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Medicare Advantage Medical Utilization Review Policy

Policy:	**Complement Inhibitors – Soliris Utilization Management Medical Policy** • Soliris® (eculizumab intravenous infusion – Alexion)
Date:	09/20/2023
Applicable Lines of Business:	Medicare Advantage - Medical
Applicable States:	NGS, J6: Wisconsin, Minnesota, Illinois NGS, JK: New York, Connecticut, Massachusetts, Maine, New Hampshire, Rhode Island, Vermont

OVERVIEW

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

- **Atypical hemolytic uremic syndrome** (aHUS), to inhibit complement-mediated thrombotic microangiopathy.
- **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.

Soliris is not indicated for the treatment of patients with Shiga toxin *E. coli* related hemolytic uremic syndrome.[1] The safety and effectiveness of Soliris for the treatment of gMG, NMOSD, and PNH in pediatric patients have not been established. 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

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 myasthenia gravis is muscle weakness that worsens after periods of activity and improves after periods of rest. Certain muscles such as those that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are often involved in the disorder; however, the muscles that control breathing and neck and limb movements may also be affected. Acquired MG results from the binding of autoantibodies to components of the neuromuscular junction, most commonly the acetylcholine receptor.[5]

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 causing 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. Uplizna™ (inebilizumab-cdon intravenous infusion) and Enspryng™ (satralizumab-mwge subcutaneous injection) are two other FDA-approved medications for treatment of NMOSD in adults who are anti-AQP4 antibody-positive.[8,9] For acute attacks, typical treatment is high-dose intravenous corticosteroids.[10,11] Plasma exchange may be effective in patients who suffer acute severe attacks that do not response to intravenous corticosteroids. For long-term control of the disease a variety of immunosuppressive drugs are utilized as first-line therapy. While all are considered off-label use, corticosteroids, azathioprine, mycophenolate mofetil, and rituximab are treatments prescribed as preventative therapy.

PNH is a rare disorder involving bone marrow failure that manifests with hemolytic anemia, thrombosis, and peripheral blood cytopenias.[12] Due to the absence of two glycosylphosphatidylinositol (GPI)-anchored proteins, CD55 and CD59, uncontrolled complement activation leads to hemolysis and other PNH manifestations.[13] GPI anchor protein deficiency is often due to mutations in phosphatidylinositol glycan class A (PIGA), a gene involved in the first step of GPI anchor biosynthesis. 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 lineages.[14] Prior to the availability of Soliris, there was no specific therapy for PNH with only supportive management in terms of the cytopenias and control of thrombotic risk. Supportive measures used include platelet transfusion, immune suppressive therapy for patients with bone marrow failure, use of erythropoietin for anemias, and aggressive anticoagulation. Soliris is the treatment of choice for patients with severe manifestations of PNH. Bone marrow transplantation is the only cure for PNH but should be reserved for patients with a suboptimal response to Soliris. Other agents indicated for the management of PNH in adults include Empaveli™ (pegcetacoplan subcutaneous infusion), a complement C3 inhibitor, and Ultomiris® (ravulizumab intravenous infusion), a complement C5 inhibitor.[15,16]

Guidelines

An international consensus guidance for the management of MG was published in 2016.[5] The guidelines recommend 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 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 these guidelines provides new recommendations for methotrexate, rituximab, and Soliris.[17] 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 generalized MG who have not tolerated or responded to steroid-sparing agents. Rituximab should be considered as an early therapeutic option in patients with 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-acetylcholine receptor antibody positive generalized MG.

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.

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.[11]

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.

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, ii and iii):
i. Patient is ≥ 18 years of age; AND
ii. Neuromyelitis optica spectrum disorder diagnosis was confirmed by blood serum test for anti-aquaporin-4 antibody positive; AND
iii. Patient has previously tried one of the following systemic therapies (1, 2, 3 or 4):
1. Azathioprine; OR
2. Corticosteroid; OR
3. Mycophenolate mofetil; OR
4. Rituximab.
Note: An exception to the requirement for a trial of a systemic therapy can be made if the patient has already tried Enspryng™ (satralizumab-mwge for subcutaneous injection) or Uplizna™ (inebilizumab-cdon injection) for neuromyelitis optica spectrum disorder. Patients who have already tried Enspryng or Uplizna for neuromyelitis optica spectrum disorder are not required to try another systemic agent.
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. Neuromyelitis optica spectrum disorder diagnosis was confirmed by blood serum test for anti-aquaporin-4 antibody positive; 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.[20]

Criteria. Approve Soliris for 1 year if the patient meets the following criteria (A and B):
A) Dense deposit disease has been proven by a biopsy;[20] AND
B) The patient has documented elevated serum levels of sC5b-9 (serum Membrane Attack Complex [sMAC]).[18]

Dosing: Induction dose is 900 mg per week for 4 weeks; maintenance dose is 1,200 mg every 2 weeks starting at week 5.[19]

Conditions Not Recommended for Approval

Soliris has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

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

REFERENCES

1. Soliris® intravenous infusion [prescribing information]. New Haven, CT: Alexion; April 2021.
2. Campistol JM, Arias M, Ariceta G, et al. An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document. *Nefrologia*. 2015;35:421–447.
3. Genetics Home Reference. Atypical hemolytic-uremic syndrome. National Institutes of Health (NIH). Available at: https://ghr.nlm.nih.gov/condition/atypical-hemolytic-uremic-syndrome#sourcesforpage. Accessed on May 27, 2021.
4. National Institute of Neurological Disorders and Stroke (NINDS). Myasthenia Gravis Fact Sheet. National Institutes of Health (NIH) Publication No. 17-768. Publication last updated: April 27, 2020. Available at: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Myasthenia-Gravis-Fact-Sheet. Accessed on May 27, 2021.
5. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. *Neurology*. 2016;87:419–425.
6. National Organization for Rare Disorders. Neuromyelitis Optica Spectrum Disorder. Available at: https://rarediseases.org/rare-diseases/neuromyelitis-optica/. Accessed May 27, 2021.
7. National Institute of Health, U.S. National Library of Medicine. Genetics Home Reference. Neuromyelitis optica. Available at: https://ghr.nlm.nih.gov/condition/neuromyelitis-optica#genes. Accessed May 27, 2021.
8. Enspryng™ subcutaneous injection [prescribing information]. South San Francisco, CA: Genentech; August 2020.
9. Uplizna™ intravenous infusion [prescribing information]. Gaithersburg, MD: Viela Bio; June 2020.
10. Bradshaw MJ, Kimbrough D. Neuromyelitis Optica Spectrum Disorders. *Practical Neurology*. 2019;76-84.
11. Siegel Rare Neuroimmune Association. Neuromyelitis Optica Spectrum Disorders. https://wearesrna.org/wp-content/uploads/2018/06/About_NMOSD_2018.pdf. Accessed on August 10, 2020.
12. Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2021;384(11):1028-1037.

13. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Hematology Am Soc Hematol Edu Program*. 2016;2016(1):208-216.
14. Roth A, Maciejewski J, Nishinura JI, et al. Screening and diagnostic clinical algorithm for paroxysmal nocturnal hemoglobinuria: Expert consensus. *Eur J Haematol*. 2018;101(1):3-11.
15. Empaveli™ subcutaneous infusion [prescribing information]. Waltham, MA: Apellis; May 2021.
16. Ultomiris® intravenous infusion [prescribing information]. Boston, MA: Alexion; October 2020.
17. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. *Neurology*. 2021 Jan 19;96(3):114-122.
18. 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 December 12, 2023.
19. Eculizumab for the Treatment of Dense-Deposit Disease. *N Engl J Med* 2012; 366:1163-1165
20. 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 December 12, 2023.

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 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.	09/09/2020

	*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 have tried Enspryng or Uplizna. For Patients Currently Receiving Soliris, criteria were added to show the patient is receiving a clinical benefit from Soliris.	09/21/2020
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