Medical Policy:

ULTOMIRIS® (ravulizumab-cwvz)

POLICY NUMBER	LAST REVIEW	ORIGIN DATE
MG.MM.PH.187	January 2, 2024	April 1, 2019

Definitions

Ultomiris is a monoclonal antibody that binds with high affinity to compliment protein C5, which inhibits its cleavage to C5a and C5b and prevents the generation of the terminal complement complex C5b9. As a result, 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). It is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS). Ultomiris is indicated for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive.

Ultomiris has a Boxed Warning for life-threatening meningococcal infections. Patients should be immunized with the meningococcal vaccines at least 2 weeks prior to administering the first dose of Ultomoris, unless the risks of delaying therapy outweigh the risks of developing meningococcal infection. In this case, patients should be provided with 2 weeks of antibacterial drug prophylaxis. Vaccination does not eliminate the risk of infection but reduces the chance. Patients should be immunized accordingly with meningococcal vaccination following most current ACIP guidelines.

Ultimoris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Prescribers must be enrolled in the REMS program to prescribe Ultimoris.

Length of Authorization

I. Initial coverage:

1. Atypical hemolytic uremic syndrome (aHUS): 6 months
2. Generalized myasthenia gravis (gMG): 6 months
3. Paroxysmal nocturnal hemoglobinuria (PNH): 12 months

II. Renewal:

1. All indications can be renewed for 1 year

Dosing Limits [Medical Benefit]

Max Units (per dose and over time):

ULTOMIRIS Vial for Intravenous (IV) Administration Weight-Based Dosing Regimen – PNH, aHUS, or gMG*

Indications	Body Weight Range (kg)	Loading Dose (mg)**	Maintenance Dose (mg) and Dosing Interval	
PNH and aHUS	5 to less than 10	600	300	Every 4 weeks
	10 to less than 20	600	600	
	20 to less than 30	900	2,100	Every 8 weeks
	30 to less than 40	1,200	2,700	
PNH, aHUS, and gMG	40 to less than 60	2,400	3,000	Every 8 weeks
	60 to less than 100	2,700	3,300	
	100 or greater	3,000	3,600	

Guideline

I. Initial Approval Criteria

Ultomiris may *be considered medically necessary if the below condition is met **AND** use is consistent with the medical necessity criteria that follows:*

1. **Paroxysmal Nocturnal Hemoglobinuria.** Approve if the patient meets ONE of the following (A or B):
   A. Initial therapy. Approve if the patient meets the following criteria (i, ii, and iii):
      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; **AND**
      iii. Patient is 1 month of age or older

B. Patient is Currently Receiving Ultomiris (intravenous or subcutaneous). Approve if the patient meets the following criteria (i and ii):
   i. Patient is continuing to derive benefit from Ultomiris (intravenous or subcutaneous), according to the prescriber.
   Note: Examples of benefit from Ultomiris (intravenous or subcutaneous) include stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis.
   ii. The medication is prescribed by or in consultation with a hematologist.

2. **Atypical Hemolytic Uremic Syndrome.** Approve if the patient meets the following criteria (A, B, and C):
   A. Patient does not have Shiga toxin *E. coli* related hemolytic uremic syndrome; **AND**
   B. Patient is at least one month of age or older and weighs ≥5 kg; **AND**
   C. The medication is prescribed by or in consultation with a nephrologist

3. **Generalized Myasthenia Gravis.** Approve if the patient meets ONE of the following criteria (A or B):
   A. Initial therapy. Approve if the patient meets the following criteria (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 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 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 tried include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, and cyclophosphamide.
      vi. Patient has evidence of unresolved symptoms of generalized myasthenia gravis, such as difficulty swallowing, difficulty breathing, or a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility); **AND**
      vii. The medication is being prescribed by or in consultation with a neurologist.
   B. Patient is Currently Receiving Ultomiris intravenous. Approve if the patient meets the following (i, ii, and iii):
      i. Patient is ≥ 18 years of age; **AND**
      ii. Patient is continuing to derive benefit from Ultomiris intravenous, according to the prescriber; **AND**
      Note: Examples of derived benefit include reductions in exacerbations of myasthenia gravis; improvements in speech, swallowing, mobility, and respiratory function.
      iii. The medication is being prescribed by or in consultation with a neurologist.

Limitations/Exclusions

Ultomiris is not considered medically necessary for when any of the following selection criteria is met:

1. Patient is not currently receiving treatment and is asymptomatic or has mild symptoms. Active surveillance is clinically appropriate, without the need for therapy in this subset of patients.
2. Patient has unresolved Neisseria meningitidis

3. Patient is currently not vaccinated against N. meningitidis, unless the risks of delaying treatment outweigh the risks of developing a meningococcal infection.
4. Will not be used in combination with other immunomodulatory biologic therapies (i.e., efgartigimod, eculizumab, pegcetacoplan, satralizumab, inebilizumab, etc.)

Applicable Procedure Codes

Code	Description
J1303	Injection, ravulizumab-cwvz, 10 mg

Applicable NDCs

Code	Description
25682-0025-xx	Ultomiris 300 mg/3 mL single-dose vials for injection
25682-0028-xx	Ultomiris 1100 mg/11 mL single-dose vials for injection

ICD-10 Diagnoses

Code	Description
D59.5	Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]
D59.3	Hemolytic-uremic syndrome
G70.00	Myasthenia gravis without (acute) exacerbation
G70.01	Myasthenia gravis with (acute) exacerbation

Revision History

Company(ies)	DATE	REVISION
EmblemHealth & ConnectiCare	1/2/2024	Annual Review: Initial Criteria: Generalized Myasthenia Gravis Updated "Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 5 to ≥ 6
EmblemHealth & ConnectiCare	04/13/2023	Annual Review: corrected formatting; Added Exclusion Criteria: Will not be used in combination with other immunomodulatory biologic therapies (i.e., efgartigimod, eculizumab, pegcetacoplan, satralizumab, inebilizumab, etc.); PNH- Criteria: Removed: C. At least 10% PNH type III red cells; AND D. Patient has an LDH level of 1.5 times the upper limit of the normal range; AND E. Patient has greater than 50% of glycosylphosphatidylinositol-anchored proteins (GPI-AP)- deficient polymorphonuclear cells (PMNs); AND F. Patient is transfusion dependent as defined by one of the following: i. Hemoglobin < 7 g/dL; OR ii. Hemoglobin < 9 g/dL AND patient is experiencing symptoms of anemia; AND G. Patient has symptoms of thromboembolic complications (abdominal pain, shortness of breath, chest pain, end organ damage; AND

		H. Patient will or has received a meningococcal vaccine at least two weeks before start Ultomiris treatment; AND I. Ultomiris is being prescribed by or in consultation with an oncologist or immunology specialist. aHUS Criteria: Removed: ii. Thrombotic thrombocytopenia purpura (TTP) (e.g., rule out ADAMTS13 deficiency); AND C. Laboratory results, signs, and/or symptoms attributed to aHUS (e.g., thrombocytopenia, microangiopathic hemolysis, thrombotic microangiopathy, acute renal failure, etc.); AND D. Patient will or has received a meningococcal vaccine at least two weeks before start Ultomiris treatment; AND E. Prescribed by a hematologist Generalized Myasthenia Gravis Criteria: Removed: -weighs >40kg; - ii. Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 6; i. Patient received or is currently receiving at least ONE agent used for the treatment of myasthenia gravis (ie, pyridostigmine, corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, cyclophosphamide); OR ii. Patient has had inadequate efficacy, a contraindication, or significant intolerance to the above; Added: b) Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 5; a) Patient 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 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 tried include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, and cyclophosphamide. Removed: II. Renewal Criteria 1. Patient has experienced an improvement in fatigue and quality of life; AND 2. Patient has demonstrated a positive clinical response from baseline (e.g., stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis) from Ultomiris, according to the prescribing physician
EmblemHealth & ConnectiCare	11/10/2022	-Updated exclusion criteria to state: 1. Patient is not currently receiving treatment and is asymptomatic or has mild symptoms.
EmblemHealth & ConnectiCare	10/26/2022	-Added newly approved indication of gMG. -Updated age restriticitons on aHUS and PNH -Updated Dosing and Max dosing limits -Updated NDC(s) available

EmblemHealth & ConnectiCare	10/28/2019	-Ultomiris definition was expanded to include PI updates for PNH, TMA, aHUS. Added in Boxed warning, and REMS program. -Length of Authorization – updated Initial coverage will be provided for 6 months for aHUS and 12 months for PNH and it may be renewed. -Updated dosing per PI for PNH, aHUS
EmblemHealth & ConnectiCare	8/15/2019	Removed code J3590, added new code J1303, effective 10/1/19.
EmblemHealth & ConnectiCare	7/1/2019	Removed unclassified code C9399. Added new Code C9052
EmblemHealth & ConnectiCare	4/1/2019	New Policy

References

1. Ultomiris® [prescribing information]. Boston, MA: Alexion Pharmaceuticals, Inc.; Accessed October 2022.
2. Micromedex® Healthcare Series: Thomson Micromedex, Greenwood Village, Co. 2022.
3. Clinical Pharmacology Elsevier Gold Standard. 2018.
4. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD. 2018.