BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 10/14/24**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE: 08/15/24**
	CURRENT EFFECTIVE DATE: 10/14/24
	LAST CRITERIA REVISION DATE:
NEXT ANNUAL REVIEW DATE: 3RD QTR 2025	**ARCHIVE DATE:**

SOLIRIS® (eculizumab)
ULTOMIRIS® (ravulizumab-cwvz)

Non-Discrimination Statement is located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.

This Evidence-Based Criteria provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Evidence-Based Criteria are subject to change as new information becomes available.

For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 10/14/24**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE: 08/15/24**
	CURRENT EFFECTIVE DATE: 10/14/24
	LAST CRITERIA REVISION DATE:
NEXT ANNUAL REVIEW DATE: 3RD QTR 2025	**ARCHIVE DATE:**

SOLIRIS® (eculizumab)
ULTOMIRIS® (ravulizumab-cwvz)

Criteria:

Refer to FDA website for current indications and dosage.

SECTION A. Atypical hemolytic uremic syndrome

- **Criteria for initial therapy:** Soliris (eculizumab) or Ultomiris (ravulizumab-cwvz) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Hematologist or Nephrologist

  2. Individual is 2 months of age or older

  3. Individual has a confirmed diagnosis of atypical hemolytic uremic syndrome (aHUS) with **ALL** of the following:

     - Clinical signs or symptoms of thrombotic microangiopathy (e.g., thrombocytopenia, acute renal failure, thrombosis, seizures, etc.)
     - Diagnosis of thrombocytopenic purpura (TTP) has been excluded (e.g., aDAMTS 13 activity ≥10%)
     - Diagnosis of Shiga toxin *Escherichia coli* related hemolytic uremic syndrome (STEC-HUS) has been excluded

  4. There are **NO** contraindications, including unresolved serious *Neisseria meningitidis* infection

  5. Individual has been vaccinated against Neisseria meningitidis at least 2 weeks prior to initiation of therapy, unless treatment cannot be delayed

  6. Prescribing physician is enrolled in the appropriate Risk Evaluation and Mitigation Strategies (REMS) program

  7. Soliris or Ultomiris will not be used in combination with another complement C5 inhibitor (e.g., Zilbrysq, Fabhalta), or other immunosuppressive biologic (e.g., Actemra, Enspryng, Kesimpta, Rinvoq, rituximab, Uplizna, etc.)

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Soliris (eculizumab) or Ultomiris (ravulizumab-cwvz) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by physician specializing in the patient's diagnosis or is in consultation with a Hematologist or Nephrologist

2. Individual's condition has responded while on therapy with response defined as **TWO** of the following:

   - Achieves and maintains an increase in platelet count from baseline
   - Achieves and maintains an improvement in kidney function from baseline
   - Decrease in plasma exchange or plasma infusion interventions
   - Normalization of serum lactate dehydrogenase (LDH)

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use including unresolved serious *Neisseria meningitidis* infection

5. Prescribing physician is enrolled in the appropriate Risk Evaluation and Mitigation Strategies (REMS) program

6. Soliris or Ultomiris will not be used in combination with another complement C5 inhibitor (e.g., Zilbrysq), Fabhalta, or other immunosuppressive biologic (e.g., Actemra, Enspryng, Kesimpta, Rinvoq, rituximab, Uplizna, etc.)

Renewal duration: 12 months

SECTION B. Generalized Myasthenia Gravis

- **Criteria for initial therapy:** Soliris (eculizumab) or Ultomiris (ravulizumab-cwvz) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist

  2. Individual is 18 years of age or older

  3. Individual has a confirmed diagnosis of generalized myasthenia gravis in individuals who are anti-acetylcholine receptor (AChR) antibody positive

  4. Individual meets **ALL** of the following:

     - Class II to IV disease per the Myasthenia Gravis Foundation of America (MGFA) classification system (see Definitions Section)
     - MG-Activities of Daily Living (MG-ADL) score of at least 6 or greater (see Definitions Section)

5. Individual has failure, contraindication per FDA label, intolerance or is not a candidate for a trial of at least 3 months to **BOTH** of the following:
   - Pyridostigmine
   - One immunosuppressive therapy (e.g., azathioprine, cyclosporine, methotrexate, mycophenolate, tacrolimus)
6. There are **NO** contraindications including unresolved serious *Neisseria meningitidis* infection
7. Individual has been vaccinated against Neisseria meningitidis at least 2 weeks prior to initiation of therapy, unless treatment cannot be delayed
8. Prescribing physician is enrolled in the appropriate Risk Evaluation and Mitigation Strategies (REMS) program
9. Soliris or Ultomiris will not be used in combination with another complement C5 inhibitor (e.g., Zilbrysq, Fabhalta), or other immunosuppressive biologic (e.g., Actemra, Enspryng, Kesimpta, Rinvoq, rituximab, Uplizna, etc.)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Soliris (eculizumab) or Ultomiris (ravulizumab-cwvz) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Neurologist
2. Individual has a confirmed diagnosis of generalized myasthenia gravis in individuals who are anti-acetylcholine receptor (AChR) antibody positive
3. Individual's condition has responded while on therapy with response defined as **BOTH** of the following:
   - Documentation of clinical benefit (e.g., decrease in frequency or severity of myasthenia gravis exacerbations, improvements in speech, swallowing, mobility, or respiratory function)
   - Improvement MG-ADL total score by 2 points or more from baseline
4. Individual has been adherent with the medication
5. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use including unresolved serious *Neisseria meningitidis* infection

6. Prescribing physician is enrolled in the appropriate Risk Evaluation and Mitigation Strategies (REMS) program

7. Soliris or Ultomiris will not be used in combination with another complement C5 inhibitor (e.g., Zilbrysq), Fabhalta, or other immunosuppressive biologic (e.g., Actemra, Enspryng, Kesimpta, Rinvoq, rituximab, Uplizna, etc.)

Renewal duration: 12 months

SECTION C. Neuromyelitis Optica Spectrum Disorder

- **Criteria for initial therapy:** Soliris (eculizumab) or Ultomiris (ravulizumab-cwvz) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of neuromyelitis optica spectrum disorder (NMOSD) with **ALL** of the following:

   - Documentation of confirmed anti-aquaporin-4 (AQP4) antibody positive
   - History of at least 1 relapse in the last 12 months or two relapses in the last 2 years [Note: Criterion may be waived if individual has documented contraindication to rituximab]
   - Attacks of NMOSD consist of at least **ONE** of the following core clinical features:

     a. Optic neuritis
     b. Acute myelitis
     c. Area postrema syndrome (episodes unexplained intractable hiccups or nausea and vomiting)
     d. Acute brainstem syndrome
     e. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
     f. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

4. Individual has failure (trial of at least 3 months), contraindication per FDA label, intolerance, or is not a candidate for **rituximab** [Note: Criterion may be waived if individual has documented failure of Enspryng or Uplizna due to lack of efficacy]

5. There are **NO** contraindications, including unresolved serious *Neisseria meningitidis* infection

6. Individual has been vaccinated against Neisseria meningitidis at least 2 weeks prior to initiation of therapy, unless treatment cannot be delayed

7. Prescribing physician is enrolled in the appropriate Risk Evaluation and Mitigation Strategies (REMS) program

8. Soliris or Ultomiris will not be used in combination with another complement C5 inhibitor (e.g., Zilbrysq), Fabhalta, or other immunosuppressive biologic (e.g., Actemra, Enspryng, Kesimpta, Rinvoq, rituximab, Uplizna, etc.)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Soliris (eculizumab) or Ultomiris (ravulizumab-cwvz) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Neurologist

2. Individual has a confirmed diagnosis of neuromyelitis optica spectrum disorder (NMOSD) and is anti-aquaporin-4 (AQP4) antibody positive

3. Individual's condition has responded while on therapy with response defined as **TWO** of the following:

   - Reduction in the number and/or severity of relapses
   - Decrease in concomitant corticosteroid or immunosuppressive therapy (e.g., azathioprine, mycophenolate, etc.)
   - Decrease in NMOSD symptoms (e.g., pain, fatigue, improvement in motor function)

4. Individual has been adherent with the medication

5. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use including unresolved serious *Neisseria meningitidis* infection

6. Prescribing physician is enrolled in the appropriate Risk Evaluation and Mitigation Strategies (REMS) program

7. Soliris or Ultomiris will not be used in combination with another complement C5 inhibitor (e.g., Zilbrysq), Fabhalta, or other immunosuppressive biologic (e.g., Actemra, Enspryng, Kesimpta, Rinvoq, rituximab, Uplizna, etc.)

Renewal duration: 12 months

- If the individual has one or more NMOSD relapse, consider changing disease modifying therapy

SECTION D. Paroxysmal Nocturnal Hemoglobinuria

- **Criteria for initial therapy:** Soliris (eculizumab) or Ultomiris (ravulizumab-cwvz) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Hematologist

  2. **For Soliris only**: Individual is 18 years of age or older

  3. **For Ultomiris only**: Individual is 1 month of age or older

  4. Individual has a confirmed diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) confirmed by **BOTH** of the following:

     - Documentation of high-sensitivity flow cytometry showing the absence or deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins (e.g., CD55, CD59) on at least 2 cell lineages (e.g., granulocytes and red blood cells)
     - Clinical sign or symptoms of PNH (e.g., red blood cell transfusion dependence, dyspnea, severe fatigue, thrombosis, organ dysfunction, uncontrolled pain)

  5. There are NO contraindications, including unresolved serious Neisseria meningitidis infection

  6. Individual has been vaccinated against Neisseria meningitidis at least 2 weeks prior to initiation of therapy, unless treatment cannot be delayed

  7. Prescribing physician is enrolled in the appropriate Risk Evaluation and Mitigation Strategies (REMS) program

  8. Soliris or Ultomiris will not be used in combination with another complement C5 inhibitor (e.g., Zilbrysq), Fabhalta, or other immunosuppressive biologic (e.g., Actemra, Enspryng, Kesimpta, Rinvoq, rituximab, Uplizna, etc.)

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Soliris (eculizumab) or Ultomiris (ravulizumab-cwvz) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

SOLIRIS® (eculizumab)
ULTOMIRIS® (ravulizumab-cwvz)

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Hematologist

2. Individual's condition has responded while on therapy with response defined as an individual has achieved and maintained **TWO** of the following:

   - Increase or stabilization of hemoglobin
   - Normalization of absolute reticulocyte count (ARC)
   - Decrease in frequency of red blood cell (RBC) transfusions
   - Decrease in lactase dehydrogenase (LDH)
   - Decrease in pain or fatigue

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use including unresolved serious *Neisseria meningitidis* infection

5. Individual has been vaccinated against Neisseria meningitidis at least 2 weeks prior to initiation of therapy, unless treatment cannot be delayed

6. Prescribing physician is enrolled in the appropriate Risk Evaluation and Mitigation Strategies (REMS) program

7. Soliris or Ultomiris will not be used in combination with another complement C5 inhibitor (e.g., Zilbrysq), Fabhalta, or other immunosuppressive biologic (e.g., Actemra, Enspryng, Kesimpta, Rinvoq, rituximab, Uplizna, etc.)

Renewal duration: 12 months

- Soliris (eculizumab) or Ultomiris (ravulizumab-cwvz) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any **ONE** or more of the following criteria are met:

  1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
  3. Insufficient evidence to support improvement of the net health outcome; or
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
  5. Insufficient evidence to support improvement outside the investigational setting.

  These indications include, *but are not limited to:*

SOLIRIS® (eculizumab)
ULTOMIRIS® (ravulizumab-cwvz)

- Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, or duration.

Description:

Soliris (eculizumab) is a complement inhibitor indicated for:
- The treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis.
- The treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy.
  - Limitation of Use: Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).
- The treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive.
- The treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

Ultomiris (ravulizumab-cwvz) is a complement inhibitor indicated for:
- The treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH).
- 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).
  - Limitations of Use: Ultomiris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).
- The treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive
- The treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive.

Atypical hemolytic syndrome

Hemolytic uremic syndrome (HUS) is categorized by occurrence of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. The most common etiology of HUS is Shiga toxin-producing *Escherichia coli* (STEC-HUS). It is associated with diarrhea and primarily affects children. Atypical hemolytic syndrome (aHUS), also known as complement-mediated thrombotic microangiopathy (CM-TMA), is a subset of thrombotic microangiopathy associated with inherited pathogenic variants in complement genes or acquired autoantibodies against complement factor H. This dysregulation of the alternative complement pathway results in the formation of the membrane attack complex. This causes kidney damage and activates the coagulations cascade and thrombotic microangiopathy. Treatment with anti-complement therapy such as eculizumab or ravulizumab can improve renal outcomes, especially if initiated early.

SOLIRIS® (eculizumab)
ULTOMIRIS® (ravulizumab-cwvz)

Myasthenia gravis (MG)

MG is an acquired, autoimmune disorder that affects the neuromuscular junction of the skeletal muscles. Approximately 90 percent of individuals with MG have serum antibodies to AChR, which are believed to play a central role in the disease pathway. Approximately 6 percent of individuals are MuSK antibody positive.

There are four primary therapies to treat MG:

- Symptomatic treatment with acetylcholinesterase inhibitors such as pyridostigmine
- Chronic immunotherapies such as glucocorticoids, Fc receptor blockers, rituximab, maintenance IVIG, and complement inhibitors
- Rapid but short-acting treatments such as plasma exchange and IVIG
- Surgical treatment with thymectomy

Neuromyelitis optica spectrum disorder (NMOSD)

NMOSD, previously known as Devic disease or neuromyelitis optica [NMO]) are inflammatory disorders of the central nervous system characterized by severe, immune-mediated demyelination and axonal damage predominantly targeting optic nerves and spinal cord.

NMOSD is distinguished from multiple sclerosis and other central nervous system inflammatory disorders by the presence of the disease-specific AQP4 antibody (also referred to as NMO-immunoglobulin G antibody). AQP4 is a water channel protein that is concentrated in the spinal cord gray matter, periaqueductal and periventricular regions, and astrocytic foot processes of the blood brain barrier. Studies have shown that serum anti-AQP4 titers correlate with disease activity, decrease after immunotherapy, and are low during remission.

NMOSD acute attacks are characterized by bilateral or rapidly sequential optic neuritis (leading to visual loss), acute transverse myelitis (often causing limb weakness and bladder dysfunction), and the area postrema syndrome (with intractable hiccups or nausea and vomiting). The acute attacks may occur over days with variable degrees of recovery that can be weeks to months. It has a relapsing course and management is directed at treating an acute attack and then preventing another attack or prolonging the time to a relapse.

The natural history of NMOSD is a stepwise deterioration from accumulating visual, motor, sensory, and bladder deficits from recurrent attacks. Mortality rate is high in NMOSD, and it is often due to neurogenic respiratory failure, which occurs with extension of cervical lesions into the brainstem or from primary brainstem lesions.

Paroxysmal nocturnal hemoglobinuria (PNH)

PNH is a rare, acquired disorder in which hematopoietic stem cells that causes reduced or absent glycosylphosphatidylinositol (GPI)-anchored proteins on the cell surface. GPI-linked complement

inhibitors prevent over activation of the alternative pathway of complement (APC) which is a component of innate immunity. The functional components of APC are C3 and C5 convertases and cytolytic membrane attack complex (MAC). Loss of the GPI-linked complement inhibitors on red blood cells (RBCs) leads to paroxysmal intravascular hemolysis (IVH) and an increased risk for thrombosis, organ dysfunction, and hypocellular or dysplastic bone marrow. Some individuals with PNH may have clinically significant aplastic anemia or myelodysplastic syndrome. Common clinical symptoms include fatigue, dyspnea, hemoglobinuria, abdominal pain, bone marrow suppression, erectile dysfunction, thrombosis, and renal insufficiency.

PNH is categorized into one of three categories: hemolytic (classical) PNH, subclinical PNH and PNH with bone marrow failure. Complement inhibitors including Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), and Empaveli (pegcetacoplan) are primarily used to treat symptomatic hemolytic PNH to manage anemia-related symptoms, thrombosis, pain, and organ dysfunction. Clinical benefit includes stabilization of hemoglobin, decreases in transfusion and reduction in hemolysis.

Definitions:

Myasthenia Gravis Foundation of America clinical classification	
Class I	Any ocular muscle weakness May have weakness of eye closure All other muscle strength is normal
Class II	Mild weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity
IIa	Predominantly affecting limb, axial muscles, or both May also have lesser involvement of oropharyngeal muscles
IIb	Predominantly affecting oropharyngeal, respiratory muscles, or both May also have lesser or equal involvement of limb, axial muscles, or both
Class III	Moderate weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity
IIIa	Predominantly affecting limb, axial muscles, or both May also have lesser involvement of oropharyngeal muscles
IIIb	Predominantly affecting oropharyngeal, respiratory muscles, or both May also have lesser or equal involvement of limb, axial muscles, or both
Class IV	Severe weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity
IVa	Predominantly affecting limb and/or axial muscles May also have lesser involvement of oropharyngeal muscles
IVb	Predominantly affecting oropharyngeal, respiratory muscles, or both May also have lesser or equal involvement of limb, axial muscles, or both

Class V	Defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.
Weakness class is assessed according to the most severely affected muscle or muscle group at the patient's maximum severity	

MG Activities of Daily Living (MG-ADL):

Grade	0	1	2	3
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal but can be understood	Difficult to understand speech
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube
Swallowing	Normal	Rare episode of choking	Frequent chocking necessitating changes in diet	Gastric tube
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence
Impairment of ability to brush teeth or comb hair	Normal	Extra effort but no rest periods needed	Rest periods needed	Cannot do one of these functions
Impairment of ability to arise from a chair	Normal	Mild, sometimes uses arms	Moderate always uses arms	Severe requires assistance
Double vision	Normal	Occurs but not daily	Daily but not constant	Constant
Eyelid droop	Normal	Occurs but not daily	Daily but not constant	Constant
The total score was the sum of all individual item scores and range from 0 to 24. Higher scores indicate more severe disability due to MG. A decrease from baseline score indicate improvement. A 2-point change in MG-ADL Score is considered clinically meaningful.				

Biologic Generalized Myasthenia Gravis therapies:

Neonatal Fc Receptor Antagonist	RYSTIGGO (rozanolixizumab)
Neonatal Fc Receptor Antagonist	VYVGART (efgartigimod alfa)
Neonatal Fc Receptor Antagonist	VYVGART HYTRULO (efgartigimod alfa and hyaluronidase)
Compliment 5 inhibitor (C5i)	SOLIRIS (eculizumab)
Compliment 5 inhibitor (C5i)	ULTOMIRIS (ravulizumab)

Compliment 5 inhibitor (C5i)	ZILBRYSQ (zilucoplan)

Neuromyelitis optica spectrum disorder (NMOSD):

Diagnostic criteria for NMOSD with AQP4-IgG
1. At least one core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses

Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status
1. At least two core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
    a. At least one core clinical characteristic must be optic neuritis, acute myelitis with longitudinally extensive transverse myelitis (LETM), or area postrema syndrome
    b. Dissemination in space (two or more different core clinical characteristics)
    c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses

Core clinical characteristics
1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: Episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status
1. Acute optic neuritis: Requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, **or** (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium enhancing lesion extending over more than one-half the optic nerve length or involving optic chiasm
2. Acute myelitis: Requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) **or** ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis
3. Area postrema syndrome: Requires associated dorsal medulla/area postrema lesions
4. Acute brainstem syndrome: Requires associated periependymal brainstem lesions

Biologic NMOSD therapies:

Interleukn-6 Receptor Antagonist	ENSPRYNG (satralizumab)

EVIDENCE-BASED CRITERIA
SECTION: SPECIALTY MEDICAL DRUGS

ORIGINAL EFFECTIVE DATE: 10/14/24
LAST REVIEW DATE: 08/15/24
CURRENT EFFECTIVE DATE: 10/14/24
LAST CRITERIA REVISION DATE:

NEXT ANNUAL REVIEW DATE: 3RD QTR 2025
ARCHIVE DATE:

SOLIRIS® (eculizumab)
ULTOMIRIS® (ravulizumab-cwvz)

Compliment 5 inhibitor (C5i)	SOLIRIS (eculizumab)
Compliment 5 inhibitor (C5i)	ULTOMIRIS (ravulizumab)
Anti-CD19 Monoclonal Antibody	UPLIZNA (inebilizumab)
Anti-CD20 Monoclonal Antibody	RIABNI* (rituximab) (off-label)
Anti-CD20 Monoclonal Antibody	RITUXAN (rituximab) (off-label)
Anti-CD20 Monoclonal Antibody	RUXIENCE* (rituximab)* (off-label)
Anti-CD20 Monoclonal Antibody	TRUXIMA* (rituximab)* (off-label)

** Biosimilar to Rituxan*

Paroxysmal Nocturnal Hemoglobinuria therapies:

Compliment Factor B inhibitor (CFBi)	FABHALTA (iptacopan)
Compliment Factor D inhibitor (CFDi)	VOYDEYA (danicopan)
Compliment 3 inhibitor (C3i)	EMPAVELI (pegcetacoplan)
Compliment 5 inhibitor (C5i)	SOLIRIS (eculizumab)
Compliment 5 inhibitor (C5i)	ULTOMIRIS (ravulizumab)

History:	**Date:**	**Activity:**
Pharmacy and Therapeutics Committee	08/15/24	Approved guideline (effective 10/14/24)
Clinical Pharmacist	05/17/24	Development

Coding:
HCPCS: J1300, J1303

SOLIRIS® (eculizumab)
ULTOMIRIS® (ravulizumab-cwvz)

Resources:

Literature reviewed 08/15/24. We do not include marketing materials, poster boards and non-published literature in our review.

1. Bird SJ. Chronic immunotherapy for myasthenia gravis. In: UpToDate, Shefner JM, Goddeau RP (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through March 2024. Topic last updated February 27, 2024. Accessed May 20, 2024.

2. Bird SJ. Overview of the treatment of myasthenia gravis. In: UpToDate, Shefner JM, Goddeau RP (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through March 2024. Topic last updated August 17, 2023. Accessed May 17, 2024.

3. Brodsky RA. Clinical manifestations and diagnosis of paroxysmal and nocturnal hemoglobinuria. In: UpToDate, Larson RA, Rosmarin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through April 2024. Topic last updated June 10, 2022. Accessed May 17, 2024.

4. Brodsky RA. Treatment and prognosis of paroxysmal and nocturnal hemoglobinuria. In: UpToDate, Larson RA, Rosmarin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through April 2024. Topic last updated November 27, 2023. Accessed May 17, 2024.

5. Damato V, Evoli A, Iorio R. Efficacy and Safety of Rituximab Therapy in Neuromyelitis Optica Spectrum Disorders: A Systematic Review and Meta-analysis. *JAMA Neurol*. 2016;73(11):1342-1348. doi: 10.1001/jamaneurol.2016.1637.

6. George JN, Nester CM. Thrombotic microangiopathies (TMAs) with acute kidney injury (AKI) in adults: CM-TMA and ST-HUS. In: UpToDate, Brodsky RA, Tirnauer JS (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through May 2024. Topic last updated August 16, 2023. Accessed June 3, 2024.

7. Glisson CC. Neuromyelitis optica spectrum disorder (NMOSD): Clinical features and diagnosis. In: UpToDate, González-Scarano F, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through April 2024. Topic last updated August 30, 2022. May 17, 2024.

8. Glisson CC. Neuromyelitis optica spectrum disorder (NMOSD): Treatment and prognosis. In: UpToDate, González-Scarano F, Dashe JF (Eds), UpToDate,

9. Narayanaswami P, Sanders DB, Wolfe G, et al. International consensus guidance for management of myasthenia gravis: 2020 update. *Neurology* 2021; 96:114-122.

10. Niaudet P, Boyer OG. Complement-mediated hemolytic uremic syndrome in children. In: UpToDate, Mattoo TK, Kremen J (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through April 2024. Topic last updated March 29, 2024. Accessed May 17, 2024.

11 Ongphichetmetha T, Jitprapaikulsan J, Siritho S, et al. Efficacy and safety of rituximab in multiple sclerosis and neuromyelitis optica spectrum disorder. *Sci Rep.* 2024;14(1):3503. doi: 10.1038/s41598-024-53838-y.

12. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. *Neurology* 2016; 87: 419-25.

13. Soliris (eculizumab) product information revised by Alexion Pharmaceuticals Inc. 03/2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 17, 2024.

14. Tania Kümpfel, Katrin Giglhuber, Orhan Aktas, et al. Update on the diagnosis and treatment of neuromyelitis optica spectrum disorders (NMOSD) – revised recommendations of the Neuromyelitis Optica Study Group (NEMOS). Part II: attack therapy and long-term management. *J Neurol*. 2023; 270(7):3341-3368. doi: 10.1007/s00415-023-11634-0.

15. Trebst C, Jarius S, Berthele A, et al. Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS). *J Neurol* 2014; 261:1-16.

16. Ultomiris (ravulizumab-cwvz) product information revised by Alexion Pharmaceuticals Inc. 03/2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 17, 2024.

17. Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through April 2024. Topic last updated April 11, 2024. Accessed May 17, 2024.

18. Wang Y, Chang H, Zhang X, Yin L. Efficacy of rituximab in the treatment of neuromyelitis optica spectrum disorders: An update systematic review and meta -analysis. *Mult Scler Relat Disord*. 2021 May;50:102843. doi: 10.1016/j.msard.2021.102843.

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 10/14/24**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE: 08/15/24**
	CURRENT EFFECTIVE DATE: 10/14/24
	LAST CRITERIA REVISION DATE:
NEXT ANNUAL REVIEW DATE: 3RD QTR 2025	**ARCHIVE DATE:**

SOLIRIS® (eculizumab)
ULTOMIRIS® (ravulizumab-cwvz)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html