556-3583.

Reference number(s)
4870-A

Standard Medicare Part B Management Wilate

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Wilate	von Willebrand factor/coagulation factor VIII complex [human]

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]

- Wilate is indicated in children and adults with von Willebrand Disease (VWD) for:
  - On-demand treatment and control of bleeding episodes
  - Perioperative management of bleeding
  - Routine prophylaxis to reduce the frequency of bleeding episodes
- Wilate is indicated in adolescents and adults with hemophilia A for:
  - Routine prophylaxis to reduce the frequency of bleeding episodes
  - On-demand treatment and control of bleeding episodes

Compendial Uses[2,3,5]

Acquired von Willebrand Syndrome

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Von Willebrand Disease[1,2,6]

Authorization of 12 months may be granted for members with VWD when either of the following criteria is met:

- Member has type 1, 2A, 2M, or 2N VWD and has had an insufficient response to desmopressin or a documented clinical reason for not using desmopressin (see Appendix B).
- Member has type 2B or type 3 VWD.

Acquired von Willebrand Syndrome[2,3,5]

Authorization of 12 months may be granted for treatment of acquired von Willebrand syndrome.

Hemophilia A[1]

Authorization of 12 months may be granted for hemophilia A when the requested medication will be used for either of the following:

- Member has mild disease (see Appendix A) and has had an insufficient response to desmopressin or a documented clinical reason for not using desmopressin (see Appendix B).
- Member has moderate or severe disease (see Appendix A).

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

Appendix

Appendix A: Classification of Hemophilia by Clotting Factor Level (% Activity) and Bleeding Episodes[4]

Factor assay levels are required to determine the diagnosis and are of value in monitoring treatment response.

Severity	Clotting Factor Level % activity	Bleeding Episodes
Severe	<1%	Spontaneous bleeding episodes, predominantly into joints and muscles Severe bleeding with trauma, injury or surgery
Moderate	1% to 5%	Occasional spontaneous bleeding episodes Severe bleeding with trauma, injury or surgery
Mild	6% to 40%	Severe bleeding with serious injury, trauma or surgery

Appendix B: Clinical Reasons For Not Utilizing Desmopressin in Patients with Hemophilia A and Type 1, 2A, 2M and 2N VWD[6-9]

- Age < 2 years
- Pregnancy
- Fluid/electrolyte imbalance
- High risk for cardiovascular or cerebrovascular disease (especially the elderly)
- Predisposition to thrombus formation
- Trauma requiring surgery
- Life-threatening bleed
- Contraindication or intolerance to desmopressin
- Severe type 1 von Willebrand disease
- Stimate Nasal Spray is unavailable due to backorder/shortage issues (where applicable)

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Wilate.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service-Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- The diagnosis, evaluation, and management of von Willebrand disease.
- World Federation of Hemophilia (WFH) Guidelines for the Management of Hemophilia, 3rd edition.
- MASAC recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Wilate are covered in addition to acquired von Willebrand syndrome.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Wilate to treat von Willebrand disease can be found in the National Institutes of Health publication called the "Diagnosis, Evaluation, and Management of von Willebrand Disease". Type 2B and type 3 VWD do not respond consistently to DDAVP therapy and therefore DDAVP is not considered clinically useful in these patients. The guideline from the National Bleeding Disorders Foundation (previously the National Hemophilia Foundation) also recommends using Wilate in VWD. Persons with type 2B and type 3 VWD, and those with type 1, 2A, 2M, and 2N who have been shown to be nonresponsive to DDAVP, should be treated with a factor VIII/VWF concentrate (such as Wilate) that is known to contain the higher molecular weight multimers of von Willebrand factor and that has been virally attenuated to eliminate transmission of HIV and hepatitis A, B, and C.

Support for using Wilate to treat acquired von Willebrand syndrome can be found in the National Institutes of Health publication called the "Diagnosis, Evaluation, and Management of von Willebrand Disease". The guideline indicates DDAVP and Wilate (VWF/FVIII) are first line therapy. If a patient had an inadequate response to DDAVP and VWF/FVIII concentrates, intravenous immunoglobulin given alone was effective in controlling bleeding and raising VWF:RCo activity.

Support for using Wilate to treat hemophilia A can be found in the National Bleeding Disorders Foundation (formerly the National Hemophilia Foundation) MASAC recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system. Recombinant factor VIII products are the recommended treatment of choice for patients with hemophilia A. A possible exception to this recommendation is a newly diagnosed individual, who should also consider with their healthcare providers initiating treatment with a plasma-derived FVIII / von Willebrand Factor (VWF) product.

References

1. Wilate [package insert]. Hoboken, NJ: Octapharma USA Inc.; December 2023.
2. National Institutes of Health. The diagnosis, evaluation, and management of von Willebrand disease. Bethesda, MD: US Dept of Health and Human Services, National Institutes of Health; 2007. NIH publication No. 08-5832.
3. Tiede A, Rand J, Budde U, et al. How I treat the acquired von Willebrand syndrome. Blood. 2011;117(25):6777-85.
4. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020 Aug;26 Suppl 6:1-158.
5. Federici A, Budde U, Castaman G, Rand J, Tiede A. Current diagnostic and therapeutic approaches to patients with acquired von Willebrand syndrome: a 2013 update. Semin Thromb Hemost. 2013;39(2):191-201.
6. National Hemophilia Foundation. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised April 2024. MASAC Document #284. https://www.bleeding.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed October 16, 2024.
7. National Hemophilia Foundation. MASAC recommendations regarding the treatment of von Willebrand disease. Revised February 2021. MASAC Document #266. https://www.hemophilia.org/sites/default/files/document/files/66.pdf. Accessed October 16, 2024.
8. Stimate [package insert]. King of Prussia, PA: CSL Behring LLC; June 2021.

9. Leissinger C, Carcao M, Gill JC, et al. Desmopressin (DDAVP) in the management of patients with congenital bleeding disorders. Haemophilia. 2014;20:158-167.

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Reference number(s)
5561-A

Standard Medicare Part B Management Xenpozyme

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Xenpozyme	olipudase alfa-rpcp

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Xenpozyme is indicated for treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in adult and pediatric patients.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- Initial requests: acid sphingomyelinase enzyme assay supporting the diagnosis.
- Continuation of therapy requests: documentation (e.g., chart notes, lab results) of a response to therapy (e.g., improvement in lung function, reduction in spleen volume, reduction in liver volume, improvement in platelet count, improvement in linear growth progression).

Reference number(s)
5561-A

Prescriber Specialties

This medication must be prescribed by or in consultation with a physician knowledgeable in the management of acid sphingomyelinase deficiency (ASMD).

Coverage Criteria

Acid Sphingomyelinase Deficiency (ASMD)[1]

Authorization of 12 months may be granted for treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) when the diagnosis is confirmed by a documented deficiency of acid sphingomyelinase as measured in peripheral leukocytes, cultured fibroblasts, or lymphocytes.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication in the coverage criteria section.
- The member is receiving benefit from therapy (e.g., improvement in lung function, reduction in spleen volume, reduction in liver volume, improvement in platelet count, improvement in linear growth progression).

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Xenpozyme.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Xenpozyme are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using an enzyme assay to confirm the diagnosis of ASMD prior to initiating treatment with Xenpozyme can be found in the clinical trials cited in the prescribing information. To be included in the trial, the patient must have had a documented deficiency of acid sphingomyelinase as measured in peripheral leukocytes, cultured fibroblasts, or lymphocytes.

References

1. Xenpozyme [package insert]. Cambridge, MA: Genzyme Corporation; December 2023.

Reference number(s)
2392-A

Standard Medicare Part B Management Xgeva and Biosimilars

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Xgeva	denosumab
Bomyntra	denosumab-bnht
Osenvelt	denosumab-bmwo
Wyost	denosumab-bbdz
Xybryk	denosumab-dssb

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1-5]

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors
- 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
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy

Compendial Uses[6]

- Treatment for osteopenia/osteoporosis in patients with systemic mastocytosis
- Thyroid cancer as palliative care for bone metastases

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Multiple Myeloma[1-6]

Authorization of 12 months may be granted for prevention of skeletal-related events in members with multiple myeloma.

Bone Metastases From a Solid Tumor[1-6]

Authorization of 12 months may be granted for either of the following:

- For prevention of skeletal-related events in members with bone metastases from a solid tumor (e.g., breast cancer, non-small cell lung cancer, thyroid carcinoma, kidney cancer, prostate cancer)
- As palliative care for bone metastases from thyroid carcinoma

Giant Cell Tumor of Bone[1-6]

Authorization of 12 months may be granted for treatment of giant cell tumor of bone.

Hypercalcemia of Malignancy[1-5]

Authorization of 2 months may be granted for treatment of hypercalcemia of malignancy.

Systemic Mastocytosis[6]

Authorization of 12 months may be granted for treatment of osteopenia or osteoporosis in members with systemic mastocytosis.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Hypercalcemia of Malignancy

Authorization for 2 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with a denosumab product.
- The requested drug is being used to treat hypercalcemia of malignancy.
- The member is receiving benefit from therapy. Benefit is defined as:
    - Disease stability, or
    - Disease improvement

All Other Indications

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with a denosumab product.
- The requested drug is being used to treat an indication in the coverage criteria other than hypercalcemia of malignancy.
- The member is receiving benefit from therapy. Benefit is defined as:
    - Disease stability, or
    - Disease improvement

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for the requested drug.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Prostate cancer
- NCCN Guideline: Multiple myeloma
- NCCN Guideline: Bone cancer
- NCCN Guideline: Non-small cell lung cancer
- NCCN Guideline: Breast cancer
- NCCN Guideline: Thyroid carcinoma
- NCCN Guideline: Kidney cancer
- NCCN Guideline: Systemic mastocytosis

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for the requested drug are covered in addition to the following:

- Treatment of osteopenia/osteoporosis in patients with systemic mastocytosis
- Palliative care for bone metastases in thyroid cancer

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using denosumab as treatment for osteopenia or osteoporosis in patients with systemic mastocytosis can be found in the National Comprehensive Cancer Network's guideline for systemic mastocytosis. The NCCN Guideline for systemic mastocytosis supports the use of denosumab as second-line therapy for osteopenia/osteoporosis in patients

with bone pain not responding to bisphosphonates or for patients who are not candidates for bisphosphonates because of renal insufficiency.

Support for using denosumab as palliative care for bone metastases in patients with thyroid cancer can be found in the National Comprehensive Cancer Network's guideline for thyroid carcinoma. The NCCN Guideline for thyroid carcinoma supports the use of denosumab as care for bone metastases for the following cancer types: papillary carcinoma, follicular carcinoma, oncocytic carcinoma, medullary carcinoma, and anaplastic carcinoma.

References

1. Xgeva [package insert]. Thousand Oaks, CA: Amgen Inc.; June 2020.
2. Bomyntra [package insert]. Lake Zurich, IL: Fresenius Kabi USA, LLC; March 2025.
3. Osenvelt [package insert]. Incheon, South Korea: Celltrion Inc.; February 2025.
4. Wyost [package insert]. Princeton, NJ: Sandoz, Inc.; March 2024.
5. Xybryk [package insert]. Incheon, South Korea: Samsung Bioepis; February 2025.
6. The NCCN Drugs & Biologics Compendium™ © 2025 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed April 8, 2025.

Reference number(s)
5047-A

Standard Medicar Part B Management
Xipere

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Xipere	triamcinolone acetonide injectable suspension

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Xipere is indicated for the treatment of macular edema associated with uveitis.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Macular edema associated with uveitis[1,2]

Authorization of 12 months may be granted for treatment of macular edema associated with uveitis when all the following criteria are met:

- The member has a diagnosis of macular edema associated with uveitis.
- The member does not have infectious uveitis.
- The member will not exceed a dose of 4 mg (0.1 mL) administered as a suprachoroidal injection per eye into the affected eye(s).

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication listed in the coverage criteria.
- The medication has been effective for treating the diagnosis or condition.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Xipere.
- The available compendium.
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Xipere are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Xipere to treat noninfectious uveitis can be found in a study by Yeh et al. The study enrolled 160 patients with ME secondary to noninfectious uveitis. Patients were required to have a best-corrected visual acuity (BCVA) of 5 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Snellen equivalent, 20/800) and 70 or fewer ETDRS letters read (Snellen equivalent, 20/40) in the study eye. Patients were randomized 3:2 to suprachoroidally injected CLS-TA or sham treatment, with administrations at day 0 and week 12. The primary end point was improvement from baseline of 15 or more ETDRS letters in BCVA at week 24. The secondary end point was reduction from baseline in central subfield thickness (CST) at week 24. In the CLS-TA arm, 47% of patients gained 15 or more ETDRS letters in BCVA versus 16% in the control arm ($P < 0.001$), meeting the primary end point. Mean reductions in CST from baseline were 153 µm versus 18 µm ($P < 0.001$). No serious adverse events (AEs) related to treatment were reported. Corticosteroid-associated AEs of elevated intraocular pressure occurred in 11.5% and 15.6% of the CLS-TA and control groups, respectively. Cataract AE rates were comparable (7.3% and 6.3%, respectively).

References

1. Xipere [package insert]. Bridgewater, NJ: Bausch & Lomb Americas, Inc.; February 2022.
2. Yeh S, Khurana RN, Shah M, et al. Efficacy and Safety of Suprachoroidal CLS-TA for Macular Edema Secondary to Noninfectious Uveitis: Phase 3 Randomized Trial. Ophthalmology. 2020;127(7):948-955.

Reference number(s)
2546-A

Standard Medicare Part B Management
Xolair

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Xolair	omalizumab

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Allergic Asthma

Treatment of moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids.

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Xolair is indicated for add-on maintenance treatment of nasal polyps in adult patients 18 years of age and older with inadequate response to nasal corticosteroids.

IgE-mediated Food Allergy

Xolair is indicated for the reduction of allergic reactions (Type 1), including anaphylaxis, that may occur with accidental exposure to one or more foods in adult and pediatric patients aged 1 year and older with IgE-mediated food allergy.

Xolair is to be used in conjunction with food-allergen avoidance.

Chronic Spontaneous Urticaria (CSU)

Treatment of chronic spontaneous urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment.

Limitations of use

- Not indicated for relief of acute bronchospasm or status asthmaticus
- Not indicated for the emergency treatment of allergic reactions, including anaphylaxis
- Not indicated for other forms of urticaria

Compendial Uses[2,7]

- Prophylaxis of seasonal or perennial allergic rhinitis
- Latex allergy prophylaxis for patients unable to avoid latex
- Adjunct to immunotherapy for seasonal allergic rhinitis
- Immune checkpoint inhibitor-related toxicities
- Systemic mastocytosis

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

Asthma

Initial Requests

- Chart notes or medical record documentation showing pre-treatment IgE level.
- Chart notes, medical record documentation, or claims history supporting previous medications tried including drug, dose, frequency, and duration. If therapy is not advisable, documentation of clinical reason to avoid therapy.

Continuation requests

Chart notes or medical record documentation supporting benefit from therapy.

CRSwNP

Initial Requests

- Chart notes or medical record documentation showing nasal endoscopy, anterior rhinoscopy, or computed tomography (CT) details (e.g., polyps location, size), or Meltzer Clinical Score or endoscopic nasal polyp score (NPS) (where applicable).
- Chart notes, medical record documentation, or claims history supporting previous medications tried (if applicable), including response to therapy. If therapy is not advisable, documentation of clinical reason to avoid therapy.

Continuation Requests

Chart notes or medical record documentation supporting benefit from therapy.

Reference number(s)
2546-A

IgE-Mediated Food Allergy

Initial Requests

Chart notes, medical record documentation, or laboratory tests showing the following (if applicable):

- Pre-treatment allergen-specific serum IgE level
- Skin-prick test wheal diameter
- Pre-treatment serum IgE level
- Positive result of a physician controlled oral food challenge
- History of a systemic reaction to a specific food

Continuation Requests

Chart notes or medical record documentation supporting benefit from therapy.

CSU

Initial Requests

Chart notes, medical record documentation, or claims history supporting previous mediations tried showing an inadequate treatment response to a second-generation H1 antihistamine.

Continuation Requests

Chart notes or medical record documentation supporting benefit from therapy.

Immune Checkpoint Inhibiter-Related Toxicity

Initial Requests

Chart notes or medical record documentation showing pre-treatment IgE level.

Continuation Requests

Chart notes or medical record documentation supporting benefit from therapy.

Systemic Mastocytosis

Initial Requests

- Chart notes or medical record documentation supporting diagnosis of systemic mastocytosis.
- Chart notes, medical record documentation, or claims history of prerequisite therapies (if applicable).

Continuation Requests

Chart notes or medical record documentation supporting benefit from therapy.

Prophylaxis of Seasonal or Perennial Allergic Rhinitis

Initial Requests

Chart notes, medical record documentation, or claims history supporting previous medications tried, including response to therapy.

Continuation Requests

Chart notes or medical record documentation supporting benefit from therapy.

Latex Allergy Prophylaxis

Initial Requests

Chart notes or medical record documentation of allergy.

Continuation Requests

Chart notes or medical record documentation supporting benefit from therapy.

Adjunct to Immunotherapy

Initial Requests

Chart notes or medical record documentation of immunotherapy use.

Continuation Requests

Chart notes or medical record documentation supporting benefit from therapy.

Coverage Criteria

Allergic Asthma[1,3-4]

Authorization of 12 months may be granted for treatment of allergic asthma when all of the following criteria are met:

- Member is 6 years of age or older.
- Member has a history of moderate to severe asthma despite current treatment with both of the following medications at optimized doses, unless the member has a clinical reason to avoid these therapies:
    - Inhaled corticosteroid
    - Additional controller (i.e., long-acting beta2-agonist, long-acting muscarinic antagonist, leukotriene modifier, or sustained-release theophylline)
- Member has a positive skin test or in vitro reactivity to at least one perennial aeroallergen.
- Member has a pre-treatment IgE level greater than or equal to 30 IU/mL.
- Member will not use the requested medication concomitantly with other biologics indicated for asthma (e.g., Cinqair, Dupixent, Fasenra, Nucala, Tezspire).

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)[1,11-13]

Authorization of 12 months may be granted for treatment of CRSwNP when all of the following criteria are met:

- Member is 18 years of age or older.
- Member has bilateral nasal polyposis and chronic symptoms of sinusitis despite intranasal corticosteroid treatment for at least 2 months unless contraindicated or not tolerated.
- Member has one of the following:
  - A bilateral nasal endoscopy, anterior rhinoscopy, or computed tomography (CT) showing polyps reaching below the lower border of the middle turbinate or beyond in each nostril.
  - Meltzer Clinical Score of 2 or higher in both nostrils.
  - A total endoscopic nasal polyp score (NPS) of at least 5 with a minimum score of 2 for each nostril.
- Member has symptoms of nasal blockage, congestion or obstruction plus one of the following additional symptoms:
  - Rhinorrhea (anterior/posterior)
  - Reduction or loss of smell
  - Facial pain or pressure
- Member will continue to use a daily intranasal corticosteroid while being treated with the requested medication, unless contraindicated or not tolerated.
- Member will not use the requested medication concomitantly with other biologics indicated for nasal polyps (e.g., Dupixent, Nucala).

IgE-Mediated Food Allergy[1,18-19,21]

Authorization of 12 months may be granted for the reduction of IgE-mediated food allergy reactions when all of the following criteria are met:

- Member is 1 year of age or older.
- The diagnosis of IgE-mediated food allergy has been confirmed by either of the following:
  - Pre-treatment allergen-specific serum IgE level greater than or equal to 6 IU/mL.
  - Skin-prick test (SPC) with wheal diameter greater than or equal to 4 mm.
- Member has either of the following:
  - A positive physician controlled oral food challenge (e.g., moderate to severe skin, respiratory, or gastrointestional [GI] symptoms)
  - History of a systemic reaction to a specific food
- Member has a pre-treatment serum IgE level greater than or equal to 30 IU/mL.
- Member will continue to follow a food-allergen avoidance diet.

Chronic Spontaneous Urticaria (CSU)[1,5,8-9]

Authorization of 12 months may be granted for treatment of CSU when all of the following criteria are met:

- Member is 12 years of age or older.
- Member has experienced a spontaneous onset of wheals (hives), angioedema, or both, for at least 6 weeks.
- Member remains symptomatic despite treatment with a second-generation H1 antihistamine (e.g., cetirizine, fexofenadine, levocetirizine, loratadine) for at least 2 weeks.

- Member has been evaluated for other causes of urticaria, including bradykinin-related angioedema and interleukin-1-associated urticarial syndromes (auto-inflammatory disorders, urticarial vasculitis).

Immune Checkpoint Inhibitor-Related Toxicity[7,20]

Authorization of 6 months may be granted for treatment of immune checkpoint inhibitor-related toxicity when both of the following criteria are met:

- The member has a refractory case of immune-therapy related severe (G3) pruritus.
- The member has elevated IgE levels.

Systemic Mastocytosis[7,10]

Authorization of 12 months may be granted for the treatment of systemic mastocytosis when both of the following are met:

- The major and at least one minor diagnostic criterion for systemic mastocytosis are present or three or more minor diagnostic criteria are present (see Appendix).
- The requested medication will be used in any of the following treatment settings:
    - Used as stepwise prophylactic treatment for chronic mast cell mediator-related cardiovascular and pulmonary symptoms when the member has tried both of the following:
        - H1 blockers and H2 blockers.
        - Corticosteroids.
    - Used for prevention of unprovoked anaphylaxis.
    - Used for prevention of hymenoptera or food-induced anaphylaxis, with negative specific IgE or negative skin test.
    - Used improve tolerability of venom immunotherapy.

Prophylaxis of Seasonal or Perennial Allergic Rhinitis[2,6]

Authorization of 12 months may be granted for prophylaxis of seasonal or perennial allergic rhinitis in patients who previously had inadequate symptom control with a combination of intranasal steroids and an intranasal antihistamine.

Latex allergy prophylaxis[2]

Authorization of 12 months may be granted for the prophylaxis of latex allergy symptoms in patients with a proven latex allergy and who are unable to avoid occupational latex (e.g., healthcare workers).

Adjunct to immunotherapy[2]

Authorization of 3 months may be granted as an adjunct to immunotherapy for seasonal allergic rhinitis.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication listed in the coverage criteria section.
- The member is receiving benefit from therapy.
- Member will not use the requested medication concomitantly with other biologics indicated for asthma or CRSwNP (e.g., Cinqair, Dupixent, Fasenra, Nucala, Tezspire).

Appendix

2022 WHO Diagnostic Criteria for Systemic Mastocytosis[10]

- Major Criteria: multifocal, dense infiltrates of mast cells (at least 15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organs
- Minor Criteria
    - Greater than 25% of all mast cells are atypical cells (type 1 or type II) on bone marrow smears or are spindle-shaped in dense and diffuse mast cell infiltrates in bone marrow or other extracutaneous organ(s).
    - Activating KIT point mutation(s) at codon 816 or in other critical regions of KIT in the bone marrow or other extracutaneous organ(s).
    - Mast cells in bone marrow, blood, or other extracutaneous organs aberrantly express one or more of the following antigens: CD2, CD25, CD30.
    - Baseline serum tryptase concentration greater than 20 ng/mL in the absence of a myeloid associated hematologic neoplasm (AHN). In the case of a known hereditary alpha-tryptasemia (HαT), the tryptase level should be adjusted.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Xolair.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention. 2023 Update.

- Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program
- Clinical Practice Guideline: Allergic Rhinitis
- Omalizumab for the Treatment of Multiple Food Allergies

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Xolair are covered in addition to the following:

- Prophylaxis of seasonal or perennial allergic rhinitis
- Latex allergy prophylaxis for patients unable to avoid latex
- Adjunct to immunotherapy for seasonal allergic rhinitis
- Immune checkpoint inhibitor-related toxicities
- Systemic mastocytosis

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Xolair for allergic asthma can be found in the manufacturer's prescribing information, the Global Initiative for Asthma (GINA): Global strategy for asthma management and prevention guidelines, and the guideline update from the National Asthma Education and Prevention Program. The prescribing information indicates the minimum labeled age for Xolair is six years of age. Xolair should be used in patients whose symptoms are inadequately controlled with inhaled corticosteroids. According to the 2022 update of the GINA Global Strategy for asthma management and prevention, Xolair should be considered as an add-on therapy that is uncontrolled on other medications such as long-acting beta2-agonists, leukotriene receptor antagonists, tiotropium, or inhaled corticosteroids-formoterol maintenance and reliever therapy (MART).

The prescribing information for Xolair as well as the European Forum for Research and Education in Allergy and Airway Diseases (Bachert et al., 2021) support using Xolair to treat nasal polyps. The prescribing information indicates Xolair should be used to treat chronic rhinosinusitis with nasal polyps in patients 18 years of age and older with inadequate response to nasal corticosteroids (e.g., mometasone). In the CRSwNP Trial cited in the package insert, patients used nasal mometasone for a 5 week run in period as well as during the treatment period with Xolair. Prior to randomization, patients were required to have evidence of bilateral polyps as determined by a nasal polyp score (NPS) ≥ 5 with NPS of 2 in each nostril, despite use of nasal mometasone during the run-in period. NPS was measured via endoscopy and scored (range 0-4 per nostril: 0= no polyps; 1=small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2=polyps reaching below the lower border of the middle turbinate; 3=large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; 4=large polyps causing complete obstruction of the inferior nasal cavity) for a total NPS (range 0-8). Patients were furthermore required to have a weekly average of nasal congestion score (NCS) > 1 prior to randomization, despite use of nasal mometasone. The co-primary endpoints in Trials 1 and 2 were NPS and average daily NCS at Week 24. In both trials, patients who received Xolair had a statistically significant greater improvement from baseline at Week 24 in NPS and weekly average NCS, than patients who received placebo. The greater improvements in NPS and NCS in the Xolair group compared to the placebo group were observed as early as the first assessment at Week 4 in both studies cited in the prescribing information. Xolair had statistically significant improvements on sense of smell score compared to placebo. Sense of smell was measured by a daily assessment on a 0 to 3 point severity scale (0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms). The LS mean difference for change from baseline at Week 24 in sense of smell score in Xolair compared to

placebo was -0.3 (95% CI: -0.6, -0.1) in Trial 1 and -0.5 (95% CI: -0.7, -0.2) in Trial 2. Xolair had statistically significant improvements on post-nasal drip compared to placebo. The LS mean difference for change from baseline at Week 24 in post-nasal drip score in Xolair compared to placebo was -0.6 (95% CI: -0.8, -0.3) in Trial 1 and -0.5 (95% CI: -0.8, -0.3) in Trial 2. Xolair had statistically significant improvements on runny nose compared to placebo. The LS mean difference for change from baseline at Week 24 in runny nose score in Xolair compared to placebo was -0.4 (95% CI: -0.7, -0.2) in Trial 1 and -0.6 (95% CI: -0.9, -0.4) in Trial 2.

Support for using Xolair for the reduction of IgE-mediated food allergy reactions can be found in the manufacturer's prescribing information, and in a double-blind, placebo-controlled trial by Wood et al. (Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen Oral Immunotherapy [OIT] in Food Allergic Children and Adults [OUtMATCH] trial). In the OUtMATCH trial, patients administered Xolair subcutaneously every 2 to 4 weeks for a total of 16 to 20 weeks, at the doses and frequency based on body weight and total IgE levels. Prior to randomization, patients were required to have history of an allergy to peanut and at least two other foods in the protocol-specified list (cashew, milk, egg, walnut, wheat, and hazelnut). If the results of skin-prick and laboratory testing confirmed the food allergies, double-blind, placebo-controlled oral food challenges followed. A total of 79 of the 118 participants (67%) who received Xolair were able to consume a single dose of at least 600 mg of peanut protein without dose-limiting symptoms during the post-treatment challenge, as compared with 4 of the 59 participants (6.8%) who received placebo. This phase 3 trial involving patients as young as 1 year of age with multiple food allergies showed that 16 weeks of treatment with Xolair substantially increased threshold reactivity to peanut and multiple other foods to levels that could protect against allergic reactions associated with accidental exposure.

Support for the above criteria for using Xolair to treat chronic spontaneous urticaria can be found in the manufacturer's prescribing information, the 2014 guidelines for the diagnosis and management of acute and chronic urticaria (Bernstein et al., 2014), and the EAACI/GA(2) LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria. The guidelines differentiate between several different causes of urticaria (autoinflammatory disorders, urticarial vasculitis, HAE) and the treatment for these indications differ from the treatment for chronic spontaneous urticaria. Zuberbier et al. (2018) suggest using 2nd generation H1 antihistamines over 1st generation H1 antihistamines for the treatment of chronic urticaria.

Bernstein et al. (2014) indicate patients with episodes of urticaria that last greater than six weeks meet the definition of chronic urticaria. The first step for treating chronic urticaria is monotherapy with second generation antihistamines and avoidance of triggers and relevant physical factors if physical urticaria/angioedema syndrome is present. The second step is dose advancement of the second-generation antihistamine, addition of another antihistamine, addition of an H2-antagonist, addition of a leukotriene antagonist or addition of a 1st generation antihistamine at bedtime. The guideline indicates omalizumab should be used in chronic urticaria refractory to these therapies.

Support for using Xolair for prophylaxis of season or perennial allergic rhinitis can be found in a multicenter, open-label study by Nayak et al. (2003), conducted during ragweed season, 287 patients (aged 12 to 75) received subcutaneous omalizumab 300 mg every 3 (IgE greater than 150 international units/mL) or 4 weeks (IgE less than or equal to 150 international units/mL) for 12 weeks beginning 2 weeks prior to ragweed season. Chlorpheniramine 4 mg and fexofenadine 60 mg was permitted as rescue medicine. Overall use of rescue medicine in both groups was very low, 84 of 287 (29.3%). At least one adverse event occurred in 47.4% of patients; headache, upper respiratory tract infection and viral infection were most commonly reported. There were no severe adverse events related to omalizumab therapy.

In a phase 3, randomized, double-blind, parallel-group design by Chervinsky et al. (2003), efficacy and safety of subcutaneous omalizumab (minimum dose 0.016 mg/kg/IgE (international units/mL) per 4 weeks) was investigated in 289 patients with moderate-to-severe PAR. All patients had a positive skin prick test, total serum IgE level of 30 to 700 international units/mL, and were chronically exposed to dust mites, dog or cat allergens. Patients ranged from 12 to 75

years of age and had the following relevant comorbid conditions: 26% with history of asthma; 17% with history of atopic dermatitis; 58% with history of intranasal steroid use; 37% had attempted desensitizing immunotherapy. Using a mean daily nasal severity score (range, 0 to 3; mean of 4-point scores for sneezing, itchy, runny, and stuffy nose) as the primary efficacy variable and compared to placebo, omalizumab was associated with larger improvements in symptoms at each of the 4-week visits and for the overall 16-week treatment period (p less than 0.001 for each). In addition, treated patients were more likely to shift to a less severe symptom category compared to the established baseline severity rating (p=0.001); symptoms were considered controlled in 28% of those on active treatment vs 10% of those on placebo. In post hoc analysis in subgroups of patients who had either previously failed desensitization or intranasal steroids, the favorable effects of omalizumab on nasal symptoms persisted. Furthermore, treated patients required antihistamines on statistically significantly fewer days than those on placebo (p=0.005), although the clinical and economic merits of the small reduction may be questioned (maximum difference between the range of days of rescue medication use was 1.2 days per month, and the proportion of rescue days reached statistically significant difference only during week 8). Other secondary measures that showed favorable improvements in the omalizumab group were quality of life measures, including larger differences deemed clinically important, and patients' global evaluation of treatment efficacy. About half of treated patients reported complete control or marked improvement in symptoms, in contrast to that degree of control in only 34% of those on placebo. Omalizumab treatment was well tolerated with the following notable occurrences: 1 patient discontinued the study due to urticaria and 1 patient experienced infectious mononucleosis, although the latter was not attributed to drug therapy. No anti-omalizumab antibodies were detected in patients' sera, and no adverse events suggested drug-induced immunologic reactions.

Support for using Xolair as latex allergy prophylaxis in healthcare workers exposed to latex on a daily basis can be found in a randomized study conducted by Leynadier and colleagues (2004). Sixteen healthcare workers with documented allergy (positive skin prick test response; elevated Ig E serum levels [30 to 700 international units/mL]) were randomized to receive either placebo or omalizumab subcutaneously every 2 to 4 weeks for 16 weeks, after which all patients could continue or start omalizumab therapy for another 16 weeks. Omalizumab was dosed according to body weight and serum IgE levels and ranged from 150 to 750 mg monthly. Efficacy was measured by mean conjunctival challenge test total score, which is the sum (rated from 0, absent to 3, severe) of physician-evaluated eye redness, eyelid swelling, chemosis, and tearing and patient-rated itching (1, mild to 4, incapacitating). A score of 7 or less is considered normal. Mean score from baseline to week 16 decreased significantly in patients receiving omalizumab compared with placebo (from 10 to 5 vs from 9.67 to 9). Overall ocular response rate after 32 weeks, was 93.8% (15 of 16 patients). Furthermore, 11 of 15 patients had negative response to a latex glove challenge after 32 weeks of treatment, with the remaining 4 having a mild response.

Support for using Xolair as an adjunct to immunotherapy for seasonal allergic rhinitis can be found in a 4-arm, double-blind, parallel-group, placebo-controlled trial by Casale et al. (2006). The trial found pretreatment with omalizumab significantly decreases the adverse effects associated with rush immunotherapy. Adult patients (n=159; ages 18 to 50 years) with a minimum 2-year history of ragweed allergic rhinitis and no recent immunotherapy were randomized to receive either immunotherapy and omalizumab, placebo immunotherapy and omalizumab, immunotherapy and placebo omalizumab, or placebo immunotherapy and placebo omalizumab. The dose of omalizumab was 0.016 mg/kg/IgE (international units/mL)/month subcutaneously every 2 to 4 weeks, depending on weight and baseline IgE levels. Rush immunotherapy consisted of ragweed extract in increasing doses up to a maximal dose of 1.2 to 4 mcg Amb a 1 within a 3-hour period, one time. Immunotherapy consisted of weekly short ragweed extract injections in increasing doses over 4 weeks, then 8 weeks of a maintenance dose. Patients in each arm underwent 9 weeks of pretreatment with omalizumab or placebo, followed by rush immunotherapy or placebo. Each arm then underwent 12 weeks in 1 of the 4 treatment arms. Patients that received omalizumab in addition to rush immunotherapy had less adverse effects than patients receiving immunotherapy by itself. In post hoc analysis of the groups receiving rush immunotherapy, the addition of

omalizumab was associated with an odds ratio of 0.17 (p=0.026) for anaphylaxis compared to groups not receiving omalizumab. Severity scores during the ragweed season were significantly improved in patients that received both omalizumab and immunotherapy compared to those who received immunotherapy by itself (0.69 vs 0.86; p=0.044)

Support for using Xolair for systemic mastocytosis can be found in the National Comprehensive Cancer Network's guideline for systemic mastocytosis. The NCCN Guideline for systemic mastocytosis supports the use of Xolair as a stepwise prophylactic treatment for chronic mast cell mediator-related cardiovascular and pulmonary symptoms. Xolair can also be used for the prevention of the following: unprovoked anaphylaxis, hymenoptera or food-induced anaphylaxis with negative specific IgE or negative skin test, or to improve tolerance while on immunotherapy.

Support for using Xolair for the management of immunotherapy-related toxicities can be found in the National Comprehensive Cancer Network's guideline for management of immunotherapy-related toxicities. The NCCN Guideline supports the use of Xolair for the management of refractory cases of immunotherapy-related severe (G3) pruritus with increased IgE levels.

References

1. Xolair [package insert]. South San Francisco, CA: Genentech, Inc.; February 2024.
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Reference number(s)
4726-A

Standard Medicare Part B Management Zepzelca

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over the counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Zepzelca	lurbinectedin

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications

Zepzelca is indicated for the treatment of adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.

Compendial Uses

- Relapsed small cell lung cancer
- Primary progressive small cell lung cancer
- Ewing sarcoma

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Small Cell Lung Cancer

Authorization of 12 months may be granted for subsequent treatment of small cell lung cancer as a single agent in any of the following settings:

- Relapse following complete or partial response or stable disease with initial treatment
- Primary progressive disease
- Metastatic disease following disease progression on or after platinum-based chemotherapy

Ewing Sarcoma

Authorization of 12 months may be granted for subsequent treatment of Ewing sarcoma as a single agent for relapsed, progressive, or metastatic disease.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The requested medication is being used to treat an indication listed in the coverage criteria section.
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on current regimen AND
    - No evidence of disease progression while on current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Zepzelca.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Small cell lung cancer
- NCCN Guideline: Bone cancer

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Zepzelca are covered in addition to the following:

- Relapsed small cell lung cancer
- Primary progressive small cell lung cancer
- Ewing sarcoma

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Zepzelca to treat small cell lung cancer and Ewing sarcoma can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen). Zepzelca is recommended as subsequent systemic therapy for patients with performance status 0-2 as a single agent for relapse following complete or partial response or stable disease with primary treatment or primary progressive disease.

References

1. Zepzelca [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; July 2023.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed July 1, 2024.

Reference number(s)
6736-A

Standard Medicare Part B Management
Ziihera

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Ziihera	zanidatamab-hrii

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication

HER2-positive Biliary Tract Cancer

Ziihera is indicated for the treatment of adults with previously treated, unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive immunohistochemistry (IHC 3+) biliary tract cancer (BTC), as detected by an FDA-approved test.

Compendial Use

- HER2-positive biliary tract cancer

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions: human epidermal growth factor receptor 2 (HER2) status (e.g., immunohistochemistry (IHC) score).

Reference number(s)
6736-A

Coverage Criteria

Biliary Tract Cancer

Authorization of 12 months may be granted for subsequent treatment of unresectable or resected gross residual (R2) disease or metastatic HER2-positive (IHC 3+) biliary tract cancer (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, or gallbladder cancer) when used as a single agent.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat an indication listed in the coverage criteria section
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Ziihera.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Ziihera are covered in addition to the following:

- Resected gross residual (R2) biliary tract cancer

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Ziihera to treat resected gross residual (R2) biliary tract cancer can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and

biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

References

1. Ziihera [package insert]. Palo Alto, CA: Jazz Pharmaceuticals Inc.; November 2024.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 27, 2024.

Reference number(s)
4816-A

Standard Medicare Part B Management Zilretta

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name	Dosage Form
Zilretta	triamcinolone acetonide extended-release	injectable suspension

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

Zilretta is indicated as an intraarticular injection for the management of osteoarthritis pain of the knee.

Limitation of Use:

The efficacy and safety of repeat administration of Zilretta have not been demonstrated.

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Osteoarthritis Pain of the Knee[1]

Authorization of one dose per knee may be granted for treatment of osteoarthritis pain of the knee.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Zilretta.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- 2021 American Academy of Orthopaedic Surgeons (AAOS) Clinical Practice Guideline Summary: Management of Osteoarthritis of the Knee

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Zilretta are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

References

1. Zilretta [package insert]. Burlington, MA: Flexion Therapeutics, Inc.; March 2022.
2. Brophy RH, Fillingham YA. American Academy of Orthopaedic Surgeons (AAOS) Clinical Practice Guideline Summary: Management of Osteoarthritis of the Knee (Nonarthroplasty), Third Edition. Published August 31, 2021.

Reference number(s)
5851-A

Standard Medicare Part B Management
Zynyz

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Zynyz	retifanlimab-dlwr

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indication[1]

Merkel cell carcinoma

Zynyz is indicated for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC).

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Compendial Uses[2]

Merkel cell carcinoma

Anal carcinoma

Coverage Criteria

Merkel Cell Carcinoma (MCC)[1,2]

Authorization of 12 months may be granted as a single agent for treatment of metastatic, primary clinical locally advanced, recurrent locally advanced, or recurrent regional MCC.

Anal Carcinoma[2]

Authorization of 12 months may be granted as a single agent for treatment of locally recurrent or progressive anal carcinoma or for subsequent treatment of metastatic anal carcinoma.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted (up to 24 months total) when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication
- The requested medication is being used to treat an indication in the coverage criteria section
- The member is receiving benefit from therapy. Benefit is defined as:
    - No evidence of unacceptable toxicity while on the current regimen AND
    - No evidence of disease progression while on the current regimen

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Zynyz.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Merkel Cell Carcinoma
- NCCN Guideline: Anal Carcinoma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Zynyz are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Zynyz to treat Merkel cell carcinoma and anal carcinoma can be found in the NCCN Drugs and Biologics

Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

References

1. Zynyz [package insert]. Wilmington, DE: Incyte Corporation; April 2024.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed November 12, 2024.