

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: 09/25/2024

COVERAGE CRITERIA FOR: All UCare Plans

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 \geq 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 \geq 1 month of age.

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).

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 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 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 B₁₂ 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.

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. 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 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. All reviews will be forwarded to a Physician Medical Director for evaluation.

Documentation: Documentation is required for use of Ultomiris 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 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 is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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 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: $\leq 3,000$ mg administered by intravenous infusion for one dose, followed by $\leq 3,600$ mg administered by intravenous infusion once every 8 weeks.

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 **[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 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 the following dose if the patient is ≥ 40 kg: $\leq 3,000$ mg administered by intravenous infusion for one dose, followed by $\leq 3,600$ mg administered by intravenous infusion once every 8 weeks.

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 Ultomiris. 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 the following dose if the patient is ≥ 40 kg: $\leq 3,000$ mg administered by intravenous infusion for one dose, followed by $\leq 3,600$ mg administered by intravenous infusion once 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 [**documentation required**]; 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 from Ultomiris 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 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: $\leq 3,000$ mg administered by intravenous infusion for one dose, followed by $\leq 3,600$ mg administered by intravenous infusion once 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 (iptacopan capsule), PiaSky (crovalimab-akkz intravenous infusion or subcutaneous injection), and Soliris (eculizumab intravenous infusion).
- 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 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.

REFERENCES

1. Ultomiris® [prescribing information]. New Haven, CT: Alexion; June 2024.
2. 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.

3. 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 September 17, 2024.
4. National Institute of Neurological Disorders and Stroke (NINDS). Myasthenia Gravis. Updated March 2020. Available at: https://www.ninds.nih.gov/sites/default/files/migrate-documents/myasthenia_gravis_e_march_2020_508c.pdf. Accessed on September 17, 2024.
5. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. *Neurology*. 2016;87:419–425.
6. National Organization for Rare Disorders. Neuromyelitis Optica Spectrum Disorder. Available at: <https://rarediseases.org/rare-diseases/neuromyelitis-optica/>. Last updated July 27, 2022. Accessed on September 17, 2024.
7. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85(2):177-189.
8. Cançado RD, da Silva Araújo A, Sandes AF, et al. Consensus statement for diagnosis and treatment of paroxysmal nocturnal haemoglobinuria. *Hematol Transfus Cell Ther*. 2021;43:341-348.
9. Shah N, Bhatt H. Paroxysmal Nocturnal Hemoglobinuria. [Updated 2023 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK562292/>. Accessed September 17, 2024.
10. 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.
11. 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.
12. Kúmpfel T, Giglhuber K, Aktas O, et al. Update on the diagnosis and treatment of neuromyelitis optica spectrum disorders (NMOSD) – revised recommendations of the Neuromyelitis Optica Study Group (NEMOS). Part II: Attack therapy and long-term management. *J Neurol*. 2024;271:141-176.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	<p>For the title and where applicable in the document, “intravenous” was added.</p> <p>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.</p>	08/31/2022

	<p>Paroxysmal Nocturnal Hemoglobinuria: “intravenous or subcutaneous” was added to Ultomiris to clarify product allowed for a patient who is currently receiving therapy.</p> <p>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.</p>	
Selected Revision	<p>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.</p>	05/31/2023
Annual Revision	<p>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.</p> <p>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.</p>	09/20/2023
Update	<p>01/17/2024: No criteria changes.</p> <p>Conditions Not Recommended for Approval: Note regarding examples of complement inhibitors was updated to include Fabhalta and Zilbrysq.</p>	--
Selected Revision	<p>Neuromyelitis Optica Spectrum Disorder: This condition and criteria for approval were added to the policy.</p> <p>Conditions Not Recommended for Approval, Enspryng (satralizumab-mwge subcutaneous injection) and Uplisna (inebilizumab-cdon intravenous infusion) were added to the criterion “Concomitant Use with a Rituximab Product, Enspryng (satralizumab-mwge subcutaneous injection), or Soliris (eculizumab intravenous infusion)”; new criterion reads:</p>	04/10/2024

	“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)”.	
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/16/2024
Annual Revision	<ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> – 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). <p>Policy name: Ultomiris Intravenous PA was changed to Ultomiris PA.</p>	09/25/2024