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

DATE REVIEWED: 05/27/2020

OVERVIEW

Soliris is a complement inhibitor and is a recombinant humanized monoclonal IgG2/4κ antibody produced by murine myeloma cell culture.[1] Soliris specifically binds to the complement protein C5 with high affinity, preventing the generation of the terminal complement complex C5b-9. Soliris inhibits terminal complement-mediated intravascular hemolysis in paroxysmal nocturnal hemoglobinuria (PNH) patients and complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS). The precise mechanism by which eculizumab exerts its therapeutic effect in generalized Myasthenia Gravis (gMG) patients is unknown, but is presumed to involve reduction of terminal complement complex C5b-9 deposition at the neuromuscular junction.

Soliris is indicated for the treatment of patients with PNH to reduce hemolysis, for the treatment of patients with aHUS to inhibit complement-mediated thrombotic microangiopathy but not Shiga toxin E. coli related hemolytic uremic syndrome, and for the treatment of adult patients with gMG who are anti-acetylcholine receptor (AchR) antibody positive, and for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.[1] The safety and effectiveness of Soliris for the treatment of PNH, gMG, and NMOSD 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

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 (TMA).[2] The TMA process that characterizes HUS can be caused by a variety of things. Atypical HUS (aHUS) is a sub-type of HUS in which TMA are 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. Various aHUS-related mutations have been identified in genes of the complement system, which can explain approximately 60% of the aHUS cases, and a number of mutations and polymorphisms have been functionally characterized. aHUS should be distinguished from a more common condition referred to as typical HUS.[3] The two disorders have different causes and different signs and symptoms. Unlike aHUS, the typical form is caused by infection with certain strains of Escherichia coli (E. coli) bacteria that produce toxic substances called Shiga-like toxins. The typical form is characterized by severe diarrhea and most often affects children < 10 years of age, and it is less likely than aHUS to involve recurrent attacks of kidney damage that lead to end stage renal disease (ESRD). The incidence of aHUS is estimated to be 1:500,000 people/year in the US; aHUS is approximately 10 times less common than typical HUS.

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 (AChR).[5] However, antibodies to other proteins, such as the muscle-specific kinase (MuSK) protein, can also lead to impaired transmission at the neuromuscular junction. MG most commonly occurs in young adult women (< 40 years of age) and older men (> 60 years of age), but it can occur at any age, including childhood. The incidence ranges from 0.3 to 2.8 per 100,000, and it is estimated to affect more than 700,000 people worldwide. Medications to treat MG include anticholinesterase agents (e.g., pyridostigmine), which slow the breakdown of acetylcholine at the neuromuscular junction and thereby improve neuromuscular transmission and increase muscle strength.[4] Immunosuppressive drugs improve muscle strength by suppressing the production of abnormal antibodies and may include prednisone, azathioprine, mycophenolate mofetil, tacrolimus, and rituximab. Plasmapheresis and intravenous immunoglobulin (IVIG) may be options in severe cases of MG by removing the destructive antibodies; however, their effectiveness frequently only lasts for a few weeks to months.

PNH is a rare disorder involving bone marrow failure that manifests with hemolytic anemia, thrombosis, and peripheral blood cytopenias.[6] Due to the absence of two glycosylphosphatidylinositol (GPI)-anchored proteins, CD55 and CD59, uncontrolled complement activation leads to hemolysis and other PNH manifestations. 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. 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.

NMOSD is a rare, chronic disorder of the brain and spinal cord dominated by inflammation of the optic nerve and inflammation of the spinal cord.[9] Most patients with NMOSD experience repeated attacks separated by periods of remission. The time between attacks may be weeks, months or years with initial stages of NMOSD potentially confused with MS. Nearly 70% of people with this disorder produce anti-AQP4 antibodies which is used in diagnosis.[10] For acute attacks, typical treatment is high-dose intravenous (IV) corticosteroids and plasma exchange may be effective in patients who suffer acute severe attacks that do not response to IV corticosteroids.[9] For long-term control of the disease a variety of immunosuppressive drugs are utilized by providers as first-line therapy. Corticosteroids, azathioprine, mycophenolate mofetil, and rituximab are the treatments most widely prescribed treatments.

Dosing Information
For adult and pediatric patients with aHUS, supplemental dosing of Soliris is required in the setting of concomitant plasmapheresis or plasma exchange, or fresh frozen plasma infusion. For plasmapheresis or plasma exchange: If the most recent dose of Soliris was 300 mg, administer a supplemental Soliris dose of 300 mg per each plasmapheresis or plasma exchange session within 60 minutes. If the most recent dose of Soliris was ≥ 600 mg, administer a supplemental Soliris dose of 600 mg per each plasmapheresis or plasma exchange session within 60 minutes. For a fresh frozen plasma infusion: If the most recent dose of Soliris was ≥ 300 mg, administer a supplemental Soliris dose of 300 mg per each fresh frozen plasma infusion given 60 minutes prior to each infusion.

Guidelines
Clinical practice guidelines for the management of aHUS published in Spain (2015) and an international consensus document (2014) recommend early, first-line treatment with Soliris in pediatric patients with aHUS due to the technical difficulties of plasma therapies (e.g., PE and PI) in pediatric patients and the potential complications, in addition to the superiority of Soliris for the recovery of renal function and the

improved prognosis.[2,8] The Spanish guidelines also recommend the initiation of Soliris earlier in adult patients with suspected aHUS following PE; PE is only recommended in adults when the diagnosis of aHUS is unclear.[2] Guidelines for the management of aHUS in the United Kingdom (UK), published in 2009 by the British Committee for Standards in Haematology and the British Transplant Society, indicate that all patients presenting with aHUS should be offered a trial of plasma exchange (PE) and/or plasma infusions (PI).[7]

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 immune suppressant (IS) therapy should be used in all patients with MG who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal IS 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 (PLEX) and IVIG are short-term treatment options in certain patients. The guidelines note that few physicians treat enough patients with MG to be comfortable with all available treatments. Given the heterogeneity of MG, the few randomized controlled trials have limited generalizability, while uncontrolled trials are limited by potential bias. The guideline does not address Soliris in gMG.

Safety
Soliris has a Boxed Warning regarding life-threatening and fatal meningococcal infections.[1] Meningococcal infections have occurred in patients receiving Soliris and may become rapidly life-threatening or fatal if not recognized and treated early. Soliris is contraindicated in patients with unresolved serious *Neisseria meningitidis* infection and 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. Soliris has a Risk Evaluation and Mitigation Strategy (REMS) program to mitigate the occurrence and morbidity associated with meningococcal infections. The REMS program also educates healthcare professionals and patients regarding the increased risk of meningococcal infections with Soliris, the early signs of invasive meningococcal infections, and the need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infections.

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 indication(s). Requests for doses outside 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). Because of the 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 approvals are provided for duration noted below. In cases where the dosing interval is provided in months, 1 month is equal to 30 days.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

1. **Atypical Hemolytic Uremic Syndrome**. Approve Soliris for 1 year if the patient meets BOTH of the following criteria (A and B):
   A) Patient does not have Shiga toxin *E. coli* related hemolytic uremic syndrome; AND

B) Soliris is being prescribed by or in consultation with a hematologist and/or a nephrologist.

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

A) Initial therapy: Approve Soliris for 6 months if the patient meets the following criteria (i, ii, iii, iv, v, and vi):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has confirmed anti-acetylcholine receptor (AchR) antibody positive generalized Myasthenia Gravis (gMG); AND
- **iii.** Patient is currently receiving or has tried and has contraindications, intolerance, or failed pyridostigmine; AND
- **iv.** Patient is currently receiving or has tried and has contraindications, intolerance, or failed two different immunosuppressant therapies over ≥ 1 year (e.g., azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, cyclophosphamide); AND
- **v.** Patient has evidence of unresolved symptoms of generalized Myasthenia Gravis (gMG), such as difficulty swallowing, difficulty breathing, or a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility); AND
- **vi.** Soliris is being prescribed by or in consultation with a neurologist.

B) Patient currently receiving Soliris: Approve Soliris for 1 year if the patient is continuing to derive benefit (e.g., reductions in exacerbations of myasthenia gravis; improvements in speech, swallowing, mobility, and respiratory function) from Soliris, according to the prescribing physician.

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. Approve Soliris for the duration noted if the patient meets ONE of the following (A or B):

A) Initial therapy: Approve Soliris for 6 months if the patient meets the following criteria (i, ii, and iii):
- **i.** 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; AND
- **iii.** Soliris is being prescribed by or in consultation with a hematologist; OR

B) Patient currently receiving Soliris: Approve Soliris for 1 year if the patient is continuing to derive benefit (e.g., stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis) from Soliris, according to the prescribing physician.

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. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Neuromyelitis optica spectrum disorder diagnosis was confirmed by blood serum test for anti-aquaporin-4 antibody positive; AND
C) Patient has previously tried one of the following systemic therapies (i, ii, iii, or iv):
- **i.** Azathioprine; OR
- **ii.** Corticosteroid; OR
- **iii.** Mycophenolate mofetil; OR
- **iv.** Rituximab; AND

D) Soliris is being 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.

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. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New policy	--	05/16/2018
Annual revision	No change to criteria.	05/29/2019
Selected revision	The following changes were made to criteria: **1. Atypical Hemolytic Uremic Syndrome**. For patients ≥ 18 years of age, the **Dosing** was changed from a specific dose to "The dose is ≤". **2. Generalized Myasthenia Gravis.** The **Dosing** was changed from a specific dose to "The dose is ≤". **3. Paroxysmal Nocturnal Hemoglobinuria.** The **Dosing** was changed from a specific dose to "The dose is ≤". **4. Neuromyelitis Optica Spectrum Disorder** approval **Criteria** and **Dosing** were added to FDA-approved indications section of the policy.	08/07/2019
Annual revision	No changes to criteria.	05/27/2020