UTILIZATION MANAGEMENT MEDICAL POLICY

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

REVIEW DATE: 08/26/2026

OVERVIEW

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

- **Atypical hemolytic uremic syndrome** (aHUS), to inhibit complement-mediated thrombotic microangiopathy in patients ≥ 1 month of age.
  Limitation of use: Ultomiris 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 ≥ 1 month of age.

For the gMG indication, Ultomiris 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]

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 is not indicated for the treatment of Shiga toxin *E. coli*-related HUS.[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]

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

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PNH is a rare genetic disorder of hematopoietic stem cells.[8,9] Variants in the X-linked phosphatidylinositol glycan class A (*PIGA*) gene result 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]

Guidance for gMG

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 certain agents, including eculizumab intravenous infusion(Soliris®, biosimilars).[9] Eculizumab should be considered in the treatment of severe, refractory, anti-AChR antibody-positive gMG.

Safety

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

POLICY STATEMENT

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

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

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

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Note: Ultomiris is administered as an intravenous infusion.

A) Patient weighs ≥ 5 kg to < 20 kg: Up to 600 mg for one dose, followed by maintenance doses (which start 2 weeks after the loading dose) of up to 600 mg every 4 weeks; OR

B) Patient weighs ≥ 20 kg: Up to 3,000 mg for one dose, followed by maintenance doses (which start 2 weeks after the loading dose) of up to 3,600 mg every 8 weeks.

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

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

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

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

- **i.** Patient is ≥ 18 years of age; AND
- **ii.** According to the prescriber, patient is continuing to derive benefit from Ultomiris; AND
  Note: Examples of benefit include reductions in exacerbations of myasthenia gravis; improvements in speech, swallowing, mobility, and respiratory function.
- **iii.** The medication is prescribed by or in consultation with a neurologist.

Dosing. Approve up to 3,000 for one dose, followed by maintenance doses (which start 2 weeks after the loading dose) of up to 3,600 mg every 8 weeks.

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

   Dosing. Approve up to 3,000 for one dose, followed by maintenance doses (which start 2 weeks after the loading dose) of up to 3,600 mg every 8 weeks.

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

   Dosing. Approve ONE of the following (A or B):
   - **A)** Patient weighs ≥ 5 kg to < 20 kg: Up to 600 mg for one dose, followed by maintenance doses (which start 2 weeks after the loading dose) of up to 600 mg every 4 weeks; OR
   - **B)** Patient weighs ≥ 20 kg: Up to 3,000 mg for one dose, followed by maintenance doses (which start 2 weeks after the loading dose) of up to 3,600 every 8 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ultomiris is not recommended in the following situations:

1. **Concomitant Use with Another Complement Inhibitor, Except Voydeya (danicopan tablets).** There is no evidence to support concomitant use of Ultomiris with another complement inhibitor, except Voydeya.
   Note: Examples of complement inhibitors are Empaveli (pegcetacoplan subcutaneous injection), Fabhalta (iptcopan capsule), PiaSky (crovalimab-akkz intravenous infusion or subcutaneous injection), and eculizumab intravenous infusion (Soliris, biosimilars).

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2. **Concomitant Use with a Rituximab Product, a Neonatal Fc Receptor Blocker, or Zilbrysq (zilucoplan subcutaneous injection)**. There is no evidence to support concomitant use of Ultomiris with a rituximab product, a neonatal Fc receptor blocker, or Zilbrysq.
   Note: Examples of neonatal Fc receptor blockers are Imaavy (nipocalimab-aahu intravenous infusion), Rystiggo (rozanolixizumab-noli subcutaneous infusion), Vyvgart (efgartigimod alfa-fcab intravenous infusion), and Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection).

3. **Concomitant Use with Enspryng (satralizumab-mwge subcutaneous injection) or Uplizna (inebilizumab-cdon intravenous infusion)**. There is no evidence to support concomitant use of Ultomiris with Enspryng or Uplizna.

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

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Ultomiris subcutaneous injection:** All references to the subcutaneous formulation were removed – subcutaneous Ultomiris will not be marketed and has been removed from the Ultomiris prescribing information. **Paroxysmal Nocturnal Hemoglobinuria, Patient is currently receiving Ultomiris:** "Improvement in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score" was added to the Note of examples of benefit. **Conditions Not Recommended for Approval, Concomitant Use with Another Complement Inhibitor, a Rituximab Product, a Neonatal Fc Receptor Blocker, Enspryng (satralizumab-mwge subcutaneous injection), or Uplizna (inebilizumab-cdon intravenous infusion):** This criterion was separated into three criteria. The Note regarding neonatal Fc receptor blockers was moved to the relevant criterion. • **Concomitant Use with Another Complement inhibitor (except Voydeya [danicopan tablets]).** PiaSky (crovalimab-akkz intravenous infusion or subcutaneous injection) was added to the Note of examples of complement inhibitors. • **Concomitant Use with a Rituximab Product, a Neonatal Fc Receptor Blocker, or Zilbrysq (zilucoplan subcutaneous injection).** • **Concomitant Use with Enspryng (satralizumab-mwge subcutaneous injection) or Uplizna (inebilizumab-cdon intravenous infusion).** **Policy name**: Ultomiris Intravenous PA was changed to Ultomiris PA.	09/25/2024
Annual Revision	**Atypical hemolytic uremic syndrome, dosing section:** Dosing recommendations were further clarified to align with the prescribing information. **Generalized myasthenia gravis, Neuromyelitis optica spectrum disorder, and Paroxysmal nocturnal hemoglobinuria, dosing section:** Dosing recommendations were split for Initial Therapy and Patient is Currently Receiving Ultomiris. All dosing recommendations align with the prescribing information. **Conditions Not Recommended for Approval,** • **Concomitant Use with Another Complement Inhibitor, Except Voydeya (danicopan tablets):** Biosimilars to Soliris were added to the Note of examples of complement inhibitors. • **Concomitant Use with a Rituximab Product, a Neonatal Fc Receptor Blocker, or Zilbrysq (zilucoplan subcutaneous injection):** Imaavy was added to the Note of examples of neonatal Fc receptor blockers.	08/06/2025
Annual Revision	**Atypical hemolytic uremic syndrome, dosing section:** Replaced "≤" with the words "Up to". **Generalized myasthenia gravis, Neuromyelitis optica spectrum disorder, and Paroxysmal nocturnal hemoglobinuria, dosing section:** Replaced "≤" with the words "Up to". Dosing recommendations for Initial Therapy and Patient is Currently Receiving Ultomiris were combined into one set of recommendations.	08/26/2026

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