Effective Date **6/15/2024**
Coverage Policy Number **IP0550**

Ravulizumab-cwvz Intravenous

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Related Coverage Resources

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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 Neuromyelitis Optica Spectrum Disorder when the individual meets ALL of the following criteria:

1. 18 years of age or older
2. Diagnosis confirmed by a positive blood serum test for anti-aquaporin-4 antibody
3. The medication is being prescribed by, or in consultation with, a neurologist

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

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. **Neuromyelitis Optica Spectrum Disorder:** Reduction in relapse rate, reduction in symptoms (e.g., pain, fatigue, motor function), and a slowing progression in symptoms.
4. **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
- **Neuromyelitis Optica Spectrum Disorder:** up to 12 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
- **Neuromyelitis Optica Spectrum Disorder:** 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**, **Enspryng (satralizumab-mwge subcutaneous injection), or Uplizna (inebilizumab-cdon intravenous infusion).** There is no evidence to support concomitant use of Ultomiris intravenous with another complement inhibitor, a rituximab product, or a neonatal Fc receptor blocker, Enspryng, or Uplizna.

   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 Vyvgart (efgartigimod alfa-fcab intravenous infusion), Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection), and Rystiggo (rozanolixizumab-noli subcutaneous infusion).

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

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

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

Disease Overview

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

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

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

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

Recommendations
There are no formal guidelines for treatment of aHUS.

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

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

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

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]

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