Policy Number	**RX501.066**
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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 generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. 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 generally accepted standards of medical care. 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.

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).

Generalized Myasthenia Gravis

Eculizumab (Soliris® and biosimilars eculizumab-aeeb [Bkemv™] and eculizumab-aagh [Epysqli]) **may be considered medically necessary** to treat generalized myasthenia gravis (gMG) in individuals who meet all the following criteria:

- Six years of age or older;
- 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).

NOTE 2: Please refer to the Policy Guidelines 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.

Other

Eculizumab (Soliris® and biosimilars eculizumab-aeeb [Bkemv™] and eculizumab-aagh [Epysqli]) **is considered experimental, investigational and/or unproven** for all other non-FDA approved indications, including the 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

Myasthenia Gravis Foundation of America (MGFA) Clinical Classification

In 1997, the Medical Scientific Advisory Board of the MGFA formed a task force to address the need for universally accepted classifications, grading systems, and analytic methods for the management of individuals undergoing therapy and for use in therapeutic research trials. As a result, the MGFA Clinical Classification was created. This classification divides myasthenia gravis (MG) into 5 main classes and several subclasses, as follows (7):

- Class I: Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.
- Class II: Mild weakness affecting muscles 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 muscles 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 muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

- IVa. Predominantly affecting limb, axial muscles, or both. 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 as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the individual in class IVb.

The Myasthenia Gravis–Specific Activities of Daily Living Scale (MG-ADL)

The Myasthenia Gravis–specific Activities of Daily Living scale was developed in the late 1990s to assess the status of symptoms and activities in MG. (8) It is an 8-item, patient reported questionnaire that can be completed in 2–3 minutes with no need for specialized equipment or training. See Table 1.

Table 1. MG Activities of Daily Living (MG-ADL) Profile

Grade	**0**	**1**	**2**	**3**	**Score (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 choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependent	
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	

Each activity is scored 0-3; and all scores are totaled to represent the overall MG-ADL score.

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. (4)

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. (5)

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. (6)

Neuromyelitis Optica Spectrum Disorder (NMOSD)
Neuromyelitis optica spectrum disorder 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. (7)

Regulatory Status

The United States (U.S.) Food and Drug Administration (FDA) approved eculizumab (Soliris®) for the following indications (1):

- "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 adult and pediatric patients six years of age and older 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) (2) and Epysqli (eculizumab-aagh) (3) 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.
- The treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive."

Per the FDA label, eculizumab is not indicated for the treatment of individuals with Shiga Toxin *E. coli* related hemolytic uremic syndrome (STEC-HUS). (1)

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. (1)

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. (1)

Rationale

This policy is based on United States (U.S.) Food and Drug Administration (FDA) approved indications for eculizumab (Soliris® and biosimilars eculizumab-aeeb [Bkemv™] and eculizumab-aagh [Epysqli]) and a specialty society recommendation.

Paroxysmal Nocturnal Hemoglobinuria (PNH) (1-3)
The safety and efficacy of Soliris in PNH patients with hemolysis were assessed in a randomized, double-blind, placebo-controlled 26-week study (PNH Study 1, NCT00122330); PNH patients were also treated with Soliris in a single arm 52 week study (PNH Study 2, NCT00122304) and in a long-term extension study (E05-001, NCT00122317). Patients received meningococcal vaccination prior to receipt of Soliris. In all studies, the dose of Soliris was 600 mg study drug every 7 ± 2 days for 4 weeks, followed by 900 mg 7 ± 2 days later, then 900 mg every 14 ± 2 days for the study duration. Soliris was administered as an intravenous infusion over 25-45 minutes.

PNH Study 1
PNH patients with at least four transfusions in the prior 12 months, flow cytometric confirmation of at least 10% PNH cells and platelet counts of at least 100,000/microliter were randomized to either Soliris (n=43) or placebo (n=44). Prior to randomization, all patients underwent an initial observation period to confirm the need for red blood cell (RBC) transfusion and to identify the hemoglobin concentration (the "set-point") which would define each patient's hemoglobin stabilization and transfusion outcomes. The hemoglobin set-point was less than or equal to 9 g/dL in patients with symptoms and was less than or equal to 7 g/dL in patients without symptoms. Endpoints related to hemolysis included the numbers of patients achieving hemoglobin stabilization, the number of RBC units transfused, fatigue, and health-related quality of life. To achieve a designation of hemoglobin stabilization, a patient had to maintain a hemoglobin concentration above the hemoglobin set-point and avoid any RBC transfusion for the entire 26 week period. Hemolysis was monitored mainly by the measurement of serum lactate dehydrogenase (LDH) levels, and the proportion of PNH RBCs was monitored by flow cytometry. Patients receiving anticoagulants and systemic corticosteroids at baseline continued these medications. Major baseline characteristics were balanced.

Patients treated with Soliris had significantly reduced ($p<0.001$) hemolysis resulting in improvements in anemia as indicated by increased hemoglobin stabilization and reduced need for RBC transfusions compared to placebo treated patients (see Table 2). These effects were seen among patients within each of the three pre-study RBC transfusion strata (4-14 units; 15-25 units; > 25 units). After 3 weeks of Soliris treatment, patients reported less fatigue and improved health-related quality of life. Because of the study sample size and duration, the effects of Soliris on thrombotic events could not be determined.

Table 2. PNH Study 1 Results

	Placebo (N=44)	**Soliris (N=43)**
Percentage of patients with stabilized hemoglobin levels	0	49

Packed RBC units transfused per patient (median)	10	0
(range)	(2 - 21)	(0 - 16)
Transfusion avoidance (%)	0	51
LDH levels at end of study (median, U/L)	2,167	239
Free hemoglobin at end of study (median, mg/dL)	62	5

LDH: lactate dehydrogenase; PNH: paroxysmal nocturnal hemoglobinuria; RBC: red blood cell.

PNH Study 2 and Extension Study

PNH patients with at least one transfusion in the prior 24 months and at least 30,000 platelets/ microliter received Soliris over a 52-week period. Concomitant medications included anti-thrombotic agents in 63% of the patients and systemic corticosteroids in 40% of the patients. Overall, 96 of the 97 enrolled patients completed the study (one patient died following a thrombotic event). A reduction in intravascular hemolysis as measured by serum LDH levels was sustained for the treatment period and resulted in a reduced need for RBC transfusion and less fatigue. One hundred eighty-seven Soliris-treated PNH patients were enrolled in a long-term extension study. All patients sustained a reduction in intravascular hemolysis over a total Soliris exposure time ranging from 10 to 54 months. There were fewer thrombotic events with Soliris treatment than during the same period of time prior to treatment. However, the majority of patients received concomitant anticoagulants; the effects of anticoagulant withdrawal during Soliris therapy was not studied.

Atypical Hemolytic Uremic Syndrome (aHUS) (1-3)

Five single-arm studies [four prospective: C08-002A/B (NCT00844545 and NCT00844844), C08-003A/B (NCT00838513 and NCT00844428), C10-003 (NCT01193348), and C10-004 (NCT01194973); and one retrospective: C09-001r (NCT01770951)] evaluated the safety and efficacy of Soliris for the treatment of aHUS. Patients with aHUS received meningococcal vaccination prior to receipt of Soliris or received prophylactic treatment with antibiotics until 2 weeks after vaccination. In all studies, the dose of Soliris in adult and adolescent patients was 900 mg every 7 ± 2 days for 4 weeks, followed by 1200 mg 7 ± 2 days later, then 1200 mg every 14 ± 2 days thereafter. The dosage regimen for pediatric patients weighing less than 40 kg enrolled in Study C09-001r and Study C10-003 was based on body weight. Efficacy evaluations were based on thrombotic microangiopathy (TMA) endpoints.

Endpoints related to TMA included the following:

- Platelet count change from baseline.
- Hematologic normalization (*maintenance of normal platelet counts and LDH levels for at least four weeks*).
- Complete TMA response (*hematologic normalization plus at least a 25% reduction in serum creatinine for a minimum of four weeks*).
- TMA-event free status (*absence for at least 12 weeks of a decrease in platelet count of >25% from baseline, plasma exchange or plasma infusion, and new dialysis requirement*).
- Daily TMA intervention rate (*defined as the number of plasma exchange or plasma infusion interventions and the number of new dialyses required per patient per day*).

aHUS Resistant to Plasma Exchange/Plasma Infusion (PE/PI) (Study C08-002A/B)

Study C08-002A/B enrolled patients who displayed signs of TMA despite receiving at least four PE/PI treatments the week prior to screening. One patient had no PE/PI the week prior to screening because of PE/PI intolerance. In order to qualify for enrollment, patients were required to have a platelet count ≤150 x 10^9/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal, without the need for chronic dialysis. The median patient age was 28 (range: 17 to 68 years). Patients enrolled in Study C08-002A/B were required to have a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity level above 5%; observed range of values in the trial were 70%-121%. Seventy-six percent of patients had an identified complement regulatory factor mutation or auto-antibody.

Patients in Study C08-002A/B received Soliris for a minimum of 26 weeks. In Study C08-002A/B, the median duration of Soliris therapy was approximately 100 weeks (range: 2 weeks to 145 weeks).

Renal function, as measured by estimated glomerular filtration rate (eGFR), was improved and maintained during Soliris therapy. The mean eGFR (± standard deviation [SD]) increased from 23 ± 15 mL/min/1.73m^2 at baseline to 56 ± 40 mL/min/1.73m^2 by 26 weeks; this effect was maintained through 2 years (56 ± 30 mL/min/1.73m^2). Four of the five patients who required dialysis at baseline were able to discontinue dialysis.

Reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of Soliris. Soliris reduced signs of complement mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. In Study C08-002A/B, mean platelet count (± SD) increased from 109 ± 32 x 10^9/L at baseline to 169 ± 72 x 10^9/L by one week; this effect was maintained through 26 weeks (210 ± 68 x 10^9/L), and 2 years (205 ± 46 x 10^9/L). When treatment was continued for more than 26 weeks, two additional patients achieved Hematologic Normalization as well as Complete TMA response. Hematologic Normalization and Complete TMA response were maintained by all responders. In Study C08-002A/B, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins. Table 3 summarizes the efficacy results for Study C08-002A/B.

Table 3. Efficacy Results for Study C08-002A/B

Efficacy Parameter	**Study C08-002A/B at 26 wks[1] (N=17)**	**Study C08-002A/B at 2 yrs[2] (N=17)**
Complete TMA response, n (%) Median Duration of complete TMA response, weeks (range)	11 (65) 38 (25, 56)	13 (77) 99 (25, 139)
eGFR improvement ≥15 mL/min/1.73 m^2, n (%) Median duration of eGFR improvement, days (range)	9 (53) 251 (70, 392)	10 (59) ND

Hematologic normalization, n (%) Median Duration of hematologic normalization, weeks (range)	13 (76) 37 (25, 62)	15 (88) 99 (25, 145)
TMA event-free status, n (%)	15 (88)	15 (88)
Daily TMA intervention rate, median (range) Before eculizumab On eculizumab treatment	 0.82 (0.04, 1.52) 0 (0, 0.31)	 0.82 (0.04, 1.52) 0 (0, 0.36)

eGFR: estimated glomerular filtration rate; TMA: thrombotic microangiopathy; wks: week(s); yrs: year(s).

[1] At data cut-off (September 8, 2010).

[2] At data cut-off (April 20, 2012).

aHUS Sensitive to PE/PI (Study C08-003A/B)

Study C08-003A/B enrolled patients undergoing chronic PE/PI who generally did not display hematologic signs of ongoing TMA. All patients had received plasma therapy (PT) at least once every two weeks, but no more than three times per week, for a minimum of eight weeks prior to the first Soliris dose. Patients on chronic dialysis were permitted to enroll in Study C08-003A/B. The median patient age was 28 years (range: 13 to 63 years). Patients enrolled in Study C08-003A/B were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 37%-118%. Seventy percent of patients had an identified complement regulatory factor mutation or auto-antibody.

Patients in Study C08-003A/B received Soliris for a minimum of 26 weeks. In Study C08-003A/B, the median duration of Soliris therapy was approximately 114 weeks (range: 26 to 129 weeks).

Renal function, as measured by eGFR, was maintained during Soliris therapy. The mean eGFR (± SD) was 31 ± 19 mL/min/1.73m^2 at baseline and was maintained through 26 weeks (37 ± 21 mL/min/1.73m^2) and 2 years (40 ± 18 mL/min/1.73m^2). No patient required new dialysis with Soliris.

Reduction in terminal complement activity was observed in all patients after the commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. Platelet counts were maintained at normal levels despite the elimination of PE/PI. The mean platelet count (± SD) was 228 ± 78 x 10^9/L at baseline, 233 ± 69 x 10^9/L at week 26, and 224 ± 52 x 10^9/L at 2 years. When treatment was continued for more than 26 weeks, six additional patients achieved Complete TMA response. Complete TMA Response and Hematologic Normalization were maintained by all responders. In Study C08-003A/B, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins.

Table 4 summarizes the efficacy results for Study C08-003A/B.

Table 4. Efficacy Results for Study C08-003A/B

Efficacy Parameter	Study C08-003A/B at 26 wks[1] (N=20)	Study C08-003A/B at 2 yrs[2] (N=20)
Complete TMA response, n (%) Median duration of complete TMA response, weeks (range)	5 (25) 32 (12, 38)	11 (55) 68 (38, 109)
eGFR improvement ≥15 mL/min/1.73 m^2, n (%)	1 (5)	8 (40)
TMA Event-free status n (%)	16 (80)	19 (95)
Daily TMA intervention rate, median (range) Before eculizumab On eculizumab treatment	 0.23 (0.05, 1.07) 0	 0.23 (0.05, 1.07) 0 (0, 0.01)
Hematologic normalization[4], n (%) Median duration of hematologic normalization, weeks (range)[3]	18 (90) 38 (22, 52)	18 (90) 114 (33, 125)

eGFR: estimated glomerular filtration rate; TMA: thrombotic microangiopathy; wks: week(s); yrs: year(s).

1. At data cut-off (September 8, 2010).

2. At data cut-off (April 20, 2012).

3. Calculated at each post-dose day of measurement (excluding Days 1 to 4) using a repeated measurement analysis of variance (ANOVA) model.

4. In Study C08-003A/B, 85% of patients had normal platelet counts and 80% of patients had normal serum LDH levels at baseline, so hematologic normalization in this population reflects maintenance of normal parameters in the absence of PE/PI.

Retrospective Study in Patients with aHUS (C09-001r)

The efficacy results for the aHUS retrospective study (Study C09-001r) were generally consistent with results of the two prospective studies. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline. Mean platelet count (± SD) increased from 171 ± 83 x 10^9/L at baseline to 233 ± 109 x 10^9/L after one week of therapy; this effect was maintained through 26 weeks (mean platelet count [± SD] at week 26: 254 ± 79 x 10^9/L).

A total of 19 pediatric patients (ages 2 months to 17 years) received Soliris in Study C09-001r. The median duration of Soliris therapy was 16 weeks (range, 4 to 70 weeks) for children <2 years of age (n=5), 31 weeks (range, 19 to 63 weeks) for children 2 to <12 years of age (n=10), and 38 weeks (range, 1 to 69 weeks) for patients 12 to <18 years of age (n=4). Fifty-three percent of pediatric patients had an identified complement regulatory factor mutation or auto-antibody.

Overall, the efficacy results for these pediatric patients appeared consistent with what was observed in patients enrolled in Studies C08-002A/B and C08-003A/B (Table 5). No pediatric patient required new dialysis during treatment with Soliris.

Table 5. Efficacy Results in Pediatric Patients Enrolled in Study C09-001r

Efficacy Parameter	<2 yrs (N=5)	2 to <12 yrs (N=10)	12 to <18 yrs (N=4)	Total (N=19)
Complete TMA response, n (%)	2 (40)	5 (50)	1 (25)	8 (42)
Patients with eGFR improvement ≥ 15 mL/min/1.73 m^2, n (%)[2]	2 (40)	6 (60)	1 (25)	9 (47)
Platelet count normalization, n (%)[1]	4 (80)	10 (100)	3 (75)	17 (89)
Hematologic Normalization, n (%)	2 (40)	5 (50)	1 (25)	8 (42)
Daily TMA intervention rate, median (range)				
Before eculizumab	1 (0, 2)	<1 (0.07, 1.46)	<1 (0, 1)	0.31 (0.00, 2.38)
On eculizumab treatment	<1 (0, <1)	0 (0, <1)	0 (0, <1)	0.00 (0.00, 0.08)

eGFR: estimated glomerular filtration rate; TMA: thrombotic microangiopathy; yrs: year(s).

[1.] Platelet count normalization was defined as a platelet count of at least 150,000 X 10^9/L on at least two consecutive measurements spanning a period of at least 4 weeks.

[2.] Of the 9 patients who experienced an eGFR improvement of at least 15 mL/min/1.73 m^2, one received dialysis throughout the study period, and another received Soliris as prophylaxis following renal allograft transplantation.

Adult Patients with aHUS (Study C10-004)

Study C10-004 enrolled patients who displayed signs of TMA. In order to qualify for enrollment, patients were required to have a platelet count < lower limit of normal range (LLN), evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal, without the need for chronic dialysis. The median patient age was 35 (range: 18 to 80 years). All patients enrolled in Study C10-004 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 28%-116%. Fifty-one percent of patients had an identified complement regulatory factor mutation or auto-antibody. A total of 35 patients received PE/PI prior to eculizumab.

Patients in Study C10-004 received Soliris for a minimum of 26 weeks. In Study C10-004, the median duration of Soliris therapy was approximately 50 weeks (range: 13 weeks to 86 weeks).

Renal function, as measured by eGFR, was improved during Soliris therapy. The mean eGFR (± SD) increased from 17 ± 12 mL/min/1.73m^2 at baseline to 47 ± 24 mL/min/1.73m^2 by 26 weeks. Twenty of the 24 patients who required dialysis at study baseline were able to discontinue dialysis during Soliris treatment. Reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. In Study C10-004, mean platelet count (± SD) increased from 119 ± 66 x 10^9/L at baseline to 200 ± 84 x 10^9/L by one week; this effect was maintained through 26 weeks (mean platelet count [± SD] at week 26: 252 ± 70 x 10^9/L). In Study C10-004, responses to Soliris were similar in patients with and without identified mutations in genes

encoding complement regulatory factor proteins or auto-antibodies to factor H. Table 6 summarizes the efficacy results for Study C10-004.

Table 6. Efficacy Results for Study C10-004

Efficacy Parameter	**Study C10-004 (N=41)**
Complete TMA response, n (%), 95% CI Median duration of complete TMA response, weeks (range)	23 (56) 40, 72 42 (6, 75)
Patients with eGFR improvement ≥ 15 mL/min/1.73 m^2, n (%)	22 (54)
Hematologic Normalization, n (%) Median duration of hematologic normalization, weeks (range)	36 (88) 46 (10, 75)
TMA Event-free Status, n (%)	37 (90)
Daily TMA Intervention Rate, median (range) Before eculizumab On eculizumab treatment	 0.63 (0, 1.38) 0 (0, 0.58)

CI: confidence interval; eGFR: estimated glomerular filtration rate; TMA: thrombotic microangiopathy.

Pediatric and Adolescent Patients with aHUS (Study C10-003)

Study C10-003 enrolled patients who were required to have a platelet count < lower limit of normal range (LLN), evidence of hemolysis such as an elevation in serum LDH above the upper limits of normal, serum creatinine level ≥97 percentile for age without the need for chronic dialysis. The median patient age was 6.5 (range: 5 months to 17 years). Patients enrolled in Study C10-003 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 38%-121%. Fifty percent of patients had an identified complement regulatory factor mutation or auto-antibody. A total of 10 patients received PE/PI prior to eculizumab.

Patients in Study C10-003 received Soliris for a minimum of 26 weeks. In Study C10-003, the median duration of Soliris therapy was approximately 44 weeks (range: 1 dose to 88 weeks).

Renal function, as measured by eGFR, was improved during Soliris therapy. The mean eGFR (± SD) increased from 33 ± 30 mL/min/1.73m^2 at baseline to 98 ± 44 mL/min/1.73m^2 by 26 weeks. Among the 20 patients with a chronic kidney disease (CKD) stage ≥2 at baseline, 17 (85%) achieved a CKD improvement of ≥1 stage. Among the 16 patients ages 1 month to <12 years with a CKD stage ≥2 at baseline, 14 (88%) achieved a CKD improvement by ≥1 stage. Nine of the 11 patients who required dialysis at study baseline were able to discontinue dialysis during Soliris treatment. Responses were observed across all ages from 5 months to 17 years of age.

Reduction in terminal complement activity was observed in all patients after commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. The mean platelet count (± SD) increased from 88 ± 42 x 10^9/L at baseline to 281 ± 123 x 10^9/L by one week; this effect was maintained through 26 weeks (mean platelet count [± SD] at week 26: 293 ± 106 x 10^9/L). In Study C10-003,

responses to Solris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins or auto-antibodies to factor H.

Table 7 summarizes the efficacy results for Study C10-003.

Table 7. Efficacy Results for Study C10-003

Efficacy Parameter	Patients 1 month to < 12 years (N=18)	All Patients (N=22)
Complete TMA response, n (%) 95% CI Median Duration of complete TMA response, weeks (range)[1]	11 (61) 36, 83 40 (14, 77)	14 (64) 41, 83 37 (14, 77)
eGFR improvement ≥15 mL/min/1.73 m^2, n (%)	16 (89)	19 (86)
Complete Hematologic Normalization, n (%) Median Duration of complete hematologic normalization, weeks (range)	14 (78) 38 (14, 77)	18 (82) 38 (14, 77)
TMA Event-Free Status, n (%)	17 (94)	21 (95)
Daily TMA Intervention rate, median (range) Before eculizumab treatment On eculizumab treatment	 0.2 (0, 1.7) 0 (0, 0.01)	 0.4 (0, 1.7) 0 (0, 0.01)

CI: confidence interval; eGFR: estimated glomerular filtration rate; TMA: thrombotic microangiopathy.
[1.] Through data cutoff (October 12, 2012).

Generalized Myasthenia Gravis (gMG)

Adults **(1-3)**

The efficacy of Soliris for the treatment of gMG was established in Study (NCT01997229), a 26-week randomized, double-blind, parallel-group, placebo-controlled, multi-center trial that enrolled adult patients who met the following criteria at screening:

1. Positive serologic test for anti-AChR antibodies,
2. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV,
3. MG-Activities of Daily Living (MG-ADL) total score ≥6,
4. Failed treatment over 1 year or more with 2 or more immunosuppressive therapies (ISTs) either in combination or as monotherapy or failed at least 1 IST and required chronic plasmapheresis or plasma exchange (PE) or intravenous immunoglobulin (IVIg).

A total of 62 patients were randomized to receive Soliris treatment and 63 were randomized to receive placebo. Baseline characteristics were similar between treatment groups, including age at diagnosis (38 years in each group), gender [66% female (eculizumab) versus 65% female (placebo)], and duration of gMG [9.9 (eculizumab) versus 9.2 (placebo) years]. Over 95% of patients in each group were receiving acetylcholinesterase (AchE) inhibitors, and 98% were receiving ISTs. Approximately 50% of each group had been previously treated with at least 3 ISTs.

Soliris was administered according to the recommended dosage regimen.

The primary efficacy endpoint for Study (NCT01997229) was a comparison of the change from baseline between treatment groups in the MG-ADL total score at Week 26. The MG-ADL is a categorical scale that assesses the impact on daily function of 8 signs or symptoms that are typically affected in gMG. Each item is assessed on a 4-point scale where a score of 0 represents normal function and a score of 3 represents loss of ability to perform that function (total score 0-24). 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 Study (NCT01997229) was the change from baseline in the Quantitative Myasthenia Gravis (QMG) total score at Week 26. The QMG is a 13-item categorical scale assessing muscle weakness. Each item is assessed on a 4-point scale where a score of 0 represents no weakness and a score of 3 represents severe weakness (total score 0-39). 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)].

The results of the analysis of the MG-ADL and QMG from Study (NCT01997229) are shown in Table 8.

Table 8. Analysis of Change from Baseline to Week 26 in MG-ADL and QMG Total Scores in Study (NCT01997229)

Efficacy Endpoints	SOLIRIS-LS Mean (N=62) (SEM)	Placebo-LS Mean (N=63) (SEM)	SOLIRIS change relative to placebo – LS Mean Difference (95% CI)	p-values
MG-ADL	-4.2 (0.49)	-2.3 (0.48)	-1.9 (-3.3, -0.6)	(0.006[a]; 0.014[b])
QMG	-4.6 (0.60)	-1.6 (0.59)	-3.0 (-4.6, -1.3)	(0.001[a]; 0.005[b])

CI: confidence interval; MG-ADL: Myasthenia Gravis-Specific Activities of Daily Living scale; QMG: Quantitative Myasthenia Gravis; SEM: Standard Error of the Mean; LS Mean: least square mean for the treatment group; LS Mean-Difference (95% CI): Difference in least square mean with 95% confidence interval.
p-values (testing the null hypothesis that there is no difference between the two treatment arms:
[a] in least square means at Week 26 using a repeated measure analysis;
[b] in ranks at Week 26 using a worst rank analysis).

In Study (NCT01997229), a clinical response was defined in the MG-ADL total score as at least a 3-point improvement and in QMG total score as at least a 5-point improvement. The proportion of clinical responders at Week 26 with no rescue therapy was statistically significantly higher for Soliris compared to placebo for both measures. For both endpoints, and also at higher response

thresholds (≥4-, 5-, 6-, 7-, or 8-point improvement on MG-ADL, and ≥6-, 7-, 8-, 9-, or 10-point improvement on QMG), the proportion of clinical responders was consistently greater for Soliris compared to placebo. Available data suggest that clinical response is usually achieved by 12 weeks of Soliris treatment.

Pediatric Patients 6 Years of Age and Older (1)
In a 26-week, single arm study evaluating the safety of Soliris in 11 pediatric patients with gMG 12 to 17 years of age (Study ECU-MG-303), adverse reactions were consistent with those observed in adult patients with gMG. The safety of Soliris in pediatric patients 6 to less than 12 years of age is expected to be similar to that of adults and pediatric patients 12 years of age and older treated with Soliris.

Neuromyelitis Optica Spectrum Disorder (NMOSD) (1)
The efficacy of Soliris for the treatment of NMOSD was established in NMOSD Study 1 (NCT01892345), a randomized, double-blind, placebo-controlled trial that enrolled 143 patients with NMOSD who were anti-aquaporin-4 (AQP4) antibody positive and met the following criteria at screening:

1. History of at least 2 relapses in last 12 months or 3 relapses in the last 24 months, with at least 1 relapse in the 12 months prior to screening,
2. Expanded Disability Status Scale (EDSS) score ≤ 7 (consistent with the presence of at least limited ambulation with aid),
3. If on immunosuppressive therapy (IST), on a stable dose regimen,
4. The use of concurrent corticosteroids was limited to 20 mg per day or less,
5. Patients were excluded if they had been treated with rituximab or mitoxantrone within 3 months or with IVIg within 3 weeks prior to screening.

A total of 96 patients were randomized to receive Soliris treatment and 47 were randomized to receive placebo.

The baseline demographic and disease characteristics were balanced between treatment groups. During the treatment phase of the trial, 76% percent of patients received concomitant IST, including chronic corticosteroids; 24% of patients did not receive concomitant IST or chronic corticosteroids during the treatment phase of the trial.

Soliris was administered according to the recommended dosage regimen.

The primary endpoint for NMOSD Study 1 was the time to the first adjudicated on-trial relapse. The time to the first adjudicated on-trial relapse was significantly longer in Soliris-treated patients 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 first adjudicated on-trial relapse with or without concomitant treatment. Soliris-treated patients had a 96% relative

reduction in the adjudicated on-trial annualized relapse rate (ARR) compared to patients on placebo, as shown in Table 9.

Table 9. Adjudicated On-trial Annualized Relapse Rate – Full Analysis Set

Variable	Statistic	Placebo (N=47)	Soliris (N=96)
Total number of relapses	Sum	21	3
Adjusted adjudicated ARR[a]	Rate	0.350	0.016
Treatment effect[a]	Rate ratio (eculizumab/placebo)	…	0.045
	p-value	…	<0.0001

ARR: annualized relapse rate.
[a] Based on a Poisson regression adjusted for randomization strata and historical ARR in 24 months prior to screening.

Compared to placebo-treated patients, Soliris-treated patients had reduced annualized rates of hospitalizations (0.04 for Soliris versus 0.31 for placebo), of corticosteroid administrations to treat acute relapses (0.07 for Soliris versus 0.42 for placebo), and of plasma exchange treatments (0.02 for Soliris versus 0.19 for placebo).

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	J1299, J3490, J3590, J9999, Q5151, Q5152, [Deleted 4/1/2025: J1300, Q5139]

*Current Procedural Terminology (CPT®) ©2024 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
12/01/2025	Document updated. The following changes were made to Coverage: 1) Updated conditional criteria for the treatment of generalized myasthenia gravis at align with FDA indication of use for those 6 years of age or older; 2) Removed conditional statements concerning the use of other biologics to treat conditions addressed by this policy; 3) Removed "but not limited to" and added “non-FDA approved” and to existing experimental, investigational and unproven statement; and 4) Replaced “Description Section” with “Policy Guidelines” in NOTE 2. References 8-10 added, others updated; some removed.

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