Utilization Review Policy 194A

POLICY: Complement Inhibitors – Soliris Utilization Management Medical Policy – Advanced Clinical Evaluation

- Soliris® (eculizumab intravenous infusion – Alexion)

EFFECTIVE DATE: 1/1/2020
LAST REVISION DATE: 09/25/2024

COVERAGE CRITERIA FOR: UCare Medical Assistance and Exchange Plans Only (PMAP, Connect, MSC+, MnCare, all Individual and Family Plans)

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, Ultomiris and Soliris Risk Evaluation and Mitigation Strategy (REMS).

The safety and effectiveness of Soliris for the treatment of gMG, NMOSD, and PNH 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), 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 **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is provided in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Soliris as well as the monitoring required for adverse events and long-term efficacy, approval requires Soliris to be prescribed by or in consultation with a physician who specializes in the condition being treated. All reviews will be forwarded to a Physician Medical Director for evaluation.

Documentation: Documentation is required for use of Soliris as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Complement Inhibitors – Soliris Advanced Clinical Evaluation Medical Policy*, and who is requesting reauthorization, the criteria utilized do NOT require re-submission of documentation for reauthorization, except for the criterion requiring documentation of a continued benefit from Soliris therapy.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Soliris is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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4. Atypical Hemolytic Uremic Syndrome. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient does not have Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome; AND

B) The medication is prescribed by or in consultation with a nephrologist.

Dosing. Approve if the dose meets ONE of 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 weekly x 4 doses, 1,200 mg at week 5; then 1,200 mg every 2 weeks; OR

ii. 30 kg to < 40 kg: 600 mg weekly x 2 doses, 900 mg at week 3; then 900 mg every 2 weeks; OR

iii. 20 kg to < 30 kg: 600 mg weekly x 2 doses, 600 mg at week 3; then 600 mg every 2 weeks; OR

iv. 10 kg to < 20 kg: 600 mg weekly x 1 dose, 300 mg at week 2; then 300 mg every 2 weeks; OR

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

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5. Generalized Myasthenia Gravis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):

i. Patient is ≥ 18 years of age; AND

ii. Patient has confirmed anti-acetylcholine receptor antibody-positive generalized myasthenia gravis **[documentation required]**; AND
iii. Patient meets BOTH of the following (a and b):
i. Myasthenia Gravis Foundation of America classification of II to IV; AND
ii. Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 6; AND
iv. Patient meets ONE of the following (a or b):
i. Patient previously received or is currently receiving pyridostigmine; OR
ii. Patient has had inadequate efficacy, a contraindication, or significant intolerance to pyridostigmine; AND
v. Patient meets ONE of the following (a or b):
i. Patient previously received or is currently receiving two different immunosuppressant therapies for ≥ 1 year; OR
ii. Patient had inadequate efficacy, a contraindication, or significant intolerance to two different immunosuppressant therapies; AND
Note: Examples of immunosuppressant therapies tried include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, and cyclophosphamide.
vi. Patient has evidence of unresolved symptoms of generalized myasthenia gravis; AND
Note: Evidence of unresolved symptoms of generalized myasthenia gravis includes difficulty swallowing, difficulty breathing, and a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility).
vii. The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Soliris. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
i. Patient is ≥ 18 years of age; AND
ii. According to the prescriber, patient is continuing to derive benefit from Soliris; AND
Note: Examples of benefit include reductions in exacerbations of myasthenia gravis, improvements in speech, swallowing, mobility, and respiratory function.
iii. The medication is prescribed by or in consultation with a neurologist.

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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6. Neuromyelitis Optica Spectrum Disorder. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
i. Patient is ≥ 18 years of age; AND
ii. Diagnosis was confirmed by a positive blood serum test for anti-aquaporin-4 antibody **[documentation required]**; AND
iii. The medication is prescribed by or in consultation with a neurologist.

B) Patients is Currently Receiving Soliris. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Diagnosis was confirmed by 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; AND
  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.
- **iv.** The medication is prescribed by or in consultation with a neurologist.

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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7. Paroxysmal Nocturnal Hemoglobinuria. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** 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 **[documentation required]**; AND
- **iii.** The medication is prescribed by or in consultation with a hematologist; OR

B) Patient is Currently Receiving Soliris. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** According to the prescriber, patient is continuing to derive benefit from Soliris; AND
  Note: Examples of benefit include stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis, improvement in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score.
- **iii.** The medication is prescribed by or in consultation with a hematologist.

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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Soliris is not recommended in the following situations:

1. **Concomitant Use with Empaveli > 4 Weeks.** Concomitant use of Soliris with Empaveli is not recommended. However, to reduce the risk of hemolysis from abrupt treatment discontinuation in a patient switching from Soliris to Empaveli, patient should use both therapies for 4 weeks; after which, Soliris is discontinued and patient is continued on Empaveli monotherapy.

2. **Concomitant Use with Another Complement Inhibitor Except Voydeya (danicopan tablets).** There is no evidence to support concomitant use of Soliris with another complement inhibitor, except Voydeya.
   Note: Examples of complement inhibitors are Fabhalta (iptacopan capsules), PiaSky (crovalimab-akkz intravenous infusion or subcutaneous injection), and Ultomiris (ravulizumab-cwzy intravenous infusion).

1. **Concomitant Use with a Rituximab Product, a Neonatal Fc Receptor Blocker, or Zilbrysq (zilucoplan subcutaneous injection)**. There is no evidence to support concomitant use of Soliris with a rituximab product, a neonatal Fc receptor blocker, or Zilbrysq.
   Note: Examples of Neonatal Fc receptor blockers are: Rystiggo (rozanolixizumab-noli subcutaneous infusion), Vyvgart (efgartigimod alfa-fcab intravenous infusion), and Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection).

2. **Concomitant Use with Enspryng (satralizumab-mwge subcutaneous injection) or Uplizna (inebilizumab-cdon intravenous infusion)**. There is no evidence to support concomitant use of Soliris with Enspryng or Uplizna.

3. 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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HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Conditions Not Recommended for Approval:** The conditions were combined and the title was changed to "**Concurrent Use with Another Complement Inhibitor, a Rituximab Product, Enspryng (satralizumab-mwge subcutaneous injection), or Vyvgart (efgartigimod alfa-fcab intravenous infusion)**". Vyvgart and Ultomiris subcutaneous were added to this condition.	08/31/2022
Selected Revision	**Generalized Myasthenia Gravis:** Revised the Myasthenia Gravis Activities of Daily Living (MG-ADL) score to ≥ 6 to align with the prescribing information; previously it was MG-ADL ≥ 5.	05/31/2023
Early Annual Revision	**Generalized Myasthenia Gravis:** Initial therapy, for the criterion regarding evidence of unresolved symptoms of generalized myasthenia gravis, the examples of evidence of unresolved symptoms of generalized myasthenia gravis were moved to a Note. **Conditions Not Recommended for Approval:** Criterion regarding concomitant use of Soliris with another complement inhibitor, a rituximab product, Enspryng, Ultomiris, Uplizna, or Vyvgart was revised to include other neonatal Fc receptor blockers (Vyvgart Hytrulo, Rystiggo). Examples of neonatal Fc receptor blockers (including Vyvgart) were added as a Note. In addition, Empaveli was removed from this statement and added as a separate criterion: Concomitant use with Empaveli > 4 weeks.	09/20/2023
Selected revision	**Conditions Not Recommended for Approval:** Criterion regarding concomitant use with other agents was revised to include Fabhalta and Zilbrysq.	01/17/2024
Selected Revision	**Neuromyelitis Optica Spectrum Disorder – Initial Therapy:** Removed criterion that requires prior use of two systemic therapies and criterion that patient has had a history of at least one relapse in the last 12 months or two relapses in the last 2 years. 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).	03/27/2024
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/16/2024
Annual Revision	• **Paroxysmal Nocturnal Hemoglobinuria, Patient is currently receiving Soliris:** "Improvement in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score" was added to the Note of examples of benefit. • **Conditions Not Recommended for Approval, Concomitant Use with a Rituximab Product, a Neonatal Fc Receptor Blocker, Enspryng (satralizumab-mwge subcutaneous injection), Fabhalta (iptacopan capsules), Ultomiris (ravulizumab-cwzy intravenous infusion or subcutaneous injection), Uplizna (inebilizumab-cdon intravenous infusion), or Zilbrysq (zilucoplan subcutaneous injection):** This criterion was separated into three criteria. The Note was moved to the relevant criterion. – **Concomitant Use with Another Complement inhibitor Except Voydeya (danicopan tablets).** Fabhalta and Ultomiris were moved to a Note and PiaSky (crovalimab-akkz intravenous infusion or subcutaneous injection) was added to the Note. – **Concomitant Use with a Rituximab Product, or a Neonatal Fc Receptor Blocker, or Zilbrysq (zilucoplan subcutaneous injection).** – **Concomitant Use with Enspryng (satralizumab-mwge subcutaneous injection) or Uplizna (inebilizumab-cdon intravenous infusion).**	09/25/2024