Policy Number	**RX501.066**
Policy Effective Date	**02/15/2025**

Eculizumab and Associated Biosimilar(s)

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted

study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

NOTE 1: Per the U.S. Food and Drug Administration (FDA) label, life-threatening and fatal meningococcal infections have occurred in patients treated with eculizumab. The use of eculizumab increases an individual's susceptibility to serious meningococcal infections (septicemia and/or meningitis) therefore, eculizumab is contraindicated in individuals who have unresolved serious *Neisseria meningitidis* infection or have or are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying eculizumab treatment outweigh the risks of developing a meningococcal infection.

Paroxysmal Nocturnal Hemoglobinuria

Eculizumab (Soliris® and biosimilars eculizumab-aeeb [Bkemv] and eculizumab-aagh [Epysqli]) **may be considered medically necessary** to reduce hemolysis for individuals who have paroxysmal nocturnal hemoglobinuria (PNH) AND meet the following criteria:

- Documentation of diagnosis of PNH through analysis by:
  - Flow cytometry of erythrocytes for CD59 deficiency; or
  - Granulocytes for either CD59 or CD55; AND
- Will not receive concurrently with other biologics used to treat paroxysmal nocturnal hemoglobinuria (PNH) (e.g., ravulizumab-cwvz).

Atypical Hemolytic Uremic Syndrome

Eculizumab (Soliris® and biosimilars eculizumab-aeeb [Bkemv] and eculizumab-aagh [Epysqli]) **may be considered medically necessary** to treat individuals with atypical hemolytic uremic syndrome (aHUS) AND meet the following criteria:

- Will not receive concurrently with other biologics used to treat atypical hemolytic uremic syndrome (aHUS) (e.g., ravulizumab-cwvz).

Generalized Myasthenia Gravis

Eculizumab (Soliris® and biosimilars eculizumab-aeeb [Bkemv] and eculizumab-aagh [Epysqli]) **may be considered medically necessary** to treat individuals 18 years of age or older with generalized myasthenia gravis (gMG) who meet all the following criteria:

- Positive serologic test for anti-acetylcholine (AChR) receptor;
- Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV;
- Myasthenia Gravis Activities of Daily Living (MG-ADL) total score ≥6; and
- ONE of the following:
  - Failed treatment over 1 year or more with a minimum of 2 immunosuppressive therapies either in combination or as monotherapy, OR
  - Failed at least 1 immunosuppressive therapy and required chronic plasmapheresis or plasma exchange or intravenous immunoglobulin (IVIG); **AND**

- Will not receive eculizumab concurrently with other biologics used to treat myasthenia gravis (e.g., ravulizumab, rituximab, intravenous immunoglobulin, rozanolixizumab-noli, efgartigimod alfa-fcab, zilucoplan).

NOTE 2: Please refer to the Description Section for the MGFA Clinical Classification Guidelines and the MG-ADL profile.

Neuromyelitis Optica Spectrum Disorder

Eculizumab (Soliris® and biosimilars eculizumab-aeeb [Bkemv] and eculizumab-aagh [Epysqli]) **may be considered medically necessary** to treat individuals:

- 18 years of age or older; AND
- Has a diagnosis of neuromyelitis optica spectrum disorder (NMOSD); AND
- Is anti-aquaporin-4 (AQP4) antibody positive; AND
- Will not receive eculizumab concurrently with other biologics used to treat NMOSD (e.g., inebilizumab-cdon, rituximab, satralizumab, ravulizumab).

Other

Eculizumab (Soliris® and biosimilars eculizumab-aeeb [Bkemv] and eculizumab-aagh [Epysqli]) **is considered experimental, investigational and/or unproven** for all other indications, including but not limited to treatment of individuals with Shiga toxin *E. coli* related hemolytic uremic syndrome (STEC-HUS).

NOTE 3: Eculizumab is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).

Policy Guidelines

None.

Description

Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH), which usually develops in adults, is a disease characterized by red blood cells that develop abnormally. Once the abnormal cells are present in the bloodstream, naturally occurring proteins (called the complement system), designed to destroy bacteria and other infection-causing organisms, break these cells down. This leads to abnormally darkened urine and, more importantly, causes anemia. Depending upon the severity of the disorder, patients with PNH may have pain, fatigue and debilitating weakness, the need for frequent blood transfusions, blood clots, and life-threatening or fatal strokes, heart attacks and intestinal disease. Soliris™ does not cure PNH, but treats the breakdown of red blood cells, the most common characteristic of PNH. Soliris acts to block the complement system activity, including the destruction of PNH red blood cells. Terminal complement inhibition with Soliris increases the susceptibility to serious meningococcal infections. (1)

Atypical Hemolytic Uremic Syndrome
Atypical hemolytic uremic syndrome (aHUS) is a rare disease that causes abnormal blood clots to form in small blood vessels in the kidneys. These clots can lead to serious medical problems if they restrict or block blood flow, including hemolytic anemia, thrombocytopenia, and kidney failure. In about 60% of aHUS, a gene mutation has been identified as a causative factor; the genes associated with genetic aHUS include C3, CD46, CFB, CFH, CFHR1, CFHR3, CFHR4, CFI, DGKE, and THBD. Although mutations in these genes do not directly cause the disease, they do increase the likelihood of developing aHUS. (2)

Generalized Myasthenia Gravis (gMG)
Myasthenia gravis is an autoimmune neuromuscular disease in which a person's immune system attacks the nervous system affecting the transmission of messages (nerve impulses) to muscle cells. This leads to overall weakness and lack of muscular control, including those muscles essential for chewing and swallowing, talking and breathing. Normally, to pass on a message to a muscle, motor neurons release a chemical called acetylcholine at the neuromuscular junction, the point where the nerve and muscle cells interact. Acetylcholine binds to acetylcholine receptors (AChRs) found on muscle cells, causing muscles to contract. In many myasthenia gravis patients, the immune system starts to produce antibodies that prevent AChRs from working and can destroy them. Soliris is designed to block part of the immune system called the terminal complement cascade, consisting of a series of reactions that trigger the damaging immune response seen in myasthenia gravis. (3)

Neuromyelitis Optica Spectrum Disorder (NMOSD)
Neuromyelitis optica spectrum disorder (NMOSD) is a rare, autoimmune disease of the central nervous system (CNS) that primarily attacks the optic nerves and spinal cord leading to blindness and paralysis. NMOSD was first described and coined in the late 1800s but only recognized to be an entity distinct from multiple sclerosis (MS) over the past 10 years with the discovery of a unique biomarker antibody that identifies the disease in up to 72 % of NMOSD patients with >99 % specificity. NMOSD accounts for approximately 1.5 % of demyelinating diseases in Caucasian populations extrapolating to a prevalence of 0.52 to 4.4 per 100,000. Although the incidence of demyelinating disease is lower in non-Caucasian countries, the percentage of demyelinating diseases made up by NMOSD is higher. (4)

Regulatory Status
The United States (U.S.) Food and Drug Administration (FDA) approved eculizumab (Soliris®) for the following indications (5):

- "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.
- The treatment of generalized myasthenia gravis (gMG) in adults who are anti-acetylcholine receptor (AchR) antibody positive.

- The treatment of neuromyelitis optica spectrum disorder (NMOSD) in adults who are anti-aquaporin-4 (AQP4) antibody positive."

In 2024, the FDA approved Bkemv (eculizumab-aeeb) (6) and Epysqli (eculizumab-aagh) (7) as biosimilars to Soliris for the following indications:

- "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."

Per the FDA label, eculizumab is not indicated for the treatment of individuals with Shiga Toxin *E. coli* related hemolytic uremic syndrome (STEC-HUS). (5)

Life-threatening and fatal meningococcal infections have occurred in patients treated with eculizumab and may become rapidly life-threatening or fatal if not recognized and treated early. For this reason, there is a specific recommendation in the FDA label to immunize patients with meningococcal vaccines at least two weeks prior to receiving the first dose of eculizumab, unless there is documentation that the risks of delaying eculizumab therapy outweigh the risk of developing a meningococcal infection. (5)

Eculizumab is given through intravenous (IV) infusion. The recommended dose of eculizumab is dependent on the indication for which the drug is administered and the age of the patient. (5)

Rationale

This policy was created in 2008 and was based on United States (U.S.) Food and Drug Administration (FDA) approved indications. The policy has been routinely updated with literature searches, particularly for off-labeled use, with the most recent update including searches in the PubMed database and standard reference compendium. The following is a summary of key literature to date.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

The U.S. FDA approval of eculizumab was based on the results of three multi-national clinical studies:

- TRIUMPH, a placebo-controlled 26-week Phase 3 study involving 87 PNH patients,
- SHEPHERD, an open-label 52-week Phase 3 trial involving 97 PNH patients, and
- E05-001, a long-term extension study.

These studies showed that eculizumab reduced hemolysis in every treated patient. Hemolysis was dramatically reduced from a baseline lactate dehydrogenase (LDH) of 2,032 U/L to 239 U/L at week 26 ($p<0.001$). The reductions in hemolysis occurred within one week of initiating treatment and were sustained for periods of up to 54 months with continued dosing of Soliris. The reduction in hemolysis expands the number of circulating PNH cells and, thereby, increases

the hemoglobin level. Hemoglobin stabilization and the number of transfused packed red blood cell units, the pivotal study's co-primary endpoints, were both achieved. Half of the eculizumab-treated patients achieved hemoglobin stabilization compared with none of the patients in the placebo group; the median number of transfusions was reduced from 10 units/patient to 0 units/patient, respectively ($p < 0.001$ in both cases). Soliris patients reported less fatigue and improved health-related quality of life. There were fewer thrombotic events with Soliris treatment than during the same period of time prior to treatment. (5-10)

Atypical Hemolytic Uremic Syndrome (aHUS)
Eculizumabs' safety and effectiveness for aHUS was evaluated in four prospective, single-arm studies (three in adult and adolescent patients and one in pediatric and adolescent patients) and one retrospective study. (5) Patients treated with eculizumab in these studies experienced a favorable improvement in kidney function, including elimination of the requirement for dialysis in several patients with aHUS that did not respond to plasma therapy. Patients treated with eculizumab also exhibited improvement in platelet counts and other blood parameters that correlate with aHUS disease activity.

There are no other FDA-approved treatments for aHUS, and the safety and effectiveness of current standard treatment, plasma therapy (plasma exchange or fresh frozen plasma infusion), have not been studied in well controlled trials.

The effectiveness of eculizumab in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function. Prospective clinical trials in additional patients are ongoing to confirm the benefit of eculizumab in patients with aHUS.

UpToDate
In 2024, UpToDate reevaluated all related evidence related to the treatment and prognosis of mediated hemolytic uremic syndrome and provided the following recommendation: (11):

- "For patients with severe forms of complement-mediated HUS (e.g., patients with *CFH* and *CFI* variants), we recommend eculizumab (Grade 1B). If eculizumab therapy is not available, plasma therapy is an alternative treatment option."
- "For kidney transplant recipients who are at risk for recurrent disease in the allograft, we suggest prophylactic administration of eculizumab rather than plasma therapy or no treatment (Grade 2C). At-risk patients include those with an identified variant in *CFH*, *CFI*, *C3*, or *CFB*, those with high titers of CFH antibodies, and those with a previous post-transplant episode of recurrent disease. If eculizumab is not available (e.g., due to cost constraints), plasma therapy is an acceptable alternative."

UpToDate classifies recommendations, based on grade of evidence.

- "Grade 1B recommendation is a strong recommendation which the best estimates of the critical benefits and risks come from RCTs with important limitations (e.g., inconsistent results, methodologic flaws, imprecise results, extrapolation from a different population or setting) or very strong evidence of some other form. Further research (if performed) is likely

to have an impact on our confidence in the estimates of benefit and risk and may change the estimates.

- Grade 2C recommendation is a very week recommendation, and other alternatives may be equally reasonable. Benefits and risks may be finely balanced, or the benefits and risks may be uncertain. Evidence comes from observational studies, unsystematic clinical experience, or from randomized controlled trials with serious flaws. Any estimate of effect is uncertain."

Generalized Myasthenia Gravis (gMG)

The efficacy of Soliris for the treatment of gMG was established in a 26-week randomized, double-blind, parallel-group, placebo-controlled, multi-center trial in which 62 patients were randomized to receive Soliris treatment and 63 were randomized to receive placebo. (5) The primary efficacy endpoint was a comparison of the change from baseline between treatment groups in the Myasthenia Gravis-Specific Activities of Daily Living scale (MG-ADL) total score at Week 26. A statistically significant difference favoring Soliris was observed in the mean change from baseline to Week 26 in MG-ADL total scores [-4.2 points in the Soliris treated group compared with -2.3 points in the placebo-treated group (p=0.006)]. A key secondary endpoint in was the change from baseline in the Quantitative Myasthenia Gravis (QMG) total score at Week 26. A statistically significant difference favoring Soliris was observed in the mean change from baseline to Week 26 in QMG total scores [-4.6 points in the Soliris-treated group compared with -1.6 points in the placebo-treated group (p=0.001)]. Available data suggest that clinical response is usually achieved by 12 weeks of Soliris treatment.

Neuromyelitis Optica Spectrum Disorder (NMOSD)

The efficacy of Soliris for the treatment of NMOSD was established in a randomized, double-blind, placebo-controlled trial that enrolled 143 NMOSD patients who were anti-aquaporin-4 (AQP4) antibody positive. (5) A total of 96 patients were randomized to receive Soliris treatment and 47 were randomized to receive placebo. The primary endpoint was the time to the first relapse. In the Soliris-treated patients, the time to relapse was significantly longer compared to placebo-treated patients (relative risk reduction 94%; hazard ratio 0.058; $p < 0.0001$). Soliris-treated patients experienced similar improvement in time to relapse with or without concomitant treatment. Compared to placebo-treated patients, Soliris-treated patients had reduced annualized rates of hospitalizations, corticosteroid administrations to treat acute relapses, and plasma exchange treatments.

Other

In 2015, Cornell et al. (12) examined outcomes beyond 1 year in eculizumab-treated positive crossmatch kidney transplants compared to a historical control group (n=48). The study demonstrated eculizumab treatment does not prevent chronic antibody-mediated rejection in recipients with persistently high B flow crossmatch after positive crossmatch kidney transplantation.

Eculizumab has been investigated for numerous off label conditions/indications, including but not limited to prevention of delayed graft function, acute antibody mediated rejection,

systemic lupus erythematosus, and stem-cell transplant-associated thrombotic microangiopathy.

Available studies reported that there were no significant improvements with eculizumab and/or the studies were limited by small and/or heterogeneous patient populations; short-term follow-ups; lack of a control group; potential reporting and publication bias; and heterogeneity of inclusion criteria, outcome measures (for example, methods for determining disease progression) and eculizumab dosing. (13-16)

Summary of Evidence
There is inadequate published peer reviewed literature to permit scientific conclusions regarding the safety and efficacy of eculizumab outside of its FDA-approved indications.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J1300, J3490, J3590, J9999

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
02/15/2025	Document updated with literature review. The following changes were made to Coverage: 1) Added biosimilars eculizumab-aeeb (Bkemv) and eculizumab-

	aagh (Epysqli) to all medically necessary statements; 2) Added biosimilars eculizumab-aeeb (Bkemv) and eculizumab-aagh (Epysqli) to the experimental, investigational and/or unproven statement; 3) Modified list of biologics on the concurrent use statements under both the myasthenia gravis and neuromyelitis optica spectrum disorder sections; and 4) Modified Notes 1 and 3 to replace "Soliris" with "eculizumab." Reference 6 and 7 added; others updated/revised. Title changed from “Eculizumab.”
02/15/2024	Document updated with literature review. The following editorial changes were made to coverage: 1) Changed “patients” to “individuals”, 2) removed coverage statement “Documentation that the individual has received a meningococcal vaccine at least two weeks prior to receiving the first dose of Soliris, OR there is documentation that the risks of delaying Soliris therapy outweigh the risk of developing a meningococcal infection.” from each section and 3) Note numbers reformatted; intent unchanged. References updated.
10/15/2022	Document updated with literature review. The following changes were made to Coverage: Added “Will not receive concurrently with other biologics used to treat paroxysmal nocturnal hemoglobinuria (PNH) (e.g., ravulizumab-cwvz);” “will not receive concurrently with other biologics used to treat atypical hemolytic uremic syndrome (aHUS) (e.g., ravulizumab-cwvz);” “Will not receive concurrently with other biologics used to treat myasthenia gravis (e.g., ravulizumab-cwvz, rituximab, intravenous immunoglobulin)” to those specific coverage indications. References updated; none added; one removed.
07/01/2021	Document updated. The following change was made to Coverage: Added “Will not receive eculizumab concurrently with other biologics used to treat NMOSD (e.g., inebilizumab-cdon, rituximab, satralizumab)” to conditional criteria for Neuromyelitis Optica Spectrum Disorder. No new references added.
02/15/2021	Reviewed. No changes.
05/01/2020	Document updated with literature review. The following changes were made to Coverage: 1) Added conditional criteria for neuromyelitis optica spectrum disorder (NMOSD); and 2) Added NOTE 3 regarding Risk Evaluation and Mitigation Strategy (REMS) program. Added references 2-5; updated 9-10. Title changed from “Soliris (eculizumab)”.
11/15/2018	Reviewed. No changes.
06/01/2018	Document updated with literature review. The following changes were made in Coverage: 1) Added requirement for documentation that the risk of delaying Soloris therapy outweigh the risk of developing a meningococcal infection to the paroxysmal nocturnal hemoglobinuria (PNH) criteria and atypical hemolytic uremic syndrome criteria. 2) Added medical necessity criteria for generalized myasthenia gravis due to new FDA approved indication; 2) Added note 1 to refer to the Description Section for the MGFA

	Clinical Classification Guidelines and the MG-ADL profile. 3) Added note 2**:** Per FDA label, life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. The use of Soliris increases a patient's susceptibility to serious meningococcal infections (septicemia and/or meningitis) therefore, Soliris is contraindicated in patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection. 4) Added references 1, 4, 8-15.
12/01/2016	Reviewed. No changes
01/01/2015	Document updated with literature review. Coverage unchanged.
12/15/2012	Document updated with literature review. The following was added: 1) Soliris (eculizumab) may be considered medically necessary to treat patients with atypical hemolytic uremic syndrome (aHUS) with documentation that the patient has received a meningococcal vaccine at least two weeks prior to receiving the first dose of Soliris. 2) Treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS) was added as an example of experimental, investigational, and unproven indications. Title changed from Soliris for the Treatment of Paroxysmal Nocturnal Hemoglobinuria (PNH).
01/01/2011	Document updated with literature review. Coverage unchanged.
02/15/2009	Coverage revised
01/15/2008	New medical document