Utilization Review Policy 199

POLICY: Complement Inhibitors – Ultomiris Utilization Management Medical Policy – Advanced Clinical Evaluation

- Ultomiris™ (ravulizumab-cwvz intravenous infusion – Alexion)

EFFECTIVE DATE: 1/1/2020
LAST REVISION DATE: 09/20/2023

COVERAGE CRITERIA FOR: All UCare Plans

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.
- **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] Patients should be immunized with a meningococcal vaccine at least 2 weeks prior to the first dose of Ultomiris, unless the risks of delaying Ultomiris outweigh the risk of developing a meningococcal infection. Vaccination reduces, but does not eliminate, the risk of meningococcal infections.

Ultomiris is available only through a restricted access program called Ultomiris Risk Evaluation and Mitigation Strategy (REMS).[1]

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]

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, genetic disorder of hematopoietic stem cells.[6,7] 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.[6,8] Prior to the availability of Soliris, there was no specific therapy for PNH; only supportive management, in terms of managing the cytopenias and controlling thrombotic risk were available. Supportive measures include platelet transfusion, immunosuppressive therapy for patients with bone marrow failure, use of erythropoietin for anemias, and aggressive anticoagulation.

Guidelines

An international consensus guidance for the management of MG was published in 2016.[5] The guidelines recommend pyridostigmine for the initial treatment in most patients with MG. The ability to discontinue pyridostigmine can indicate that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or immunosuppressant therapy should be used in all patients with MG who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal immunosuppressant agents used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Plasma exchange and intravenous immunoglobulin can be used as short-term treatments in certain patients. A 2020 update to these guidelines provides new recommendations for methotrexate, rituximab, and Soliris.[9] 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.

POLICY STATEMENT

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

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

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

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

   Dosing. Approve ONE of the following weight-based regimens (A or B):
   - **A)** ≥ 5 kg to < 20 kg: ≤ 600 mg administered by intravenous infusion for one dose, followed by ≤ 600 mg administered by intravenous infusion once every 4 weeks; OR
   - **B)** ≥ 20 kg: ≤ 3,000 mg administered by intravenous infusion for one dose, followed by ≤ 3,600 mg administered by intravenous infusion once every 8 weeks.

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2. **Generalized Myasthenia Gravis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial therapy. Approve for 6 months if the patient meets the following (i, ii, iii, iv, v, vi, and vii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has confirmed anti-acetylcholine receptor antibody-positive generalized myasthenia gravis **[documentation required]**; AND
     - **iii.** Patient meets both of the following (a and b):
       - **a)** Myasthenia Gravis Foundation of America classification of II to IV; AND
       - **b)** Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 6; AND
     - **iv.** Patient meets one of the following (a or b):
       - **a)** Patient received or is currently receiving pyridostigmine; OR
       - **b)** Patient has had inadequate efficacy, a contraindication, or significant intolerance to pyridostigmine; AND
     - **v.** Patient meets one of the following (a or b):
       - **a)** Patient received or is currently receiving two different immunosuppressant therapies for ≥ 1 year; OR
       - **b)** Patient had inadequate efficacy, a contraindication, or significant intolerance to two different immunosuppressant therapies; AND

         Note: Examples of immunosuppressant therapies include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, and cyclophosphamide.
     - **vi.** Patient has evidence of unresolved symptoms of generalized myasthenia gravis; AND

       Note: Evidence of unresolved symptoms of generalized myasthenia gravis includes difficulty swallowing, difficulty breathing, or a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility).
     - **vii.** The medication is being prescribed by or in consultation with a neurologist.
   - **B)** Patient is Currently Receiving Ultomiris intravenous. Approve for 1 year if the patient meets the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient is continuing to derive benefit from Ultomiris intravenous, according to the prescriber; AND

       Note: Examples of derived benefit include reductions in exacerbations of myasthenia gravis; improvements in speech, swallowing, mobility, and respiratory function.
     - **iii.** The medication is being prescribed by or in consultation with a neurologist.

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

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

   Dosing. Approve ONE of the following weight-based regimens (A or B):
   - **A)** ≥ 5 kg to < 20 kg: ≤ 600 mg administered by intravenous infusion for one dose, followed by ≤ 600 mg administered by intravenous infusion once every 4 weeks; OR
   - **B)** ≥ 20 kg: ≤ 3,000 mg administered by intravenous infusion for one dose, followed by ≤ 3,600 mg administered by intravenous infusion once every 8 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

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

1. **Concomitant Use with Another Complement Inhibitor, a Rituximab Product, 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.
   Note: Examples of complement inhibitors are Empaveli (pegcetacoplan subcutaneous [SC] infusion and Soliris (eculizumab intravenous [IV] infusion).
   Note: Examples of neonatal Fc receptor blockers are Vyvgart (efgartigimod alfa-fcab IV infusion], Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc SC injection), and Rystiggo (rozanolixizumab-noli SC infusion).

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

REFERENCES

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8. Roth A, Maciejewski J, Nishinura JI, et al. Screening and diagnostic clinical algorithm for paroxysmal nocturnal hemoglobinuria: Expert consensus. *Eur J Haematol*. 2018;101(1):3-11.
9. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. *Neurology*. 2021 Jan 19;96(3):114-122.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	For the title and where applicable in the document, "intravenous" was added. **Generalized Myasthenia Gravis:** "intravenous" was added to Ultomiris to clarify product allowed for a patient who is currently receiving therapy. **[documentation required]** was added to the requirement for confirmed anti-acetylcholine receptor antibody positive generalized myasthenia gravis. **Paroxysmal Nocturnal Hemoglobinuria:** "intravenous or subcutaneous" was added to Ultomiris to clarify product allowed for a patient who is currently receiving therapy. **Concurrent Use with Another Complement Inhibitor or Vyvgart (efgartigimod alfa-fcab intravenous infusion):** The title was changed to this instead of stating specific complement inhibitors. Vyvgart was also added as a product to this condition.	08/31/2022
Selected Revision	**Generalized Myasthenia Gravis:** Revised the Myasthenia Gravis Activities of Daily Living (MG-ADL) score to ≥ 6 to align with the prescribing information; previously it was MG-ADL ≥ 5.	05/31/2023
Annual Revision	**Generalized Myasthenia Gravis:** Initial therapy, for the criterion regarding evidence of unresolved symptoms of generalized myasthenia gravis, the examples of evidence of unresolved symptoms of generalized myasthenia gravis were moved to a Note. **Conditions Not Recommended for Approval:** Criterion regarding concomitant use of Ultomiris IV with another complement inhibitor or Vyvgart was revised to add rituximab and other neonatal Fc receptor blockers (Vyvgart Hytrulo, Rystiggo). Examples of complement inhibitors and neonatal Fc receptor blockers were moved to a Note.	09/20/2023