Utilization Review Policy 194B

POLICY: Soliris® (eculizumab injection, for intravenous use – Alexion)

EFFECTIVE DATE: 1/1/2020
LAST REVISION DATE: 09/16/2024

COVERAGE CRITERIA FOR: UCare Medicare Plans Only (UCare Medicare, EssentiaCare, Group Plans, MSHO, Connect + Medicare, UCare Your Choice)

OVERVIEW
Soliris, a complement inhibitor, is indicated for the following uses:[1]

- **Atypical hemolytic uremic syndrome** (aHUS), to inhibit complement-mediated thrombotic microangiopathy.
  Limitation of Use. Soliris is not indicated for the treatment of patients with Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome.
- **Generalized myasthenia gravis** (gMG), in adults who are anti-acetylcholine receptor (AChR) antibody-positive.
- **Neuromyelitis optica spectrum disorder** (NMOSD), in adults who are anti-aquaporin-4 (AQP4) antibody positive.
- **Paroxysmal nocturnal hemoglobinuria** (PNH), to reduce hemolysis.

The Soliris prescribing information has a Boxed Warning about serious meningococcal infections.[1] Soliris is only available through a restricted access program, Soliris Risk Evaluation and Mitigation Strategy (REMS).

The safety and effectiveness of Soliris for the treatment of PNH, gMG, and NMOSD in pediatric patients have not been established.[1] The safety and effectiveness of Soliris in pediatric patients for aHUS is supported by evidence from four adequate and well-controlled clinical studies assessing the safety and effectiveness of Soliris for the treatment of aHUS.

Disease Overview
Hemolytic uremic syndrome (HUS) is defined as the triad of non-immune hemolytic anemia, thrombocytopenia, and acute renal failure, in which the underlying lesions are mediated by systemic thrombotic microangiopathy.[2] aHUS should be distinguished from a more common condition referred to as typical HUS.[3] aHUS is a sub-type of HUS in which thrombotic microangiopathy is the consequence of endothelial damage in the microvasculature of the kidneys and other organs due to a dysregulation of the activity of the complement system. The typical form is caused by infection with certain strains of *E. coli* bacteria that produce toxic substances called Shiga-like toxins; Soliris is not indicated for the treatment of Shiga toxin *E. coli*-related hemolytic uremic syndrome.[1-3]

Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs.[4] The hallmark of MG is muscle weakness that worsens after periods of activity and improves after periods of rest. Acquired MG results from the binding of autoantibodies to components of the neuromuscular junction, most commonly the AChR.[5] Soliris was studied in patients with gMG with anti-AChR antibodies with a Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV and a Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score ≥ 6.[1]

NMOSD is a rare, relapsing, autoimmune disorder of the brain and spinal cord with optic neuritis and/or myelitis as predominate characteristic symptoms.[6] NMOSD often causes significant, permanent damage to vision and/or spinal cord function resulting in blindness or impaired mobility.[7] Patients may experience pain, paralysis, loss of bowel and bladder control, loss of visual acuity, uncontrolled motor functions, and complications can cause death.

PNH is a rare, genetic disorder of hematopoietic stem cells.[8,9] The mutation in the X-linked gene phosphatidylinositol glycan class A (PIGA) results in a deficiency in the glycosylphosphatidylinositol (GPI) protein, which is responsible for anchoring other protein moieties to the surface of the erythrocytes. Loss of anchoring of these proteins causes cells to hemolyze and leads to complications such as hemolytic anemia, thrombosis, and peripheral blood cytopenias. PNH is a clinical diagnosis that should be confirmed with peripheral blood flow cytometry to detect the absence or severe deficiency of GPI-anchored proteins on at least two cell lineages.[8,10] Prior to the availability of complement inhibitors, only supportive measures, in terms of managing the cytopenias and controlling thrombotic risk were available. Supportive measures include platelet transfusion, immunosuppressive therapy for patients with bone marrow failure, use of erythropoietin for anemias, and aggressive anticoagulation.

Recommendations
There are no formal guidelines for treatment of aHUS.

A consensus statement for the diagnosis and treatment of PNH was published in 2021.[8] Treatment options for PNH are supportive care, allogeneic hematopoietic stem cell transplantation, and complement blockade by the anti-C5 monoclonal antibody (Soliris). Supportive care include use of oral iron to replace the large urinary losses; folate and vitamin B_{12} supplementation; red blood cell transfusion when these measures do not maintain adequate hemoglobin levels; use of antibiotics to treat bacterial infections as soon as possible since infections can exacerbate hemolytic crises in patients with PNH; use of corticosteroids to reduce the severity and duration of the hemolytic crises; use of Soliris as primary prophylaxis in patients with high PNH clone size (granulocyte close > 50%), high level of D dimer, pregnancy, perioperative condition, and other associated thrombophilia risk factors; and use of immunosuppressives in patients with PNH and aplastic anemia and bone marrow deficiency.

An international consensus guidance for the management of MG was published in 2016.[5] The consensus guidance recommends pyridostigmine for the initial treatment in most patients with MG. The ability to discontinue pyridostigmine can indicate that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or immunosuppressant

therapy should be used in all patients with MG who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal immunosuppressant agents used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Plasma exchange and intravenous immunoglobulin can be used as short-term treatments in certain patients. A 2020 update to this consensus guidance provides new recommendations for methotrexate, rituximab, and Soliris.[11] All recommendations should be considered extensions or additions to recommendations made in the initial international consensus guidance. Oral methotrexate may be considered as a steroid-sparing agent in patients with gMG who have not tolerated or responded to steroid-sparing agents. Rituximab should be considered as an early therapeutic option in patients with anti-muscle specific kinase antibody-positive MG who have an unsatisfactory response to initial immunotherapy. Soliris should be considered in the treatment of severe, refractory, anti-AChR antibody-positive MG.

The Neuromyelitis Optica Study Group (NEMOS) published revised recommendations for the treatment of NMOSD in 2024.[12] The standard of care for the treatment of NMOSD attacks (for both AQP4-IgG-positive and double-negative cases) are high-dose glucocorticoids and/or apheresis therapy. Long term immunotherapy is recommended for patients with AQP4-IgG-positive NMOSD. NEMOS notes the first-choice therapies for the treatment of AQP4-IgG-positive NMOSD are Soliris, Ultomiris® (ravulizumab-cwyz intravenous infusion and subcutaneous injection) [awaiting FDA approval], Enspryng® (satralizumab-mwge subcutaneous injection), Uplizna® (inebilizumab-cdon intravenous infusion), and rituximab. The order of preference for these therapies is unclear and further comparative trials and real-world data are needed. The choice of treatment is dependent on several factors, including disease activity and severity, mode and onset of action, possibility to combine it with immunosuppressive drugs, effect on autoimmune and other comorbidities, gender (family planning issues), frequency and route of administration, side effect profile, as well as patient and physician preference. In general, if a patient fails a first-choice treatment, another first-choice treatment should be tried; other options include use of a second-choice treatment (azathioprine, mycophenolate mofetil, low-dose oral glucocorticoids) or the addition of a second-choice treatment to the regimen.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Soliris. Approval is recommended for those who meet the conditions of coverage in the **Criteria** and **Dosing** for the listed indication(s). All approvals for initial therapy are provided for the initial approval duration noted below. In cases where the dosing interval is provided in months, 1 month is equal to 30 days.

This policy incorporates Medicare coverage guidance as set forth in National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs), as well as in companion policy articles and other guidance applicable to the relevant service areas. These documents are cited in the References section of this policy. In some cases, this guidance includes specific lists of HCPCS and ICD-10 codes to help inform the coverage determination process. The Articles that include specific lists for billing and coding purposes will be included in the Reference section of this policy. However, to the extent that this policy cites such lists of HCPCS and ICD-10 codes,

they should be used for reference purposes only. The presence of a specific HCPCS or ICD-10 code in a chart or companion article to an LCD is not by itself sufficient to approve coverage. Similarly, the absence of such a code does not necessarily mean that the applicable condition or diagnosis is excluded from coverage.

Note: Conditions for coverage outlined in this Medicare Advantage Medical Policy may be less restrictive than those found in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles. Examples of situations where this clinical policy may be less restrictive include, but are not limited to, coverage of additional indications supported by CMS-approved compendia and the exclusion from this policy of additional coverage criteria requirements outlined in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles.

Indications with a ^ below are also covered (and, if applicable, further detailed/referenced) in the corresponding Commercial Care Continuum (CC) Policy. Note: Additional criteria requirements for coverage of the same indication as outlined in the Commercial CC Policy and this Medicare Advantage CC Policy may NOT be the same.

Indications with a # below are not listed as covered indications in the corresponding CC Policy but ARE listed as covered indications in Local Coverage Determination (L33394).

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

1. Atypical Hemolytic Uremic Syndrome. ^

Criteria. Approve for 1 year if the patient does not have signs of Shiga toxin *E. coli* related hemolytic uremic syndrome.

Dosing. Approve if the dose meets the following (A or B):

A) For patients ≥ 18 years of age, the dose is administered intravenously and meets ONE of the following (i or ii):
- **i.** The dose is ≤ 900 mg weekly for the first 4 weeks; OR
- **ii.** The dose is ≤ 1,200 mg every 2 weeks thereafter.

B) For patients < 18 years of age, the dose is administered intravenously and meets ONE of the following (i, ii, iii, iv, or v):
- **i.** ≥ 40 kg: 900 mg intravenously weekly x 4 doses, 1,200 mg at week 5; then 1,200 mg every 2 weeks.
- **ii.** 30 kg to < 40 kg: 600 mg intravenously weekly x 2 doses, 900 mg at week 3; then 900 mg every 2 weeks.
- **iii.** 20 kg to < 30 kg: 600 mg intravenously weekly x 2 doses, 600 mg at week 3; then 600 mg every 2 weeks.
- **iv.** 10 kg to < 20 kg: 600 mg intravenously weekly x 1 dose, 300 mg at week 2; then 300 mg every 2 weeks.

v. 5 kg to < 10 kg: 300 mg intravenously weekly x 1 dose, 300 mg at week 2; then 300 mg every 3 weeks.

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2. Generalized Myasthenia Gravis. ^

Criteria. Approve Soliris if the patient meets ONE of the following criteria (A or B):

A) Initial therapy: Approve for 6 months if the patient meets the following criteria (i, ii, and iii):
- **i.** The patient is ≥ 18 years of age; AND
- **ii.** The patient has confirmed anti-acetylcholine receptor antibody positive generalized Myasthenia Gravis; AND
- **iii.** The patient received or is currently receiving or has had inadequate efficacy, a contraindication, or significant intolerance to at least one conventional therapy. Note: Examples of conventional therapy include pyridostigmine, azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, cyclophosphamide).

B) Patient currently receiving Soliris: Approve for 1 year if the patient meets the following (i and ii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** The patient is continuing to derive benefit from Soliris, according to the prescriber.
  Note: Examples of derived benefit include reductions in exacerbations of myasthenia gravis, improvements in speech, swallowing, mobility, and respiratory function.

Dosing. Approve if the dose is administered intravenously and meets ONE of the following (A or B):

A) The dose is ≤ 900 mg weekly for the first 4 weeks; OR

B) The dose is ≤ 1,200 mg every 2 weeks thereafter.

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3. Paroxysmal Nocturnal Hemoglobinuria. ^

Criteria. Approve if the patient meets ONE of the following (A or B):

A) Initial therapy: Approve for 6 months if the patient meets the following criteria (i and ii):
- **i.** The patient is ≥ 18 years of age; AND
- **ii.** Paroxysmal nocturnal hemoglobinuria diagnosis was confirmed by peripheral blood flow cytometry results showing the absence or deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins on at least two cell lineages; OR

B) Patient currently receiving Soliris: Approve for 1 year if the patient meets the following (i and ii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** The patient is continuing to derive benefit from Soliris, according to the prescriber.

Note: Examples of derived benefit include stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis.

Dosing. Approve if the dose is administered intravenously and meets ONE of the following (A or B):
A) The dose is ≤ 600 mg weekly for the first 4 weeks; OR
B) The dose is ≤ 900 mg every 2 weeks thereafter.

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4. Neuromyelitis Optica Spectrum Disorder. ^

Criteria. Approve if the patient meets ONE of the following criteria (A or B):
A) Initial Therapy. Approve for 1 year if the patient meets the following criteria (i and ii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Diagnosis was confirmed by a positive blood serum test for anti-aquaporin-4 antibody.

B) Patients Currently Receiving Soliris. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Diagnosis was confirmed by a positive blood serum test for anti-aquaporin-4 antibody; AND
- **iii.** According to the prescriber, patient has had clinical benefit from the use of Soliris.
  Note: Examples of clinical benefit include reduction in relapse rate, reduction in symptoms (e.g., pain, fatigue, motor function), and a slowing progression in symptoms.

Dosing. Approve if the dose is administered intravenously and meets ONE of the following (A or B):
A) The dose is ≤ 900 mg weekly for the first 4 weeks; OR
B) The dose is ≤ 1,200 mg every 2 weeks thereafter.

OTHER USES WITH SUPPORTIVE EVIDENCE

5. Dense Deposit Disease.[15] #

Criteria. Approve Soliris for 1 year if the patient meets the following criteria (A and B):
i. Dense deposit disease has been proven by a biopsy;[15] AND
ii. The patient has documented elevated serum levels of sC5b-9 (serum Membrane Attack Complex [sMAC]).[13]

Dosing: Induction dose is 900 mg per week for 4 weeks; maintenance dose is 1,200 mg every 2 weeks starting at week 5.[14]

Conditions Not Recommended for Approval
Coverage of Soliris is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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13. Centers for Medicare and Medicaid Services, National Government Services, Inc, Local Coverage Article: Billing and Coding: Eculizumab (Soliris®) - Related to LCD L33394 (A54548) (Original effective date 10/1/15, Revision date 10/1/2022). Accessed on April 22, 2024.
14. Eculizumab for the Treatment of Dense-Deposit Disease. *N Engl J Med* 2012; 366:1163-1165

15. Centers for Medicare and Medicaid Services, National Government Services, Inc, Local Coverage Determination (LCD): Drugs and Biologicals, Coverage of, for Label and Off-Label Uses (L33394) [original date 10/01/2015; revision effective date 11/1/2022]. Accessed on April 22, 2024.

Type of Revision	Summary of Changes	Date
Policy created	New Medicare Advantage Medical Policy	07/11/2018
Policy revision	Reviewed and revised original policy created 07/11/2018 in accordance with Local Coverage Article A54548 and Soliris Utilization Review Policy.	08/28/2019
Policy revision	Completion of 2019 monthly monitoring process. Removed criteria for Neuromyelitis Optica Spectrum Disorder to align with LCA A54548.	11/06/2019
Policy revision	Completion of 2019 monthly monitoring process in accordance with Local Coverage Determination L33394, Local Coverage Article A54548, and Complement Inhibitors – Soliris Utilization Review Policy.	11/27/2019
Policy revision	Non-clinical update to policy to add the statement "This policy incorporates Medicare coverage guidance as set forth in National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs), as well as in companion policy articles and other guidance applicable to the relevant service areas. These documents are cited in the References section of this policy. In some cases, this guidance includes specific lists of HCPCS and ICD-10 codes to help inform the coverage determination process. The Articles that include specific lists for billing and coding purposes will be included in the Reference section of this policy. However, to the extent that this policy cites such lists of HCPCS and ICD-10 codes, they should be used for reference purposes only. The presence of a specific HCPCS or ICD-10 code in a chart or companion article to an LCD is not by itself sufficient to approve coverage. Similarly, the absence of such a code does not necessarily mean that the applicable condition or diagnosis is excluded from coverage."	1/30/2020
Policy revision	*Added the following to the Policy Statement "Note: Conditions for coverage outlined in this Medicare Advantage Medical Policy may be less restrictive than those found in applicable National Coverage Determinations, Local Coverage Determinations and/or	09/09/2020

	Local Coverage Articles. Examples of situations where this clinical policy may be less restrictive include, but are not limited to, coverage of additional indications supported by CMS-approved compendia and the exclusion from this policy of additional coverage criteria requirements outlined in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles." *Updated references *removed criteria requiring evidence of clinically significant hemolysis or documented history of a major adverse event from thromboembolism from PNH indication. *removed from aHUS indication the following criterai: Thrombotic thrombocytopenic purpura (TTP) has been ruled out (for example, normal ADAMTS 13 activity and no evidence of an ADAMTS 13 inhibitor); OR If TTP cannot be ruled out by laboratory and clinical evaluation, a trial of plasma exchange has not resulted in clinical improvement. also removed continuation criteria from this indication. *removed continuation criteria from dense deposit disease.	
Policy Revision	**Generalized Myasthenia Gravis (gMG).**For patients currently receiving Soliris, examples of the patient continuing to derive benefit was changed to a Note and prescribing physician was changed to prescriber. **Paroxysmal Nocturnal Hemoglobinuria.** For patients currently receiving Soliris, examples of the patient continuing to derive benefit was changed to a Note and prescribing physician was changed to prescriber. **Neuromyelitis Optica Spectrum Disorder.** Criteria was separated into Initial Therapy and Patients Currently Receiving Soliris. For both sections, criteria for approval duration, age restriction, diagnosis confirmation, and specialist requirement remained the same as before. For Initial Therapy, a Note was created to allow an exception to previously tried systemic therapies for patients who	09/21/2020

	have tried Enspryng or Uplizna. For Patients Currently Receiving Soliris, criteria were added to show the patient is receiving a clinical benefit from Soliris.	
Policy revision	**Generalized Myasthenia Gravis:** For a patient who is currently receiving Soliris, age requirement of ≥ 18 years of age was added as criteria. **Paroxysmal Nocturnal Hemoglobinuria:** For a patient who is currently receiving Soliris, age requirement of ≥ 18 years of age was added as criteria.	06/21/2021
Policy revision	**Generalized Myasthenia Gravis:** Wording in the requirements for a trial of conventional therapy was changed from "has tried and has contraindications, intolerance, or failed" to "has tried and has had inadequate efficacy, a contraindication, or significant intolerance to".	12/30/2021
Policy review	No Criteria Changes	05/24/2023
Policy review	No Criteria Changes	09/20/2023
Policy review	No Criteria Changes (based on review of commercial policy update)	02/21/2024
Policy revision	**Neuromyelitis Optica Spectrum Disorder – Initial Therapy:** Removed criterion that required prior use of two systemic therapies. Soliris is listed as a first-line treatment option in the Neuromyelitis Optica Study Group (NEMOS) recommendations for the treatment of Neuromyelitis Optica Spectrum Disorder (2024).	4/22/2024
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/16/2024