Department:	Pharmacy	**Original Approval:**	07/27/2018
Policy #:	PM150	**Last Approval:**	08/27/2018
Title:	Soliris® (eculizumab injection, for intravenous use – Alexion)		
Approved By:	UM Committee		

Documentation required to determine medical necessity for Soliris® (eculizumab injection) for subcutaneous use: History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis -Age -Prescribed by or in consultation with an hematologist, nephrologist, or neurologist -Labs/diagnostics - Medication list (current and past) to include start and end dates of previous trials for all prior therapies.

BACKGROUND

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. 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.

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.[1]

DEFINITIONS

None

INDICATIONS/CRITERIA

Medicaid Members	***Continue to criteria for approval below.***
Medicare Members	***Step-utilization of Part D drugs not required.***

FDA-Approved Indications

1. Atypical Hemolytic Uremic Syndrome (aHUS).

Criteria. 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.

Soliris is indicated for the treatment of patients with aHUS to inhibit complement-mediated thrombotic microangiopathy.[1] Limitation of Use: Soliris is not indicated for the treatment of patients with Shiga toxin *E. coli* related hemolytic uremic syndrome (STEC-HUS).

Dosing in aHUS.[1]

- For patients ≥ 18 years of age, Soliris dosing is 900 mg weekly for the first 4 weeks, followed by 1,200 mg for the fifth dose 1 week later, then 1,200 mg every 2 weeks thereafter.
- For patients < 18 years of age, Soliris is dosed based on body weight:
  - ≥ 40 kg: 900 mg weekly x 4 doses, 1,200 mg at week 5; then 1,200 mg every 2 weeks.
  - 30 kg to < 40 kg: 600 mg weekly x 2 doses, 900 mg at week 3; then 900 mg every 2 weeks.
  - 20 kg to < 30 kg: 600 mg weekly x 2 doses, 600 mg at week 3; then 600 mg every 2 weeks.
  - 10 kg to < 20 kg: 600 mg weekly x 1 dose, 300 mg at week 2; then 300 mg every 2 weeks.
  - 5 kg to < 10 kg: 300 mg weekly x 1 dose, 300 mg at week 2; then 300 mg every 3 weeks.

Administer Soliris at the recommended dosage regimen time points, or within 2 days of these time points.

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.

Approval duration. *Initial/Extended Approval*. Approve for 1 year.

Duration of Therapy in aHUS. Indefinite if the patient is responding.

Labs/Diagnostics. None required.

2. Generalized Myasthenia Gravis (gMG).

Criteria. 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.

Soliris is indicated for the treatment of adult patients with gMG who are anti-acetylcholine receptor (AchR) antibody positive.[1] The safety and effectiveness of Soliris for the treatment of generalized Myasthenia Gravis in pediatric patients have not been established. An international consensus guidance for the management of MG recommend pyridostigmine for the initial treatment in most patients with MG.[5] 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.

Dosing in gMG.[1] Soliris dosing is 900 mg weekly for the first 4 weeks, followed by 1,200 mg for the fifth dose 1 week later, then 1,200 mg every 2 weeks thereafter.[1] Administer Soliris at the recommended dosage regimen time points, or within 2 days of these time points.

For adult patients with gMG, supplemental dosing of Soliris is required in the setting of concomitant plasmapheresis or plasma exchange, or fresh frozen plasma infusion (PE/PI).[1] 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.

Initial Approval/Extended Approval. See criteria above.

Duration of Therapy in gMG. Indefinite if the patient is responding.

Labs/Diagnostics. None required.

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3. Paroxysmal Nocturnal Hemoglobinuria (PNH).

Criteria. 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.** PNH 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.

The safety and effectiveness of Soliris for the treatment of PNH in pediatric patients have not been established.[1] 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.[6]

Dosing in PHN.[1] For patients 18 years of age and older, Soliris dosing is 600 mg weekly for the first 4 weeks, followed by 900 mg for the fifth dose 1 week later, then 900 mg every 2 weeks thereafter. Administer Soliris at the recommended dosage regimen time points, or within 2 days of these time points.

Initial Approval/Extended Approval. See criteria above.

Duration of Therapy in PHN. Indefinite if the patient is responding.

Labs/Diagnostics. None required.

SPECIAL CONSIDERATIONS

Enter all special considerations here.

LIMITATIONS/EXCLUSIONS

Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

CFR		
WAC	WAC 284-43-2050	
RCW		
Contract Citation	☐ WAH	
	☐ IMC	
	☐ MA	
Other Requirements		
NCQA Elements		
References	1. Soliris® injection [prescribing information]. New Haven, CT: Alexion Pharmaceuticals, Inc.; February 2018. 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 April 27, 2018. 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: May 9, 2017. Available at: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Myasthenia-Gravis-Fact-Sheet. Accessed on April 27, 2018. 5. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. Neurology. 2016;87:419–425. 6. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood. 2014;124(18):2804–2811. 7. Taylor CM, Machin S, Wigmore SJ, et al. Clinical Practice Guidelines for the management of atypical Haemolytic Uraemic Syndrome in the United Kingdom. Br J Haematol. 2010;148(1):37-47. 8. Loirat C, Fakhouri F, Ariceta G, et al. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. Pediatr Nephrol. 2016;31(1):15-39.	

	Other References Utilized • Martí-Carvajal AJ, Anand V, Cardona AF, et al. Eculizumab for treating patients with paroxysmal nocturnal hemoglobinuria. Cochrane Database Syst Rev. 2014;10: CD010340. • Patwa HS, Chaudhry V, Katzberg H, et al. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2012;78(13):1009-15.

Revision History

Revision Date	Revision Description	Revision Made By
07/27/2018	New policy	Jennifer Farley, PharmD
08/27/2018	Approval	UM Committee