Reference number(s)
2836-A

Standard Medicare Part B Management Ultomiris

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Ultomiris	ravulizumab-cwvz

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1]

- Ultomiris is indicated for the treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH).
- Ultomiris is indicated for the treatment of adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).
- Ultomiris is indicated for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive.
- Ultomiris is indicated for the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive.

Limitations of Use

Ultomiris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions:

- For initial requests:
  - Paroxysmal nocturnal hemoglobinuria: Flow cytometry used to show results of glycosylphosphatidylinositol-anchored proteins (GPI-APs) deficiency.
  - Generalized myasthenia gravis:
    - Positive anti-acetylcholine receptor (AChR) antibody test.
    - Myasthenia Gravis Foundation of America (MGFA) clinical classification.
    - MG activities of daily living score.
    - Previous medications tried, including response to therapy. If therapy is not advisable, documentation of clinical reasons to avoid therapy.
  - Neuromyelitis optica spectrum disorder: immunoassay used to confirm anti-aquaporin-4 (AQP4) antibody is present.
- For continuation requests: Chart notes or medical record documentation supporting benefit from therapy.

Coverage Criteria

Paroxysmal Nocturnal Hemoglobinuria (PNH)[1-5,8]

Authorization of 6 months may be granted for treatment of paroxysmal nocturnal hemoglobinuria (PNH) when all of the following criteria are met:

- The diagnosis of PNH was confirmed by detecting a deficiency of glycosylphosphatidylinositol-anchored proteins (GPI-APs) (e.g., at least 5% PNH cells, at least 51% of GPI-AP deficient poly-morphonuclear cells).
- Flow cytometry is used to demonstrate GPI-APs deficiency.
- Member has and exhibits clinical manifestations of disease (e.g., LDH > 1.5 ULN, thrombosis, renal dysfunction, pulmonary hypertension, dysphagia).
- The requested medication will not be used in combination with another complement inhibitor (e.g., Empaveli, Fabhalta, Piasky, Soliris) for the treatment of PNH (concomitant use with Voydeya is allowed).

Atypical Hemolytic Uremic Syndrome (aHUS)[1]

Authorization of 6 months may be granted for treatment of atypical hemolytic uremic syndrome (aHUS) that is not caused by Shiga toxin when all of the following criteria are met:

- Absence of Shiga toxin.
- The requested medication will not be used in combination with another complement inhibitor (e.g., Soliris) for the treatment of aHUS.

Generalized Myasthenia Gravis (gMG)[1,6,7,9]

Authorization of 6 months may be granted for treatment of generalized myasthenia gravis (gMG) when all of the following criteria are met:

- Anti-acetylcholine receptor (AChR) antibody positive.
- Myasthenia Gravis Foundation of America (MGFA) clinical classification II to IV.
- MG activities of daily living (MG-ADL) total score of greater than or equal to 5.
- Meets one of the following:
    - Member has had an inadequate response or intolerable adverse event to at least two immunosuppressive therapies over the course of at least 12 months (e.g., azathioprine, corticosteroids, cyclosporine, methotrexate, mycophenolate, tacrolimus).
    - Member has had an inadequate response or intolerable adverse event to at least one immunosuppressive therapy and intravenous immunoglobulin (IVIG) over the course of at least 12 months.
    - Member has a documented clinical reason to avoid therapy with immunosuppressive agents and IVIG.
- The requested medication will not be used in combination with another complement inhibitor (e.g., Soliris, Zilbrysq) or neonatal Fc receptor blocker (e.g., Vyvgart, Vyvgart Hytrulo, Rystiggo).

Neuromyelitis Optica Spectrum Disorder (NMOSD)[1,10]

Authorization of 6 months may be granted for treatment of neuromyelitis optica spectrum disorder (NMOSD) when all of the following criteria are met:

- Anti-aquaporin-4 (AQP4) antibody positive.
- Member exhibits one of the following core clinical characteristics of NMOSD:
    - Optic neuritis
    - Acute myelitis
    - Area postrema syndrome (episode of otherwise unexplained hiccups or nausea and vomiting)
    - Acute brainstem syndrome

  - Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
  - Symptomatic cerebral syndrome with NMOSD-typical brain lesions
- The member will not receive the requested medication concomitantly with other biologics for the treatment of NMOSD.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy (e.g., improvement in hemoglobin levels, normalization of lactate dehydrogenase [LDH] levels).
- The requested medication will not be used in combination with another complement inhibitor (e.g., Empaveli, Fabhalta, Piasky, Soliris) for the treatment of PNH (concomitant use with Voydeya is allowed).

Atypical Hemolytic Uremic Syndrome (aHUS)

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy (e.g., normalization of lactate dehydrogenase [LDH] levels, platelet counts).
- The requested medication will not be used in combination with another complement inhibitor (e.g., Soliris) for the treatment of aHUS.

Generalized Myasthenia Gravis (gMG)

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy (e.g., improvement in MG-ADL score, MG Manual Muscle Test (MMT), MG Composite).
- The requested medication will not be used in combination with another complement inhibitor (e.g., Soliris, Zilbrysq) or neonatal Fc receptor blocker (e.g., Vyvgart, Vyvgart Hytrulo, Rystiggo).

Neuromyelitis Optica Spectrum Disorder (NMOSD)

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with the requested medication.
- The member is receiving benefit from therapy (e.g., reduction in number of relapses as compared to baseline).
- The member will not receive the requested medication concomitantly with other biologics for the treatment of NMOSD.

Dosage and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Ultomiris.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- Management of paroxysmal nocturnal hemoglobinuria in the era of complement inhibitory therapy.
- Guidelines for the Diagnosis and Monitoring of Paroxysmal Nocturnal Hemoglobinuria and Related Disorders by Flow Cytometry.
- International consensus guidance for management of myasthenia gravis.
- International consensus diagnostic criteria for neuromyelitis optica spectrum disorders.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Ultomiris are covered.

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using percentage of PNH cells or percentage of GPI-AP deficiency poly-morphonuclear cells can be found in the guidelines for diagnosis of PNH (Borowitz et al and Preis et al). Flow cytometry is the gold standard for assessing the percentage of GPI-AP deficient poly-morphonuclear cells. Classic PNH is defined as greater than 50% of GPI-AP deficient PMNs. It is also possible to diagnose PNH by assessing the percentage of PNH cells. Most clinical trials for the complement inhibitors required at least 10% PNH cells, but the trials associated with Ultomiris only required 5% PNH cells. Therefore, the baseline requirement for all complement inhibitor programs will be at least 5%.

Currently there are no treatment guidelines or literature supporting the concomitant use of complement inhibitors (e.g., Empaveli, Fabhalta, Piasky, Soliris) for the treatment of PNH.

Currently there are no treatment guidelines or literature supporting the concomitant use of complement inhibitors (e.g., Soliris) for the treatment of aHUS.

Support for Myasthenia Gravis Activities of Daily Living (MG-ADL) total score of greater than or equal to 5 can be found in the trials associated with Vyvgart and Vyvgart Hytrulo. Most clinical trials of myasthenia gravis agents required a MG-ADL of greater than or equal to 6, however, to align myasthenia gravis programs the baseline requirement will be greater than or equal to 5. MG-ADL is a scale that assesses the impact of myasthenia gravis on daily functions. This scale was used as an assessment tool to evaluate response to myasthenia gravis treatment from baseline in the clinical trials.

Support for the trial of immunosuppressive agents and IVIG before initiating therapy with Ultomiris can be found in the 2020 update to the international consensus guidance for management of myasthenia gravis. The update was completed prior to the approval of several new myasthenia gravis agents; however, the guidance includes recommendations for initiating treatment with a complement inhibitor (eculizumab [Soliris]). The recommendations indicate that eculizumab should be considered in the treatment of severe, refractory myasthenia gravis (after trials of other immunotherapies have been unsuccessful in meeting treatment goals).

Currently there are no treatment guidelines or literature supporting the concomitant use of complement inhibitors (e.g., Soliris, Ultomiris, Zilbrysq) or neonatal Fc receptor blockers (e.g., Vyvgart, Vyvgart Hytrulo, Rystiggo).

Support for the list of core clinical characteristics of NMOSD can be found in the International Consensus Diagnostic Criteria for Neuromyelitis Optica Spectrum Disorder (Wingerchuk et al). There are six clinical characteristics cited in the diagnostic criteria:

- Optic neuritis
- Acute myelitis
- Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
- Acute brainstem syndrome
- Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical
- diencephalic MRI lesions

- Symptomatic cerebral syndrome with NMOSD-typical brain lesions

Currently there are no treatment guidelines or literature supporting the concomitant use with other biologics for the treatment of NMOSD.

Dosage and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

References

1. Ultomiris [package insert]. Boston, MA: Alexion Pharmaceuticals, Inc.; September 2024.
2. Parker CJ. Management of paroxysmal nocturnal hemoglobinuria in the era of complement inhibitory therapy. Hematology. 2011; 21-29.
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4. Borowitz MJ, Craig F, DiGiuseppe JA, et al. Guidelines for the Diagnosis and Monitoring of Paroxysmal Nocturnal Hemoglobinuria and Related Disorders by Flow Cytometry. Cytometry B Clin Cytom. 2010: 78: 211-230.
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7. Tuan Vu, Andreas Meisel, Renato Mantegazza, et al. Terminal Complement Inhibitor Ravulizumab in Generalized Myasthenia Gravis. NEJM Evid 2022; 1 (5).
8. Dezern AE, Borowitz MJ. ICCS/ESCCA consensus guidelines to detect GPI-deficient cells in paroxysmal nocturnal hemoglobinuria (PNH) and related disorders part 1 - clinical utility. Cytometry B Clin Cytom. 2018 Jan;94(1):16-22.
9. Barnett C, Herbelin L, Dimachkie MM, Barohn RJ. Measuring Clinical Treatment Response in Myasthenia Gravis. Neurol Clin. 2018 May;36(2):339-353.
10. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015; 85:177-189.