Medical Policy Manual **Approved Rev: Do Not Implement until 1/30/27**

Ravulizumab-cwvz (Ultomiris®)

Requires Step Therapy See "Step Therapy Requirements for Provider Administered Specialty Medications" Document at: https://www.bcbst.com/docs/providers/Comm_BC_PAD_Step_Therapy_Guide.pdf

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the medical policy and a health plan or government program (e.g., TennCare), the express terms of the health plan or government program will govern.

POLICY

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

- 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 are considered experimental/investigational and not medically necessary.

DOCUMENTATION

Submission of the following information is necessary to initiate the prior authorization review:

- For initial requests:
  - Paroxysmal nocturnal hemoglobinuria: Flow cytometry used to show results of glycosylphosphatidylinositol-anchored proteins (GPI-APs) deficiency.
  - Atypical hemolytic uremic syndrome: ADAMTS 13 level.
  - Generalized myasthenia gravis:
    - Positive anti-acetylcholine receptor (AChR) antibody test.
    - Myasthenia Gravis Foundation of America (MGFA) clinical classification.
    - MG activities of daily living (MG-ADL) 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 positive clinical response.

PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with one of the following:

- Generalized myasthenia gravis (gMG) and neuromyelitis optica spectrum disorder (NMOSD): neurologist.

COVERAGE CRITERIA

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Authorization of 12 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., lactate dehydrogenase [LDH] > 1.5 upper limit of normal [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)

Authorization of 12 months may be granted for treatment of atypical hemolytic uremic syndrome (aHUS) not caused by Shiga toxin when all of the following criteria are met:

- Absence of Shiga toxin.
- ADAMTS 13 activity level above 5%.
- 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 of 12 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), neonatal Fc receptor blocker (e.g., Imaavy, Vyvgart, Vyvgart Hytrulo, Rystiggo) or Uplizna.

Neuromyelitis Optica Spectrum Disorder (NMOSD)

Authorization of 12 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

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization when all of the following criteria are met:

- There is no evidence of unacceptable toxicity or disease progression while on the current regimen.
- The member demonstrates a positive response to 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 of 12 months may be granted for continued treatment in members requesting reauthorization when all of the following criteria are met:

- There is no evidence of unacceptable toxicity or disease progression while on the current regimen.
- The member demonstrates a positive response to 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 of 12 months may be granted for continued treatment in members requesting reauthorization when all of the following criteria are met:

- There is no evidence of unacceptable toxicity or disease progression while on the current regimen.
- The member demonstrates a positive response to 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), neonatal Fc receptor blocker (e.g., Imaavy, Vyvgart, Vyvgart Hytrulo, Rystiggo) or Uplizna.

Neuromyelitis Optica Spectrum Disorder (NMOSD)

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization when all of the following criteria are met:

- There is no evidence of unacceptable toxicity or disease progression while on the current regimen.
- The member demonstrates a positive response to therapy (e.g., reduction in number of relapses).
- 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.

MEDICATION QUANTITY LIMITS

Drug Name	Diagnosis	Maximum Dosing Regimen
Ultomiris (Ravulizumab)	Atypical Hemolytic Uremic Syndrome (aHUS)	Route of Administration: Intravenous ≥1 month(s) 5-9kg: Initial: 600mg once Maintenance: 300mg every 4 weeks, starting 2 weeks after loading dose 10-19kg: Initial: 600mg once Maintenance: 600mg every 4 weeks, starting 2 weeks after loading dose 20-29kg: Initial: 900mg once Maintenance: 2100mg every 8 weeks, starting 2 weeks after loading dose 30-39kg: Initial: 1200mg once Maintenance: 2700mg every 8 weeks, starting 2 weeks after loading dose 40-59kg: Initial: 2400mg once Maintenance: 3000mg every 8 weeks, starting 2 weeks after loading dose 60-99kg: Initial: 2700mg once Maintenance: 3300mg every 8 weeks, starting 2 weeks after loading dose >100kg: Initial: 3000mg once Maintenance: 3600mg every 8 weeks, starting 2 weeks after loading dose

Ultomiris (Ravulizumab)	Generalized Myasthenia Gravis (gMG)	Route of Administration: Intravenous ≥18 year(s) 40-59kg Initial: 2400mg once Maintenance: 3000mg every 8 weeks, starting 2 weeks after loading dose 60-99kg Initial: 2700mg once Maintenance: 3300mg every 8 weeks, starting 2 weeks after loading dose >100kg Initial:3000mg once Maintenance: 3600mg every 8 weeks, starting 2 weeks after loading dose
Ultomiris (Ravulizumab)	Neuromyelitis Optica Spectrum Disorder (NMOSD)	Route of Administration: Intravenous ≥18 year(s) 40-59kg Initial: 2400mg once Maintenance: 3000mg every 8 weeks, starting 2 weeks after loading dose 60-99kg Initial: 2700mg once Maintenance: 3300mg every 8 weeks, starting 2 weeks after loading dose >100kg Initial: 3000mg once Maintenance: 3600mg every 8 weeks, starting 2 weeks after loading dose
Ultomiris (Ravulizumab)	Paroxysmal Nocturnal Hemoglobinuria (PNH)	Route of Administration: Intravenous ≥1 month(s) 5-9kg Initial: 600mg once Maintenance: 300mg every 4 weeks, starting 2 weeks after loading dose 10-19kg Initial: 600mg once Maintenance: 600mg every 4 weeks, starting 2 weeks after loading dose 20-29kg Initial: 900mg once Maintenance: 2100mg every 8 weeks, starting 2 weeks after loading dose 30-39kg Initial: 1200mg once Maintenance: 2700mg every 8 weeks, starting 2 weeks after loading dose 40-59kg Initial: 2400mg once Maintenance: 3000mg every 8 weeks, starting 2 weeks after loading dose 60-99kg

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		Initial: 2700mg once Maintenance: 3300mg every 8 weeks, starting 2 weeks after loading dose >100kg Initial: 3000mg once Maintenance: 3600mg every 8 weeks, starting 2 weeks after loading dose

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

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Policy

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