Oscar Clinical Guideline: Ultomiris (ravulizumab-cwvz) (PG189, Ver. 1)

Ultomiris (ravulizumab-cwvz)

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Ultomiris (ravulizumab-cwvz) is a humanized monoclonal antibody that specifically binds to the complement protein C5, inhibiting its cleavage into C5a and C5b, thereby preventing the generation of the terminal complement complex C5b-9. By inhibiting the terminal complement pathway, Ultomiris (ravulizumab-cwvz) reduces intravascular hemolysis in PNH, complement-mediated TMA in aHUS, and anti-AChR antibody-induced complement damage at the NMJ in gMG. Ultomiris (ravulizumab-cwvz) is FDA-approved for the treatment of PNH and aHUS in adults and children ≥ 1 month of age, and anti-AChR antibody positive gMG in adults. It is available as an intravenous formulation for all indications and a subcutaneous formulation for adult patients with PNH and aHUS.

Definitions

"**Atypical hemolytic uremic syndrome (aHUS)**" is an ultra-rare, life-threatening genetic disorder caused by chronic, uncontrolled activation of the alternative complement pathway, resulting in complement-mediated thrombotic microangiopathy (TMA).

"**Generalized myasthenia gravis (gMG)**" is an autoimmune neuromuscular disease caused by antibodies that attack components of the neuromuscular junction (NMJ), impairing transmission between nerve and muscle, resulting in muscle weakness and fatigue.

"**Myasthenia Gravis Activities of Daily Living (MG-ADL) score**" is a validated, 8-item patient-reported scale that assesses the impact of myasthenia gravis on daily functions.

"**Myasthenia Gravis Foundation of America (MGFA) Clinical Classification**" is a commonly used classification system that defines myasthenia gravis severity based on the degree and distribution of muscle weakness.

"**Paroxysmal nocturnal hemoglobinuria (PNH)**" refers to a rare, acquired, life-threatening disease of the blood characterized by complement-mediated hemolysis, thrombosis, and bone marrow failure.

"**Quantitative Myasthenia Gravis (QMG) score**" is a 13-item physician-administered scale that measures the severity of myasthenia gravis based on muscle weakness assessment.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Ultomiris (ravulizumab-cwvz)** medically necessary when **ALL** the following criteria are met for the applicable indication listed below:

1. Prescribed by, or in consultation with, a physician who specializes in the treatment of the specific condition:
    a. Atypical hemolytic uremic syndrome (aHUS) - hematologist or nephrologist; ***or***
    b. Generalized myasthenia gravis (gMG) - neurologist or neuromuscular disease specialist; ***or***
    c. Paroxysmal Nocturnal Hemoglobinuria (PNH) - hematologist; ***AND***
2. Will not be used concomitantly with other immunomodulatory biologic therapies (e.g., eculizumab, efgartigimod alfa, rituximab, rozanolixizumab, zilucoplan, etc.); ***AND***
3. Dosing is consistent with FDA-approved labeling **OR** is supported by compendia or evidence-based published dosing guidelines based on indication, weight, and age; ***AND***

4. The member meets the medical necessity criteria for the applicable indication listed below:

For members currently receiving Soliris (eculizumab):

5. The member has a confirmed diagnosis of ONE of the following:
    a. Atypical hemolytic uremic syndrome (aHUS)***; or***
    b. Generalized myasthenia gravis (gMG)***; or***
    c. Paroxysmal Nocturnal Hemoglobinuria (PNH)***; AND***
6. The member is currently receiving treatment with Soliris (eculizumab)***; AND***
7. The member has had an adequate response to Soliris (eculizumab) therapy, as evidenced by improvement or stabilization in disease-related signs and symptoms specific to their condition.

Atypical hemolytic uremic syndrome (aHUS)

5. The member is at least 1 month of age; ***AND***
6. The member has a diagnosis of diagnosis of aHUS confirmed by ruling out:
    a. Thrombotic thrombocytopenic purpura (TTP), e.g., ADAMTS13 activity level above 5%; ***and***
    b. Shiga toxin E. coli-related HUS (STEC-HUS), e.g., STEC-test negative in members with a history of bloody diarrhea in the preceding 2-weeks; ***AND***
7. The member has documented presence of thrombotic microangiopathy, as evidenced by ALL of the following:
    a. Microangiopathic hemolytic anemia (e.g., anemia, increased LDH, decreased haptoglobin, increased indirect bilirubin, increased AST, elevated reticulocyte count, presence of schistocytes, helmet cells, and burr cells on peripheral blood smear)***; and***
    b. Thrombocytopenia, defined as a platelet count below 150,000/microliter***; and***
    c. Acute kidney injury (e.g., elevated serum creatinine, oliguria, presence of hematuria, proteinuria, pyuria, casts on urinalysis) or member requires dialysis.

Generalized myasthenia gravis (gMG)

5. The member is 18 years of age or older; ***AND***
6. The member has a confirmed diagnosis of generalized myasthenia gravis (gMG) **AND** documentation of **ALL** of the following:
    a. Positive serologic test for anti-acetylcholine receptor (anti-AChR) antibodies; ***and***
    b. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV (*see* Appendix*, **Table 1***); ***and***

c. Baseline Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score of at least (≥) 6; ***AND***

7. **T**he member is unable to use, limited by toxicity, or has adequately tried and failed or experienced insufficient response to at least **TWO** standard therapies for gMG, such as:
    a. Cholinesterase inhibitors (eg, pyridostigmine); ***and/or***
    b. Corticosteroids (e.g., prednisone) or inability to taper steroids below a reasonably acceptable level without return of symptoms; ***and/or***
    c. Immunosuppressive therapies (e.g., azathioprine, cyclosporine, mycophenolate mofetil, cyclophosphamide, tacrolimus).

<u>Paroxysmal Nocturnal Hemoglobinuria (PNH)</u>

5. The member is at least 1 month of age; ***AND***
6. Diagnosis of PNH confirmed by flow cytometry demonstrating a deficiency of glycosylphosphatidylinositol-anchored proteins (GPI-APs) with EITHER of the following::
    a. at least 5% PNH cells; ***or***
    b. at least 51% of GPI-deficient poly-morphonuclear cells; ***AND***
7. The member has documentation of one or more of the following:
    a. Hemoglobin ≤ 9 g/dL with symptomatic anemia, or hemoglobin ≤ 7 g/dL; ***and/or***
    b. Absolute reticulocyte count ≥ 2 times the upper limit of normal; ***and/or***
    c. Thrombosis; ***and/or***
    d. Transfusion dependence (≥ 2 transfusions in the last 12 months).

<u>If the above prior authorization criteria are met, Ultomiris (ravulizumab-cwvz) will be authorized for 6-months.</u>

Medical Necessity Criteria for Reauthorization

Reauthorization for 12-months will be granted if the member has recent (within the last 3 months) clinical chart documentation demonstrating **ALL** of the following criteria:

1. Prescribed by, or in consultation with, a physician who specializes in the treatment of the specific condition:
    a. Atypical hemolytic uremic syndrome (aHUS) - hematologist or nephrologist; ***or***
    b. Generalized myasthenia gravis (gMG) - neurologist or neuromuscular disease specialist; ***or***
    c. Paroxysmal Nocturnal Hemoglobinuria (PNH) - hematologist; ***AND***

2. There is no unacceptable toxicity or adverse reaction to therapy, such as:
    a. Serious infections (e.g. serious respiratory or urinary tract infections); ***and/or***
    b. Severe hypersensitivity reactions; ***and/or***
    c. Severe immunosuppression; ***and/or***
    d. Other intolerable side effects or reactions; ***AND***
3. Will not be used concomitantly with other immunomodulatory biologic therapies (e.g., eculizumab, efgartigimod alfa, rituximab, rozanolixizumab, zilucoplan, etc.); ***AND***
4. Dosing is consistent with FDA-approved labeling **OR** is supported by compendia or evidence-based published dosing guidelines based on indication, weight, and age; ***AND***
5. Ongoing therapy is required to maintain disease stability and control; ***AND***
6. Documentation of positive clinical response to therapy, such as ANY of the following:
    a. Atypical Hemolytic Uremic Syndrome (aHUS)
        i. Improvement or normalization of lactate dehydrogenase (LDH) levels and/or haptoglobin; ***and/or***
        ii. Improvement or normalization of platelet counts; ***and/or***
        iii. Improvement in serum creatinine from baseline and/or stabilization of renal function; ***and/or***
        iv. Reduction or absence of schistocytes or fragmented red blood cells on peripheral blood smear; ***and/or***
        v. Improvement in hemoglobin levels from baseline; ***or***
    b. Generalized Myasthenia Gravis
        i. Improvement in Myasthenia Gravis-Activities of Daily Living (MG-ADL) **OR** Quantitative Myasthenia Gravis (QMG) score from baseline; ***and/or***
        ii. Achievement of minimal symptom expression or pharmacological remission; ***and/or***
        iii. Lack of relapses or reduced frequency/severity of relapses compared to baseline; ***or***
    c. Paroxysmal Nocturnal Hemoglobinuria (PNH)
        i. Stabilization of hemoglobin levels; ***and/or***
        ii. Decreased transfusion requirements; ***and/or***
        iii. Reduced hemolysis; ***and/or***
        iv. Improvement in PNH symptoms; ***and/or***
        v. Improvement or normalization of lactate dehydrogenase (LDH) levels.

Experimental or Investigational / Not Medically Necessary

Ultomiris (ravulizumab-cwvz) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Concomitant use with other targeted immunomodulating biologics.
- Other complement-mediated diseases or conditions not listed above as medically necessary.
- Prevention of delayed graft function (DGF) in kidney transplant recipients.
- Shiga toxin Escherichia coli related hemolytic uremic syndrome (STEC-HUS).
- Subcutaneous administration for the treatment of generalized myasthenia gravis.
- Subcutaneous administration in pediatric patients for any indication.
- Treatment of amyotrophic lateral sclerosis (ALS).
- Treatment of thrombotic thrombocytopenic purpura (TTP).
- Use in patients who have unresolved serious *Neisseria meningitidis* infection or are not adequately vaccinated against *Neisseria meningitidis*.

Applicable Billing Codes (HCPCS/CPT Codes)

Service(s) name	
CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
96415	Chemotherapy administration, intravenous infusion technique; each additional hour (List separately in addition to code for primary procedure)
J1303	Injection, ravulizumab-cwvz, 10 mg
ICD-10 codes considered medically necessary if criteria are met:	
Code	*Description*

D59.3	Hemolytic-uremic syndrome
D59.30	Hemolytic-uremic syndrome, unspecified
D59.31	Infection-associated hemolytic-uremic syndrome
D59.32	Hereditary hemolytic-uremic syndrome
D59.39	Other hemolytic-uremic syndrome
D59.5	Paroxysmal nocturnal hemoglobinuria
G70.00	Myasthenia gravis without (acute) exacerbation
G70.01	Myasthenia gravis with (acute) exacerbation

Appendix

Table 1: Summary of Myasthenia Gravis Foundation of America (MGFA) Disease Clinical Classification

Class	*Description*
I	Ocular muscle weakness; All other muscles - normal strength
II	Mild generalized weakness
IIa	Predominantly limb/axial weakness; Lesser oropharyngeal involvement possible
IIb	Predominantly oropharyngeal/respiratory weakness; Lesser limb/axial involvement possible
III	Moderate generalized weakness
IIIa	Predominantly limb/axial weakness; Lesser oropharyngeal involvement possible
IIIb	Predominantly oropharyngeal/respiratory weakness; Lesser limb/axial involvement possible
IV	Severe generalized weakness
IVa	Predominantly limb/axial weakness; Lesser oropharyngeal involvement possible
IVb	Predominantly oropharyngeal/respiratory weakness; Lesser limb/axial involvement possible

V	Intubation, with or without ventilation; Not for routine postoperative care

NOTE: The preceding table summarizes key aspects of the Myasthenia Gravis Foundation of America (MGFA) Disease Classifications. This is provided only for quick reference. For the exact definitions and details on the MGFA Disease Classifications, please refer to the original MGFA Classification document available at https://myasthenia.org/Portals/0/MGFA%20Classification.pdf.

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