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Section:	Prescription Drugs	**Effective Date:**	April 1, 2024
Subsection:	Hematological Agents	**Original Policy Date:**	January 11, 2019
Subject:	Ultomiris	**Page:**	1 of 7

Last Review Date: March 8, 2024

Ultomiris

Description

Ultomiris (ravulizumab-cwvz)

Background
Ultomiris (ravulizumab-cwvz) is a terminal complement inhibitor indicated for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and generalized myasthenia gravis (gMG). Ultomiris specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex) and preventing the generation of the terminal complement complex C5b9. Ultomiris inhibits terminal complement-mediated intravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH) and complement-mediated thrombotic microangiopathy (TMA) in patients with atypical hemolytic uremic syndrome (aHUS). The precise mechanism by which Ultomiris exerts its therapeutic effect in gMG is presumed to involve reduction of terminal complement complex C5b-9 deposition at the neuromuscular junction (1).

Regulatory Status
FDA-approved indications: Ultomiris is a complement inhibitor indicated for: (1)

1. the treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH).
2. the treatment of adults and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).

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

3. the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive.

The International Consensus Guidance for Management of Myasthenia Gravis recommends the use of chronic IVIG and immunosuppressants (2).

Ultomiris includes a boxed warning citing the risk of life-threatening and fatal meningococcal infections/sepsis. Additionally, all patients must be vaccinated with a meningococcal vaccine at least 2 weeks prior to receiving their first Ultomiris dose, unless the risks of delaying therapy outweigh the risks of developing a meningococcal infection (1).

Ultomiris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Ultomiris REMS, prescribers must enroll in the program (1).

In addition, Ultomiris has warnings regarding infusion-related reactions and using caution when administering Ultomiris to patients with any other systemic infections. Ultomiris blocks terminal complement activation; therefore, patients may have increased susceptibility to infections, specifically encapsulated bacteria (1).

Ultomiris is contraindicated in patients with unresolved Neisseria meningitidis infection, and in patients who are not currently vaccinated against Neisseria meningitidis, unless risk of delaying Ultomiris treatment outweighs the risks of developing a meningococcal infection (1).

The safety and effectiveness of Ultomiris for PNH or aHUS in pediatric patients less than one month of age have not been established. The safety and effectiveness of Ultomiris for gMG in pediatric patients less than 18 years of age have not been established (1).

Related policies
Empaveli, Soliris

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Ultomiris may be considered **medically necessary** if the conditions indicated below are met.

Ultomiris may be considered **investigational** for all other indications.

Prior-Approval Requirements

Diagnoses

Patient must have **ONE** of the following:

1. Paroxysmal nocturnal hemoglobinuria (PNH)
    a. 1 month of age or older
    b. Documented baseline value for serum lactate dehydrogenase (LDH)
    c. **NO** dual therapy with another Prior Authorization (PA) medication for PNH (see Appendix 1)
2. Atypical hemolytic uremic syndrome (aHUS)
    a. 1 month of age or older
    b. Documented baseline value for serum lactate dehydrogenase (LDH)
    c. Patient does **NOT** have Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS)
    d. **NO** dual therapy with another Prior Authorization (PA) medication for aHUS (see Appendix 2)
3. Generalized myasthenia gravis (gMG)
    a. 18 years of age or older
    b. Positive serologic test for anti-AChR antibodies
    c. Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV
    d. Documented baseline Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score ≥ 6
    (*http://c.peerview.com/inReview/programs/150204324/downloads/PVI_practiceaids_RMU.pdf*)
    e. Patient has had an inadequate treatment response, intolerance, or contraindication to an acetylcholinesterase inhibitor and at least **ONE** immunosuppressive therapy either in combination or as monotherapy, such as:
        i. azathioprine
        ii. cyclosporine
        iii. mycophenolate mofetil
        iv. tacrolimus
        v. methotrexate
        vi. cyclophosphamide

f. **NO** dual therapy with another Prior Authorization (PA) C5 complement inhibitor for gMG (see Appendix 3)

AND ALL of the following:

a. Vaccination against Neisseria meningitidis at least 2 weeks prior to initiation [unless Ultomiris (ravulizumab-cwvz) treatment cannot be delayed]
b. Prescriber is enrolled in Ultomiris REMS program

Prior – Approval *Renewal* Requirements

Diagnoses

Patient must have **ONE** of the following:

1. Paroxysmal nocturnal hemoglobinuria (PNH)
    a. 1 month of age or older
    b. Decrease in serum LDH from pretreatment baseline
    c. **NO** dual therapy with another Prior Authorization (PA) medication for PNH (see Appendix 1)
2. Atypical hemolytic uremic syndrome (aHUS)
    a. 1 month of age or older
    b. Decrease in serum LDH from pretreatment baseline
    c. Patient does **NOT** have Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS)
    d. **NO** dual therapy with another Prior Authorization (PA) medication for aHUS (see Appendix 2)
3. Generalized myasthenia gravis (gMG)
    a. 18 years of age or older
    b. Decrease of MG-ADL total score from baseline of ≥ 2 points (*http://c.peerview.com/inReview/programs/150204324/downloads/PVI_practiceaids_RMU.pdf*)
    c. **NO** dual therapy with another Prior Authorization (PA) C5 complement inhibitor for gMG (see Appendix 3)

AND ALL of the following:

a. Absence of unacceptable toxicity from the drug
b. Prescriber is enrolled in Ultomiris REMS program

Policy Guidelines

Pre – PA Allowance

None

Prior - Approval Limits

Duration 6 months

Prior – Approval *Renewal* Limits

Duration 12 months

Rationale

Summary

Ultomiris (ravulizumab-cwvz) is a terminal complement inhibitor indicated for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and generalized myasthenia gravis (gMG). Ultomiris includes a boxed warning citing the risk of life-threatening and fatal meningococcal infections/sepsis. Ultomiris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). The safety and effectiveness of Ultomiris for PNH or aHUS in pediatric patients less than one month of age have not been established. The safety and effectiveness of Ultomiris for gMG in pediatric patients less than 18 years of age have not been established (1).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Ultomiris while maintaining optimal therapeutic outcomes.

References

1. Ultomiris [package insert]. Boston, MA: Alexion Pharmaceuticals, Inc.; July 2022.
2. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: Executive summary. *Neurology*. 2016; 87(4):419. Epub 2016 Jun 29.

Policy History

Date	Action
January 2019	Addition to PA
March 2019	Annual review
June 2019	Annual review

November 2019	Addition of indication: aHUS. Addition of requirement to not have STEC-HUS and vaccination requirement is only necessary if Ultomiris treatment can be delayed
December 2019	Annual review
September 2020	Annual review
June 2021	Addition of Appendices 1 and 2. Updated no dual therapy requirements. Lowered age requirement for PNH to 1 month and older from 18 years and older per package insert
September 2021	Annual review
May 2022	Addition of indication generalized myasthenia gravis (gMG). Moved requirement of no STEC-HUS under aHUS indication per PI. Addition of Appendix 3
June 2022	Annual review
November 2022	Revised to align with BCBS association policy: removed initiation requirement of t/f of chronic IVIG, revised requirement to include t/f of an acetylcholinesterase inhibitor, added continuation requirement that patient has had fewer relapses on treatment, revised continuation requirement to specify a ≥ 2 point drop in MG-ADL. Changed policy number to 5.85.033
March 2023	Annual review and reference update
June 2023	Annual review
September 2023	Association policy alignment: removed gMG requirement for fewer relapses, changed duration of initiation approval from 12 months to 6 months
December 2023	Annual review
March 2024	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 8, 2024 and is effective on April 1, 2024.

Appendix 1 - List of PA Medications for PNH

Generic Name	Brand Name
eculizumab	Soliris
pegcetacoplan	Empaveli
ravulizumab-cwvz	Ultomiris

Appendix 2 - List of PA Medications for aHUS

Generic Name	Brand Name
eculizumab	Soliris
ravulizumab-cwvz	Ultomiris

Appendix 3 - List of PA C5 complement inhibitors for gMG

Generic Name	Brand Name
eculizumab	Soliris
ravulizumab-cwvz	Ultomiris