

## 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 paroxysmal nocturnal hemoglobinuria (PNH), complement-mediated thrombotic microangiopathy (TMA) in atypical hemolytic uremic syndrome (aHUS), anti-acetylcholine receptor (AChR) antibody-induced complement damage at the neuromuscular junction (NMJ) in generalized myasthenia gravis (gMG), and aquaporin-4 (AQP4) antibody-induced complement-mediated damage in neuromyelitis optica spectrum disorder (NMOSD). Ultomiris (ravulizumab-cwvz) is FDA-approved for:

- Treatment of PNH and aHUS in adults and children  $\geq$  1 month of age
- Treatment of anti-AChR antibody positive gMG in adults
- Treatment of anti-AQP4 antibody positive NMOSD in adults

## 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.

"Neuromyelitis optica spectrum disorder (NMOSD)" is a rare autoimmune disorder of the central nervous system that primarily affects the optic nerves and spinal cord, characterized by inflammation and demyelination caused by aquaporin-4 antibodies.

"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; *or*
  - d. Neuromyelitis optica spectrum disorder (NMOSD) - neurologist or neuro-ophthalmologist; *AND*
2. Will not be used concomitantly with other immunomodulatory biologic therapies (e.g., eculizumab [Soliris], efgartigimod alfa [Vyvgart], rituximab [Rituxan], rozanolixizumab [Rystiggo], zilucoplan[Zilbrysq], 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 (1) of the following:
  - a. Atypical hemolytic uremic syndrome (aHUS); *or*
  - b. Generalized myasthenia gravis (gMG); *or*
  - c. Neuromyelitis optica spectrum disorder (NMOSD) who are anti-AQP4 antibody positive;  
*or*
  - d. 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 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 ( $\geq$ ) 6; *AND*

7. The member is unable to use, limited by toxicity, or has adequately tried and failed or experienced insufficient response to at least TWO (2) 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).

#### Neuromyelitis Optica Spectrum Disorder (NMOSD)

5. The member is 18 years of age or older; *AND*
6. The member has confirmed diagnosis of NMOSD, as evidenced by a positive serologic test for anti-aquaporin-4 (AQP4) antibodies; *AND*
7. The member must have experienced at least 1 relapse in the last 12 months; *AND*
8. The member has an Expanded Disability Status Scale (EDSS) score of  $\leq 7$  (i.e., presence of at least limited ambulation with aid) (see [Appendix](#), Table 2).

#### Paroxysmal Nocturnal Hemoglobinuria (PNH)

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 ONE (1) of the following:
  - a. At least 5% PNH cells (i.e., cells lacking GPI-AP expression); *or*
  - b. At least 51% of GPI-deficient poly-morphonuclear cells (e.g., neutrophils deficient in GPI-APs); *AND*
7. The member has documentation of ONE (1) or more of the following:
  - a. Hemoglobin  $\leq 9$  g/dL with symptomatic anemia, or hemoglobin  $\leq 7$  g/dL; *and/or*
  - b. Absolute reticulocyte count  $\geq 2$  times the upper limit of normal; *and/or*
  - c. Thrombosis; *and/or*
  - d. Transfusion dependence ( $\geq 2$  transfusions in the last 12 months).

If the above prior authorization criteria are met, Ultomiris (ravulizumab-cwvz) will be authorized for up to 6-months.

#### Medical Necessity Criteria for Reauthorization

Reauthorization for up to 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. Neuromyelitis Optica Spectrum Disorder (NMOSD) - neurologist or neuro-ophthalmologist; *or*
  - d. 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. Neuromyelitis Optica Spectrum Disorder (NMOSD)
    - i. Absence of new lesions on MRI; *and/or*
    - ii. Improvement or stabilization of neurologic symptoms; *and/or*
    - iii. Reduction in relapse frequency/severity; *and/or*
    - iv. Reduced hospitalizations; *and/or*
    - v. Reduction/discontinuation in plasma exchange treatment; *or*
  - d. 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. Ultomiris (ravulizumab-cwvz) has not been studied in combination with other targeted immunomodulating biologics.
- Other complement-mediated diseases or conditions not listed above as medically necessary. There is not enough high-quality studies to support the safety and efficacy of Ultomiris (ravulizumab-cwvz) for the management of other complement-mediated diseases or conditions not listed above as medically necessary
- Prevention of delayed graft function (DGF) in kidney transplant recipients. There is not enough high-quality studies to support the safety and efficacy of Ultomiris (ravulizumab-cwvz) for the management of delayed graft function (DGF) in kidney transplant recipients.
- Shiga toxin Escherichia coli related hemolytic uremic syndrome (STEC-HUS). Ultomiris (ravulizumab-cwvz) is explicitly not indicated for the management of (STEC-HUS).
- Subcutaneous administration for the treatment of generalized myasthenia gravis. Ultomiris (ravulizumab-cwvz) is only intended to be administered intravenously for the treatment of generalized myasthenia gravis.
- Subcutaneous administration in pediatric members for any indication. Ultomiris (ravulizumab-cwvz) is only intended to be administered intravenously to pediatric individuals for any indication.
- Treatment of amyotrophic lateral sclerosis (ALS). Only one randomized controlled trial studied Ultomiris (ravulizumab-cwvz) for the management of ALS. After 50 weeks, there was no difference in ALS Functional Rating Scale, and the study was terminated early due to futility.
- Treatment of thrombotic thrombocytopenic purpura (TTP). Studies assessing Ultomiris (ravulizumab-cwvz) have excluded those with thrombotic thrombocytopenic purpura (TTP).
- Use in members who have unresolved serious *Neisseria meningitidis* (*N. meningitidis*) infection or are not adequately vaccinated against *Neisseria meningitidis*. Those receiving Ultomiris (ravulizumab-cwvz) are at increased risk for invasive disease caused by *N. meningitidis*, even if they develop antibodies following vaccination.

#### Applicable Billing Codes (HCPCS/CPT Codes)

Service(s) name
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CPT/HCPCS Codes considered medically necessary if criteria are met:	
<i>Code</i>	<i>Description</i>
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:	
<i>Code</i>	<i>Description</i>
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
G36.0	Neuromyelitis optica
G70.00	Myasthenia gravis without (acute) exacerbation
G70.01	Myasthenia gravis with (acute) exacerbation
G70.02	Congenital and developmental myasthenia

## Appendix

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

<i>Class</i>	<i>Description</i>
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>.

Table 2: Expanded Disability Status Scale (EDSS)

Score	Description
0	Normal neurological examination, no disability in any functional system
1.0	No disability, minimal signs in one functional system
1.5	No disability, minimal signs in more than one functional system
2.0	Minimal disability in one functional system
2.5	Mild disability in one functional system or minimal disability in two functional systems
3.0	Moderate disability in one functional system, or mild disability in three or four functional systems. No walking impairment
3.5	Moderate disability in one functional system and more than minimal disability in several others. No walking impairment
4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m
4.5	Significant disability but up and about much of the day. Able to work a full day. May otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m



5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m
5.5	Disability severe enough to prevent full daily activities. Able to walk without aid or rest for 100m
6.0	Requires a walking aid – cane, crutch, etc. – to walk about 100m with or without resting
6.5	Requires two walking aids – pair of canes, crutches, etc. – to walk about 20m without resting
7.0	Unable to walk beyond approximately 5m even with aid. Essentially restricted to a wheelchair; though wheels a standard wheelchair and able to get in and out alone. Up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps. Restricted to a wheelchair and may need help getting in and out. Can wheel but cannot carry on in a standard wheelchair for a full day and may require a motorised wheelchair
8.0	Essentially restricted to a bed or chair or being pushed in wheelchair. May be out of bed much of the day. Retain many self-care functions. Generally has effective use of arms
8.5	Essentially restricted to a bed for much of the day. Has some effective use of arms, retains some self-care functions
9.0	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10.0	Death due to MS

**NOTE:** The preceding table summarizes key aspects of the Expanded Disability Status Scale (EDSS). This is provided only for quick reference. For the exact definitions and details on the EDSS, please refer to the original EDSS document available at <https://mstrust.org.uk/a-z/expanded-disability-status-scale-edss>

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