Effective Date **4/15/2024**
Coverage Policy Number **IP0550**

Ravulizumab-cwvz Intravenous

Table of Contents

Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for ravulizumab intravenous (**Ultomiris®**).

Receipt of sample product does not satisfy any criteria requirements for coverage.

Initial Approval Criteria

Ravulizumab (Ultomiris) is considered medically necessary for the treatment of complement-mediated hemolytic uremic syndrome (atypical hemolytic uremic syndrome) when the individual meets ALL of the following criteria:

1. Diagnosis of thrombocytopenic purpura (TTP) has been excluded (for example, normal ADAMTS 13 activity) OR a trial of plasma exchange did not result in clinical improvement
2. Absence of Shiga toxin-producing escherichia coli (E. coli) infection
3. Has been vaccinated against meningococcal infection (at least 2 weeks prior to treatment, if not previously vaccinated), where and when clinically appropriate

4. Medication is prescribed by, or in consultation, with a hematologist and/or a nephrologist

Dosing. The recommended intravenous dose for Complement-mediated hemolytic uremic syndrome (atypical hemolytic uremic syndrome) is **ONE** of the following weight based dosing:

1. 5 kg to less than 10 kg:
    A. Induction: 600 mg for one dose
    B. Maintenance: 300 mg once every 4 weeks
2. 10 kg to less than 20 kg:
    A. Induction: 600 mg for one dose
    B. Maintenance: 600 mg once every 4 weeks
3. 20 kg to less than 30 kg:
    A. Induction: 900 mg for one dose
    B. Maintenance: 2,100 mg once every 8 weeks
4. 30 to less than 40 kg:
    A. Induction: 1,200 mg for one dose
    B. Maintenance: 2,700 mg once every 8 weeks
5. 40 to less than 60 kg:
    A. Induction: 2,400 mg for one dose
    B. Maintenance: 3,000 mg once every 8 weeks
6. 60 to less than 100 kg:
    A. Induction: 2,700 mg for one dose
    B. Maintenance: 3,300 mg once every 8 weeks
7. 100 kg or more:
    A. Induction: 3,000 mg for one dose
    B. Maintenance: 3,600 mg once every 8 weeks

Ravulizumab (Ultomiris) is considered medically necessary for the treatment of generalized myasthenia gravis when the individual meets ALL of the following criteria:

1. 18 years of age or older
2. Documentation that the individual has confirmed anti-acetylcholine receptor antibody positive generalized myasthenia gravis
3. Myasthenia Gravis Foundation of America (MGFA) clinical classification class of II-IV (prior to starting therapy with Ultomiris) [See APPENDIX 1]
4. Myasthenia Gravis-Activities of Daily Living (MG-ADL) score of 6 or higher (prior to starting therapy with Ultomiris) [See APPENDIX 2]
5. Documentation of **ONE** of the following:
    A. Is currently receiving pyridostigmine
    B. Failure, contraindication, or intolerance to pyridostigmine
6. Documentation of **ONE** of the following:
    A. Is currently receiving two different immunosuppressant therapies (for example, azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, cyclophosphamide, prednisone) for 1 year or longer
    B. Failure, contraindication, or intolerance to two different immunosuppressant therapies
7. Has objective evidence of unresolved symptoms of generalized myasthenia gravis, such as difficulty swallowing, difficulty breathing, or a functional disability resulting in the discontinuation of physical activity (for example, double vision, talking, impairment of mobility)
8. The medication is prescribed by, or in consultation with a neurologist

Dosing. The recommended intravenous dose for Generalized Myasthenia Gravis is **ONE** of the following weight based dosing:

1. 40 kg to less than 60 kg:
    A. Induction: 2,400 mg for one dose
    B. Maintenance: 3,000 mg once every 8 weeks

2. 60 kg to less than 100 kg:
    A. Induction: 2,700 mg for one dose
    B. Maintenance: 3,300 mg once every 8 weeks
3. 100 kg or more:
    A. Induction: 3,000 mg for one dose
    B. Maintenance: 3,600 once every 8 weeks

Ravulizumab (Ultomiris) is considered medically necessary for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) when the individual meets ALL of the following criteria:

1. Flow cytometry demonstrates one of the following:
    A. At least 10% PNH type III red cells
    B. Greater than 50% of glycosylphosphatidylinositol-anchored proteins (GPI-AP)- deficient polymorphonuclear cells (PMNs)
2. At least one transfusion related to anemia secondary to PNH **OR** occurrence of a thromboembolic event
3. Has been vaccinated against meningococcal infection (at least 2 weeks prior to treatment, if not previously vaccinated) where and when clinically appropriate
4. Medication is prescribed by, or in consultation, with a hematologist

Dosing. The recommended intravenous dose for Paroxysmal nocturnal hemoglobinuria (PNH) is **ONE** of the following weight based dosing:

1. 5 kg to less than 10 kg:
    A. Induction: 600 mg for one dose
    B. Maintenance: 300 mg once every 4 weeks
2. 10 kg to less than 20 kg:
    A. Induction: 600 mg for one dose
    B. Maintenance: 600 mg once every 4 weeks
3. 20 kg to less than 30 kg:
    A. Induction: 900 mg for one dose
    B. Maintenance: 2,100 mg once every 8 weeks
4. 30 to less than 40 kg:
    A. Induction: 1,200 mg for one dose
    B. Maintenance: 2,700 mg once every 8 weeks
5. 40 to less than 60 kg:
    A. Induction: 2,400 mg for one dose
    B. Maintenance: 3,000 mg once every 8 weeks
6. 60 to less than 100 kg:
    A. Induction: 2,700 mg for one dose
    B. Maintenance: 3,300 mg once every 8 weeks
7. 100 kg or more:
    A. Induction: 3,000 mg for one dose
    B. Maintenance: 3,600 mg once every 8 weeks

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Continuation of Therapy Criteria

Continuation of ravulizumab (Ultomiris) is considered medically necessary for **ALL** covered diagnoses when initial criteria are met AND beneficial response is demonstrated by **ANY** of the following:

1. **Complement-mediated Hemolytic Uremic Syndrome (atypical hemolytic uremic syndrome):** Reduced hemolysis, improved thrombocytopenia or renal function
2. **Generalized Myasthenia Gravis:** Reductions in exacerbations of MG; improvements in speech, swallowing, mobility, and respiratory function, improvement in MG-ADL or QMG scores
3. **Paroxysmal Nocturnal Hemoglobinuria (PNH):** Stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis

Authorization Duration

Initial approval duration:

- **Complement-mediated Hemolytic Uremic Syndrome (atypical hemolytic uremic syndrome):** up to 6 months
- **Generalized Myasthenia Gravis:** up to 6 months
- **Paroxysmal Nocturnal Hemoglobinuria (PNH):** up to 6 months

Reauthorization approval duration:

- **Complement-mediated Hemolytic Uremic Syndrome (atypical hemolytic uremic syndrome):** up to 12 months
- **Generalized Myasthenia Gravis:** up to 12 months
- **Paroxysmal Nocturnal Hemoglobinuria (PNH):** up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Concomitant Use with Another Complement Inhibitor, a Rituximab Product, or a Neonatal Fc Receptor Blocker**. There is no evidence to support concomitant use of Ultomiris intravenous with another complement inhibitor, a rituximab product, or a neonatal Fc receptor blocker.

   Examples of complement inhibitors are Empaveli (pegcetacoplan subcutaneous injection), Fabhalta (iptacopan capsule), Soliris (eculizumab intravenous infusion), and Zilbrysq (zilucoplan subcutaneous injection).

   Examples of neonatal Fc receptor blockers are Rystiggo (rozanolixizumab-noli subcutaneous infusion), Vyvgart (efgartigimod alfa-fcab intravenous infusion], and Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection).

Coding Information

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J1303	Injection, ravulizumab-cwvz, 10 mg

Background

OVERVIEW

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

- **Atypical hemolytic uremic syndrome** (aHUS), in patients ≥ one month of age.
- **Generalized myasthenia gravis** (gMG), in adults who are anti-acetylcholine receptor (AChR) antibody positive.
- **Paroxysmal nocturnal hemoglobinuria** (PNH), in patients ≥ one month of age.

Ultomiris is also available in a subcutaneous formulation that is indicated for maintenance therapy of aHUS and PNH in adults.[1] The recommended dosing regimen consists of a weight-based loading dose (dosage range: 600 mg to 3,000 mg) followed by maintenance dosing (dosage range: 300 mg to 3,600 mg), administered by intravenous infusion.[1] Starting 2 weeks after the loading dose administration, begin maintenance doses at a once every 4-week interval for patients ≥ 5 kg to < 20 kg or at a once every 8-week interval for patients ≥ 20 kg.

Disease Overview

Hemolytic uremic syndrome (HUS) is defined as the triad of non-immune hemolytic anemia, thrombocytopenia, and acute renal failure, in which the underlying lesions are mediated by systemic thrombotic microangiopathy.[4] The thrombotic microangiopathy process that characterizes HUS can be caused by a variety of things. aHUS is a sub-type of HUS in which thrombotic microangiopathy is the consequence of endothelial damage in the microvasculature of the kidneys and other organs due to a dysregulation of the activity of the complement system. Various aHUS-related mutations have been identified in genes of the complement system, which can explain approximately 60% of the aHUS cases, and a number of mutations and polymorphisms have been functionally characterized. aHUS should be distinguished from a more common condition referred to as typical HUS.[5] The two disorders have different causes and different signs and symptoms. Unlike aHUS, the typical form is caused by infection with certain strains of *Escherichia coli* bacteria that produce toxic substances called Shiga-like toxins. The typical form is characterized by severe diarrhea and most often affects children < 10 years of age, and it is less likely than aHUS to involve recurrent attacks of kidney damage that lead to end stage renal disease. The incidence of aHUS is estimated to be 1:500,000 people/year in the US; aHUS is approximately 10 times less common than typical HUS.

MG is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs.[6] The hallmark of myasthenia gravis is muscle weakness that worsens after periods of activity and improves after periods of rest. Certain muscles such as those that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are often involved in the disorder; however, the muscles that control breathing and neck and limb movements may also be affected. Acquired MG results from the binding of autoantibodies to components of the neuromuscular junction, most commonly the acetylcholine receptor.[7]

PNH is a rare disorder involving bone marrow failure that manifests with hemolytic anemia, thrombosis, and peripheral blood cytopenias.[2] Due to the absence of two glycosylphosphatidylinositol (GPI)-anchored proteins, CD55 and CD59, uncontrolled complement activation leads to hemolysis and other PNH manifestations. GPI anchor protein deficiency is often due to mutations in phosphatidylinositol glycan class A (PIGA), a gene involved in the first step of GPI anchor biosynthesis. PNH clinical diagnosis should be confirmed with peripheral blood flow cytometry to detect the absence or severe deficiency of GPI-anchored proteins on at least two lineages. Prior to the availability of Soliris® (eculizumab intravenous infusion) [a complement inhibitor],[3] there was no specific therapy for PNH with only supportive management in terms of the cytopenias and control of thrombotic risk. Supportive measures used include platelet transfusion, immune suppressive therapy for patients with bone marrow failure, use of erythropoietin for anemias, and aggressive anticoagulation. A complement inhibitor is the treatment of choice for patients with severe manifestations of PNH. Bone marrow transplantation is the only cure for PNH but should be reserved for patients with a suboptimal response to medication.

Guidelines

An international consensus guidance for the management of MG was published in 2016.[7] The guidelines recommend pyridostigmine for the initial treatment in most patients with MG. The ability to discontinue pyridostigmine can indicate that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or immunosuppressant therapy should be used in all patients with MG who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal immunosuppressant agents used for MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. It is usually

necessary to maintain some immunosuppression for many years, sometimes for life. Plasma exchange and intravenous immunoglobulin can be used as short-term treatments in certain patients. A 2020 update to these guidelines provides new recommendations for methotrexate, rituximab, and Soliris.[8] All recommendations should be considered extensions or additions to recommendations made in the initial international consensus guidance. Oral methotrexate may be considered as a steroid-sparing agent in patients with generalized MG who have not tolerated or responded to steroid-sparing agents. Rituximab should be considered as an early therapeutic option in patients with muscle specific kinase antibody positive MG who have an unsatisfactory response to initial immunotherapy. Soliris should be considered in the treatment of severe, refractory, anti-acetylcholine receptor antibody positive generalized MG.

APPENDIX 1
[Myasthenia Gravis Foundation of America (MGFA) classification]
The Myasthenia Gravis Foundation of America (MGFA) classification is aimed at separating patients in groups based on disease severity and the localization of the symptoms, and does not have an evaluative purpose. The MGFA classes are pure ocular (class I), mild generalized (class II), moderate generalized (class III), severe generalized (class IV), and intubation/myasthenic crisis (class V). Within the generalized categories II, III, and IV, patients are subclassified as class A if their symptoms are predominantly generalized or class B if their symptoms are predominantly bulbar.[1] The MGFA also has a system to classify patients based on postintervention outcomes and includes remission, defined as 1 year or longer without signs or symptoms and without any symptomatic (pyridostigmine) treatment, and which can be divided in complete (no pharmacologic treatment at all) or pharmacologic remission. Minimal manifestation status is defined as minimal signs or symptoms (no specific time-frame was defined) and pyridostigmine use may be accepted. Additionally, patients can be improved, unchanged, worse, experiencing an MG exacerbation, or have died of MG.[1] Because the original MGFA severity classification does not take into account those patients who are asymptomatic, many MG studies use a hybrid, whereby symptomatic patients are classified based on the I to V class system, and asymptomatic or oligosymptomatic patients are classified as remission or minimal manifestation status.[2]

APPENDIX 2
[Myasthenia Gravis Activities of Daily Living (MG-ADL)]
The Myasthenia Gravis Activities of Daily Living (MG-ADL) is a patient-reported outcome that combines 2 items on daily life activities—ability to brush teeth or comb hair, and limitations in the ability to rise from a chair—with 6 items reflecting other MG symptoms: diplopia, ptosis, chewing, swallowing, voice/speech problems, and respiratory symptoms.[3] Each item is scored between 0 and 3 and total scores range from 0 to 24, where higher scores indicate more disease severity. The main advantages of the MG-ADL are that it is very easy to use, and it is completely patient reported. A drawback is that it does not have a specific recall time frame (eg, 2 or 4 weeks) because it relies on comparing with the last visit, and that it is prone to floor effects.[4]

References

1. Ultomiris® intravenous infusion and subcutaneous injection [prescribing information]. New Haven, CT: Alexion; July 2022.
2. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. *Blood*. 2014;124(18):2804–2811.
3. Soliris® intravenous infusion [prescribing information]. New Haven, CT: Alexion; July 2022.
4. Campistol JM, Arias M, Ariceta G, et al. An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document. *Nefrologia*. 2015;35:421–447.
5. Genetics Home Reference. Atypical hemolytic-uremic syndrome. National Institutes of Health (NIH). Available at: https://ghr.nlm.nih.gov/condition/atypical-hemolytic-uremic-syndrome#sourcesforpage. Accessed on November 7, 2022.
6. National Institute of Neurological Disorders and Stroke (NINDS). Myasthenia Gravis Fact Sheet. National Institutes of Health (NIH) Publication No. 17-768. Available at: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Myasthenia-Gravis-Fact-Sheet. Accessed on November 7, 2022.
7. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. *Neurology*. 2016;87:419–425.
8. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. *Neurology*. 2021 Jan 19;96(3):114-122.