Drug Coverage Policy

Effective Date.....10/1/2025
Coverage Policy Number.....IP0550
Policy Title.....Ultomiris

Complement Inhibitors – Ultomiris

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

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. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. 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

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.

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 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.

Coverage Policy

POLICY STATEMENT

Prior Authorization is required for 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 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.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information.

Ultomiris is considered medically necessary when ONE of the following is met (1, 2, 3, or 4):

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):
   Note: Ultomiris is administered as an intravenous infusion.
   A) Patient weighs ≥ 5 kg to < 20 kg: ≤ 600 mg for one dose, followed by maintenance doses (which start 2 weeks after the loading dose) of ≤ 600 mg every 4 weeks; OR
   B) Patient weighs ≥ 20 kg: ≤ 3,000 mg for one dose, followed by maintenance doses (which start 2 weeks after the loading dose) of ≤ 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 **[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 ONE of the following (A or B):

A) Initial Therapy. ≤ 3,000 for one dose, followed by maintenance doses (which start 2 weeks after the loading dose) of ≤ 3,600 mg every 8 weeks; OR

B) Patient is Currently Receiving Ultomiris: ≤ 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 **[documentation required]**; 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 ONE of the following (A or B):

A) Initial Therapy. ≤ 3,000 for one dose, followed by maintenance doses (which start 2 weeks after the loading dose) of ≤ 3,600 mg every 8 weeks; OR

B) Patient is Currently Receiving Ultomiris: ≤ 3,600 mg every 8 weeks.

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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 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) Initial Therapy. Approve ONE of the following (i or ii):

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

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

B) Patientis Currently Receiving Ultomiris: Approve ONE of the following (i or ii):

i. Patient weighs ≥ 5 kg to < 20 kg: ≤ 600 mg every 4 weeks; OR

ii. Patient weighs ≥ 20 kg: ≤ 3,600 mg every 8 weeks.

Conditions Not Covered

Ultomiris for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

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).

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.

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

References

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5. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. *Neurology*. 2016;87:419–425.
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7. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85(2):177-189.
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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.
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12. Kűmpfel 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.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	Policy title updated from *Ravulizumab-cwvz Intravenous* to *Complement Inhibitors – Ultomiris* Documentation requirements were updated throughout the policy. **Atypical Hemolytic Uremic Syndrome. Updated** approval duration from 6 months to 1 year. **Removed** "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." **Removed** "Has been vaccinated against meningococcal	08/15/2025

	infection (at least 2 weeks prior to treatment, if not previously vaccinated), where and when clinically appropriate." **Updated** dosing. **Generalized Myasthenia Gravis. Updated** dosing. **Paroxysmal Nocturnal Hemoglobinuria. Updated** "Flow cytometry demonstrates one of the following: At least 10% PNH type III red cells; or Greater than 50% of glycosylphosphatidylinositol-anchored proteins (GPI-AP)- deficient polymorphonuclear cells (PMNs)" **to** now read "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." **Removed** "At least one transfusion related to anemia secondary to PNH OR occurrence of a thromboembolic event and "Has been vaccinated against meningococcal infection (at least 2 weeks prior to treatment, if not previously vaccinated) where and when clinically appropriate." **Updated** dosing.	
Annual Revision	**Atypical hemolytic uremic syndrome, Generalized myasthenia gravis, Neuromyelitis optica spectrum disorder, Paroxysmal nocturnal hemoglobinuria, Dosing section:** Dosing recommendations were further clarified to align with the prescribing information. **Generalized myasthenia gravis, Neuromyelitis optica spectrum disorder, Paroxysmal nocturnal hemoglobinuria, Dosing section:** Dosing recommendations were split for Initial Therapy and Patient is Currently Receiving Eculizumab. All dosing recommendations align with the prescribing information. **Conditions Not Covered, 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.	10/1/2025

The policy effective date is in force until updated or retired.