Corporate Medical Policy: Eculizumab (Soliris®) **Notification** **POLICY EFFECTIVE DECEMBER 1, 2024**

Restricted Product(s):

- eculizumab (Soliris®) intravenous infusion for administration by a healthcare professional

FDA Approved Use:

- For treatment of patients with paroxysmal nocturnal hemoglobinuria to reduce hemolysis
- For treatment of patients with atypical hemolytic uremic syndrome to inhibit complement-mediated thrombotic microangiopathy
  - Limitation of use: Not for treatment of Shiga toxin E. coli related hemolytic uremic syndrome
- For treatment of adult patients with generalized myasthenia gravis who are anti-acetylcholine receptor (AchR) antibody positive
- For treatment of adult patients with neuromyelitis optica spectrum disorder who are anti-aquaporin-4 (AQP4) antibody positive

Criteria for Medical Necessity:

The restricted product(s) may be considered medically necessary when the following criteria are met:

Initial Criteria for Approval:

1. The patient has a diagnosis of **paroxysmal nocturnal hemoglobinuria (PNH) [medical record documentation required]**; **AND**
   a. The patient is 18 years of age or older; **AND**
   b. ONE of the following:
      i. The patient is transfusion-dependent prior to starting therapy with the requested agent, defined by at least one transfusion in the previous 24 months due to documented hemoglobin < 9 g/dL in patients with symptoms from anemia OR hemoglobin < 7 g/dL in patients without anemic symptoms **[medical record documentation required]**; **OR**
      ii. The patient has a documented history of major adverse vascular events from thromboembolism **[medical record documentation required]**; **AND**
   c. The patient will NOT be using the requested agent in combination with another complement inhibitor used to treat PNH (e.g., iptacopan, crovalimab, ravulizumab, pegcetacoplan) **[medical record documentation required]**; **AND**
   d. The patient has tried and had an inadequate response to ravulizumab (Ultomiris®) AND pegcetacoplan (Empaveli™) **[medical record documentation required]**; **OR**
   e. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to BOTH ravulizumab (Ultomiris®) and pegcetacoplan (Empaveli™) **[medical record documentation required]**; **OR**

2. The patient has a diagnosis of **atypical hemolytic uremic syndrome (aHUS) [medical record documentation required]**; **AND**
    a. The patient is 2 months of age or older; **AND**
    b. The patient does NOT have Shiga toxin *E.coli* related hemolytic uremic syndrome (STEC-HUS) **[medical record documentation required]**; **AND**
    c. The patient will NOT be using the requested agent in combination with another complement inhibitor used to treat aHUS (e.g., ravulizumab) **[medical record documentation required]**; **AND**
    d. The patient has tried and had an inadequate response to ravulizumab (Ultomiris®) **[medical record documentation required]**; **OR**
    e. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to ravulizumab (Ultomiris®) **[medical record documentation required]**; **OR**

3. The patient has a diagnosis of **refractory generalized myasthenia gravis (gMG) [medical record documentation required]**; **AND**
    a. The patient is 18 years of age or older; **AND**
    b. The patient has class II to IV disease according to Myasthenia Gravis Foundation of America (MGFA) classification criteria, or as scored by a comparable standardized rating scale that reliably measures MG disease severity **[medical record documentation required]**; **AND**
    c. The patient is anti-acetylcholine receptor (AchR) antibody positive **[medical record documentation required]**; **AND**
    d. The patient has impaired activities of daily living defined by a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of 6 or higher, or as scored by a comparable standardized rating scale that reliably measures MG disease severity **[medical record documentation required]**; **AND**
    e. The patient has tried and had an inadequate response to THREE prior lines of non-steroidal chronic immunomodulating therapies used alone or in combination, for at least one year **[medical record documentation required]**; **OR**
    f. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to ALL non-steroidal chronic immunomodulating therapies **[medical record documentation required]**; **AND**
    g. The patient will NOT be using the requested agent in combination with another biologic immunomodulator agent used to treat gMG (e.g., rozanolixizumab, ravulizumab, efgartigimod alfa/efgartigimod alfa and hyaluronidase, zilucoplan) **[medical record documentation required]**; **AND**
    h. The patient has tried and had an inadequate response to rozanolixizumab (Rystiggo®), ravulizumab (Ultomiris®), AND efgartigimod (Vyvgart®, Vyvgart® Hytrulo) **[medical record documentation required]**; **OR**
    i. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to ALL of the following: rozanolixizumab (Rystiggo®), ravulizumab (Ultomiris®), and efgartigimod (Vyvgart®, Vyvgart® Hytrulo) **[medical record documentation required]**; **OR**

4. The patient has a diagnosis of **neuromyelitis optica spectrum disorder (NMOSD)**; **AND**
    a. The patient is 18 years of age or older; **AND**
    b. The patient is anti-aquaporin-4 (AQP4) antibody seropositive **[medical record documentation required]**; **AND**

c. The diagnosis has been confirmed by the presence of at least one of the following core clinical characteristics **[medical record documentation required]**:
    i. Optic neuritis; **OR**
    ii. Acute myelitis; **OR**
    iii. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting; **OR**
    iv. Acute brainstem syndrome; **OR**
    v. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions; **OR**
    vi. Symptomatic cerebral syndrome with NMOSD-typical brain lesions; **AND**
d. The patient has NOT been treated with rituximab or mitoxantrone during the previous 3 months, or intravenous immune globulin (IVIG) during the previous 3 weeks **[medical record documentation required]**; **AND**
e. The patient will NOT be using the requested agent in combination with another biologic immunomodulator agent used to treat NMOSD (e.g., inebilizumab, ravulizumab, satralizumab) **[medical record documentation required]**; **AND**
f. The patient has tried and had an inadequate response to inebilizumab (Uplizna®), ravulizumab (Ultomiris®), AND satralizumab (Enspryng™) **[medical record documentation required]**; **OR**
g. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to ALL of the following: inebilizumab (Uplizna®), ravulizumab (Ultomiris®), and satralizumab (Enspryng™) **[medical record documentation required]**; **AND**

5. The patient has received a meningococcal vaccine at least two weeks prior to starting therapy with the requested agent **[medical record documentation required]**; **AND**
6. The patient is revaccinated according to current medical guidelines for vaccine use while on therapy with the requested agent; **AND**
7. The requested quantity does NOT exceed the maximum units allowed for the duration of approval (see table below); **AND**
8. For requests for injection or infusion administration of the requested medication in an **inpatient or outpatient hospital setting,** Site of Care Criteria applies (outlined below)*

Duration of Approval: 180 days (6 months)

Continuation Criteria for Approval:

1. The patient was approved through Blue Cross NC initial criteria for approval; **OR**
2. The patient would have met initial criteria for approval at the time they started therapy; **AND**

3. For patients with a diagnosis of **paroxysmal nocturnal hemoglobinuria (PNH)**:

   a. The patient has had either stabilization or improvement of symptoms from baseline while using the requested agent, as demonstrated by the following **[medical record documentation required]**:
      i. Significant reduction in transfusion requirements **[medical record documentation required]**; **AND**
      ii. No thromboembolism events persisting while using the requested agent **[medical record documentation required]**; **AND**
   b. The patient will NOT be using the requested agent in combination with another complement inhibitor used to treat PNH (e.g., iptacopan, crovalimab, ravulizumab, pegcetacoplan) **[medical record documentation required]**; **OR**

4. For patients with a diagnosis of **atypical hemolytic uremic syndrome (aHUS)**:
   a. The patient has demonstrated a positive clinical response as measured by hematological parameters or thrombotic microangiopathy (TMA) response while using the requested agent **[medical record documentation required]**; **AND**
   b. The patient will NOT be using the requested agent in combination with another complement inhibitor used to treat aHUS (e.g., ravulizumab) **[medical record documentation required]**; **OR**

5. For patients with a diagnosis of refractory **generalized myasthenia gravis (gMG)**:
   a. The patient has demonstrated either stabilization or improvement of symptoms (i.e., improved MG-ADL total score, improved score of another comparable standardized rating scale that reliably measures MG disease severity) from baseline while using the requested agent **[medical record documentation required]**; **AND**
   b. The patient will NOT be using the requested agent in combination with another biologic immunomodulator agent used to treat gMG (e.g., rozanolixizumab, ravulizumab, efgartigimod alfa/efgartigimod alfa and hyaluronidase, zilucoplan) **[medical record documentation required]**; **OR**

6. For patients with a diagnosis of **neuromyelitis optica spectrum disorder (NMOSD)**:
   a. The patient has demonstrated clinical benefit while using the requested agent (i.e., reduction of relapses or disease stabilization) **[medical record documentation required]**; **AND**
   b. The patient will NOT be using the requested agent in combination with another biologic immunomodulator agent used to treat NMOSD (e.g., inebilizumab, ravulizumab, satralizumab) **[medical record documentation required]**; **AND**

7. The patient is revaccinated according to current medical guidelines for vaccine use while on therapy with the requested agent; **AND**
8. The requested quantity does NOT exceed the maximum units allowed for the duration of approval (see table below); **AND**
9. For requests for injection or infusion administration of the requested medication in an **inpatient or outpatient hospital setting,** Site of Care Criteria applies (outlined below)*

Duration of Approval: 365 days (1 year)

FDA Label Reference				
Medication	**Indication**	**Dosing^**	**HCPCS**	**Maximum Units***
eculizumab (Soliris®) intravenous (IV) infusion	PNH in patients ≥18 years old	PNH: • 600 mg IV weekly for the first 4 weeks, then • 900 mg IV for the 5th dose 1 week later, then • 900 mg IV every 2 weeks thereafter	J1300	**PNH:** Initial: 1320 Continuation: 2340
	aHUS in patients ≥2 months old	aHUS: ≥ 18 years old: • 900 mg IV weekly for the first 4 weeks, then • 1200 mg IV for the 5th dose 1 week later, then • 1200 mg IV every 2 weeks thereafter < 18 years old (weight-based): • ≥ 40 kg: 900 mg IV weekly x 4 doses, then 1200 mg at week 5, then 1200 mg every 2 weeks • 30 kg to < 40 kg: 600 mg IV weekly x 2 doses, then 900 mg at week 3, then 900 mg every 2 weeks • 20 kg to < 30 kg: 600 mg IV weekly x 2 doses, then 600 mg at week 3, then 600 mg every 2 weeks • 10 kg to < 20 kg: 600 mg IV weekly x 1 dose, then 300 mg at week 2, then 300 mg every 2 weeks • 5 kg to < 10 kg: 300 mg IV weekly x 1 dose, then 300 mg at week 2, then 300 mg every 3 weeks		**aHUS:** Initial: 1800 Continuation: 3120

FDA Label Reference				
Medication	**Indication**	**Dosing^**	**HCPCS**	**Maximum Units***
	gMG in patients ≥18 years old	gMG: • 900 mg IV weekly for the first 4 weeks, then • 1200 mg IV for the 5th dose 1 week later, then • 1200 mg IV every 2 weeks thereafter		**gMG:** Initial: 1800 Continuation: 3120
	NMOSD in patients ≥18 years old	NMOSD: • 900 mg IV weekly for the first 4 weeks, then • 1200 mg IV for the 5th dose 1 week later, then • 1200 mg IV every 2 weeks thereafter		**NMOSD:** Initial: 1800 Continuation: 3120

^Supplemental dosing of eculizumab (Soliris) is required for aHUS, gMG, and NMOSD in the setting of concomitant plasmapheresis or plasma exchange, or fresh frozen plasma infusion

***Maximum units allowed for duration of approval**

***Site of Care Medical Necessity Criteria**

1. For requests for injection or infusion administration in an **inpatient setting**, the injection or infusion may be given if the above medical necessity criteria are met AND the inpatient admission is NOT for the sole purpose of administering the injection or infusion; **OR**
2. For requests for injection or infusion administration in an **outpatient hospital setting**, the injection or infusion may be given if the above medical necessity criteria are met AND ONE of the following must be met:
    a. History of mild adverse events that have not been successfully managed through mild pre-medication (e.g., diphenhydramine, acetaminophen, steroids, fluids, etc.); **OR**
    b. Inability to physically and cognitively adhere to the treatment schedule and regimen complexity; **OR**
    c. New to therapy, defined as initial injection or infusion OR less than 3 months since initial injection or infusion; **OR**
    d. Re-initiation of therapy, defined as ONE of the following:
        i. First injection or infusion after 6 months of no injections or infusions for drugs with an approved dosing interval less than 6 months duration; **OR**
        ii. First injection or infusion after at least a 1-month gap in therapy outside of the approved dosing interval for drugs requiring every 6 months dosing duration; **OR**
    e. Requirement of a change in the requested restricted product formulation; **AND**
3. If the Site of Care Medical Necessity Criteria in #1 or #2 above are not met, the injection or infusion will be administered in a **home-based infusion** or physician office setting with or without supervision by a certified healthcare professional.

References: all information referenced is from FDA package insert unless otherwise noted below.

1. Brodsky RA, Young NS, Antonioli E, et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. *Blood*. 2008;111(4):1840-7.
2. Dmytrijuk A, Robie-Suh K, Cohen MH, et al. FDA report: eculizumab (Soliris) for the treatment of patients with paroxysmal nocturnal hemoglobinuria. *Oncologist*. 2008;13(9):993-1000.
3. Gilhus, NE. Myasthenia Gravis. *N Engl J Med*. 2016;375:2570-81.
4. Hillmen P, Muus P, Röth A, et al. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol*. 2013 Apr 25.
5. Howard JF Jr, Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in antiacetylcholine receptor antibody-positive refractory generalized myasthenia gravis (REGAIN): a phase 3, randomized, double-blind, placebo-controlled, multicentre study. *Lancet Neurol*. 2017.pii: S1474-4422(17)30369-1.
6. Lapeyraque AL, Malina M, Fremeaux-Bacchi V, et al. Eculizumab in severe Shiga-toxinassociated HUS. *N Engl J Med*. 2011 Jun 30;364(26):2561-3.
7. Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic–uremic syndrome. *N Engl J Med*. 2013;368:2169-81.
8. Narayanaswami P, Sanders DB, Wolfe GI, et al. International consensus guidance for management of myasthenia gravis: 2020 update. *Neurology*. 2021;96(3):114-122.
9. Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. *N Engl J Med*. 2019;381:614-25.
10. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: executive summary. *Neurology*. 2016;87:419-25.
11. Schrezenmeier H, Muus P, Socié G, Szer J, Urbano-Ispizua A, et al. Baseline characteristics and disease burden in patients in the International Paroxysmal Nocturnal Hemoglobinuria Registry. Haematologica. 2014 May;99(5):922-9.

Policy Implementation/Update Information: Criteria and treatment protocols are reviewed annually by the Blue Cross NC P&T Committee, regardless of change. This policy is reviewed in Q2 annually.

December 2024: Criteria change: For NMOSD indication, added requirement for trial and failure of ravulizumab (Ultomiris) to existing required trial and failure of Uplizna and Enspryng. Updated requirement within initial and continuation sections that Soliris will not be used in combination with ravulizumab for clarity. For PNH indication, updated requirement within initial and continuation sections that Soliris will not be used in combination with newly approved crovalimab for clarity. For gMG indication, added requirement within initial and continuation sections for clarity that Soliris will not be used in combination with the following products: rozanolixizumab, ravulizumab, efgartigimod

alfa/efgartigimod alfa and hyaluronidase, and zilucoplan. Formatting changes made throughout FDA label reference table for clarity with no change to policy intent. **Policy notification given 10/1/2024 for effective date 12/1/2024**.
January 2024: Criteria update: For PNH indication, updated list of complement inhibitors not to be used concomitantly for clarity.
September 2023: Criteria change: Updated trial and failure requirements for gMG indication to include newly approved Rystiggo. Updated scoring classification diagnostic criteria to include a comparable standardized rating scale that reliably measures MG disease severity. Updated references.
August 2022: Criteria change: Added requirement for trial and failure of both ravulizumab (Ultomiris) AND efgartigimod (Vyvgart) for gMG indication. **Policy notification given 6/1/2022 for effective date 8/1/2022**.
October 2021: Criteria change: Changed requirement for trial and failure of both ravulizumab (Ultomiris) AND pegcetacoplan (Empaveli) for PNH indication. **Policy notification given 8/2/2021 for effective date 10/1/2021**.
June 2021: Criteria change: Added maximum units; medical policy formatting change. **Policy notification given 4/16/2021 for effective date 6/16/2021**.
*Further historical criteria changes and updates available upon request from Medical Policy and/or Corporate Pharmacy.