Medical Coverage Policy | Eculizumab (Soliris)

EFFECTIVE DATE: 02|01|2018
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OVERVIEW

Eculizumab (Soliris) is a monoclonal antibody that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. It is used for the following indications:

- treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis
- treatment of patients with atypical hemolytic uremic syndrome (aHUS)* to inhibit complement-mediated thrombotic microangiopathy
- treatment of adult patients with generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive

MEDICAL CRITERIA

BlueCHiP for Medicare and Commercial Products

Soliris (eculizumab) will be approved when ALL of the following are met:

1. The patient does not have any FDA labeled contraindications to therapy with the requested agent
   AND
2. The prescriber is a specialist in the area of the patient's disease or the prescriber has consulted with a specialist in the area of the patient's disease
   AND
3. ONE of the following:
   a. The patient is an adult (≥18 years old) who has a diagnosis of generalized **Myasthenia Gravis (gMG)** and ALL of the following:
      i. The patient has a positive serological test for anti-AChR antibodies
         AND
      ii. The patient has a Myasthenia Gravis Foundation of America (MGFA) clinical classification class of II-IV (documentation provided)
         AND
      iii. The patient has a MG-Activities of Daily Living total score of greater than or equal to 6 (documentation provided)
         AND
      iv. The prescriber has evaluated the patient's current drugs that may unmask or worsen myasthenia gravis (e.g., beta blockers, procainamide, quinidine, magnesium, anti-programmed death receptor-1 monoclonal antibodies, hydroxychloroquine, aminoglycosides, etc) and has discontinued them when appropriate
         AND
      v. ONE of the following:
         1. The patient has tried and failed pyridostigmine
            OR
         2. The prescriber has submitted documentation that the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to pyridostigmine

AND

vi. The patient has tried and failed treatment over the last 365 days with ONE of the following:
    1. At least 2 or more immunosuppressive therapies (e.g., azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide) either in combination or in monotherapy
    OR
    2. At least 1 immunosuppressive therapy (see 3.a.v.1) and ONE of the following:
        a. chronic intravenous immunoglobulin (IVIg)
        OR
        b. plasmapheresis/plasma exchange given at least four times per year for 12 months without symptom control
    OR
    3. The prescriber has submitted documentation that the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL immunosuppressive therapies, IVIg, and plasmapheresis/plasma exchange

OR

b. The patient has a diagnosis of **Paroxysmal nocturnal hemoglobinuria (PNH)** and the following:
    i. Flow cytometry has been performed with at least 2 independent flow cytometry reagents on at least 2 cell lineages (e.g., RBCs and WBCs) demonstrating that the patient's peripheral blood cells are deficient in glychophosphatidylinositol (GPI)-linked proteins confirming the diagnosis of paroxysmal nocturnal hemoglobinuria (prescriber must provide supportive documentation)

OR

c. The patient has a diagnosis of **atypical Hemolytic Uremic Syndrome (aHUS)** and ALL of the following:
    i. The patient has demonstrated complement dysregulation by at least ONE of the following:
        1. Genetic mutation (e.g., *CFH, CD46, CFI, C3, CFB, THBD, CFHR1, CFHR5*)
        OR
        2. Antibodies to complement factors
        OR
        3. A differential diagnosis of complement-mediated HUS has been demonstrated [i.e. screening for Shiga toxin-producing E. coli (STEC) for STEC-HUS, pneumococcal culture of blood/sputum/cerebrospinal or pleural fluid for pneumococcal-associated HUS, ADAMTS13 (A Disintegrin And Metalloprotease with a ThromboSpondin type 1 motif, member 13) <10% activity for thrombotic thrombocytopenic purpura (TTP), screening for defective cobalamine metabolism]
    AND
    ii. The patient is negative for Shiga toxin-producing *E. coli* (STEC)

AND

4. The requested dose is within FDA approved labeling

Length of Approval: generalized Myasthenia Gravis: 3 months
Paroxysmal Nocturnal Hemoglobuinuria: 6 months
atypical Hemolytic Uremic Syndrome: 6 months

Soliris (eculizumab) will also be approved when the following are met:

1. The use of the target agent is for an indication that is supported by compendia. (NCCN Compendium™[level of evidence 1, 2A], AHFS, DrugDex [FDA approved Class I or Class IIa]), or the prescriber has submitted additional documentation (the use is supported by clinical research in 2 or more peer reviewed medical journals) supporting the requested therapeutic use (approval by the Clinical Review Pharmacist required).
   AND
2. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
   AND
3. The requested dose is within FDA labeling or is supported by compendia. (NCCN Compendium™[level of evidence 1, 2A], AHFS, DrugDex [FDA approved Class I or Class IIa]), or the prescriber has submitted additional documentation (the dose is supported by clinical research in 2 or more peer reviewed medical journals) supporting the requested therapeutic dose (approval by the Clinical Review Pharmacist required)

Length of Approval: 12 months

Renewal Evaluation

Soliris (eculizumab) will be approved for continued use when ALL of the following are met:

1. The patient was previously approved for the requested agent through the BCBSRI Medical Drug Review process
   AND
2. The patient does not have any FDA labeled contraindications to therapy with the requested agent
   AND
3. The prescriber is a specialist in the area of the patient's disease or the prescriber has consulted with a specialist in the area of the patient's disease
   AND
4. The provider has provided documentation indicating the patient has a history of beneficial response to eculizumab therapy for the treatment of ONE of the following indications:
   a. Paroxysmal nocturnal hemoglobinuria (PNH) – e.g., decreased requirement for transfusions, stabilization of hemoglobin, reduction of lactate dehydrogenase (LDH)
   b. Atypical hemolytic uremic syndrome (aHUS) – e.g., improved platelet count, reduction of lactate dehydrogenase (LDH), improved renal function
   c. generalized Myasthenia Gravis – e.g., improved MG-ADL total score, quantitative myasthenia gravis total score

   AND
5. The requested dose is within FDA approved labeling

Length of Approval: 12 months

PRIOR AUTHORIZATION

Prior authorization is required for BlueCHiP for Medicare and recommended for Commercial Products

POLICY STATEMENT

Eculizumab(Soliris) is medically necessary when the criteria above has been met.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for applicable physician administered infused drug benefit.

BACKGROUND

Eculizumab is a monoclonal antibody that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9.[1]

Atypical hemolytic uremic syndrome (aHUS)

Soliris inhibits terminal complement-mediated intravascular hemolysis in patients with atypical hemolytic uremic syndrome (aHUS).[1]

Hemolytic uremic syndrome (HUS) is often diagnosed when there is simultaneous occurrence of macroangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury; however, there are some individuals that will not present with these three findings. The most common cause of HUS is due to Shiga toxin-producing *Escherichia* coli (STEC) and complement dysregulation accounts for most of the non-STEC cases of HUS. Currently HUS is divided into 2 categories: primary causes without coexisting disease (e.g., complement dysregulation/atypical HUS) and secondary causes (e.g., infection, drug toxicity, pregnancy).[10,12] Atypical hemolytic uremic syndrome is a genetic, chronic, and progressive inflammatory disease caused by defects in regulation of the complement system. Patients have a risk of systemic clinical complications of complement-mediated thrombotic microangiopathy (TMA), including damage to multiple organ systems.[1,5]

Most often, the diagnosis of complement-mediated HUS is based on the clinical presentation of the classical triad of macroangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury, and also the demonstration of complement dysregulation (due to gene mutations, complement proteins, or antibodies to complement factors). The minimum set of genes that should be screened includes *CFH, CD46, CFI, C3, CFB, THBD, CFHR1, CFHR5,* and *DGKE* (effectiveness of eculizumab for individuals that have a DGKE mutation have not been established presumably because the underlying defect does not involve complement proteins[12]). However, screening for mutations and antibodies to complement proteins is not widely available. A differential diagnosis of complement-mediated HUS includes HUS due to other causes and conditions that are present concomitantly with anemia, thrombocytopenia, and acute kidney injury [e.g., screening for Shiga toxin-producing *E. coli* (STEC) for STEC-HUS, pneumococcal culture of blood/sputum/cerebrospinal or pleural fluid for pneumococcal-associated HUS, ADAMTS13 (A Disintegrin And Metalloprotease with a ThromboSpondin type 1 motif, member 13) <10% activity for thrombotic thrombocytopenic purpura (TTP), screening for defective cobalamine metabolism (a rare cause of HUS)].[10]

Studies have found eculizumab treated patients to have reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts compared to placebo.[5] Despite plasma exchange, the standard treatment of aHUS for decades, the renal prognosis for patients with aHUS has remained poor.[6] Eculizumab treatment was associated with significant time-dependent improvement in renal function in terms of estimated glomerular filtration rate (eGFR).[5]

Generalized myasthenia gravis (gMG)

The precise mechanism by which Soliris 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.

Myasthenia gravis is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles as a result of antibody-mediated, T-cell dependent immunologic attack directed at proteins in the postsynaptic membrane of the neuromuscular junction. Typically, there is a fluctuating degree and variable combination of weakness in ocular, bulbar, limb, and respiratory muscles affected.[1-3]

Paroxysmal nocturnal hemoglobinuria (PNH)

Similar to aHUS, Soliris inhibits terminal complement-mediated intravascular hemolysis in paroxysmal nocturnal hemoglobinuria (PNH) patients.[1]

PNH is a rare acquired hematopoietic stem cell disorder characterized by complement mediated hemolysis resulting in anemia, hemoglobinuria, complications related to presence of free hemoglobin (depletion of nitric oxide), and several other unusual groupings of clinical findings.[7,11] Although hemoglobinuria can occur at any time in PNH, paroxysms of hemolysis at night leading to hemoglobinuria (characterized by red/pink/black urine) give the disorder its name.[11] PNH is mainly a disease of adults with a median age of onset in the thirties.[11] Flow cytometry is the most useful and accepted method to confirm the diagnosis of PNH in the appropriate clinical setting (e.g., Coombs-negative hemolytic anemia).[11] Flow cytometry is performed by incubating the patient's peripheral blood cells with fluorescently-labeled monoclonal antibodies that bind to glycosylphosphatidylinositol (GPI) anchored proteins, which are reduced or absent on blood cells in PNH.[11] Since different blood cell lineages display different combinations of GPI-linked proteins, and some proteins bind to cell surfaces via both GPI-linked and GPI-independent mechanisms, it is recommended that at least **two independent flow cytometry reagents** be used on **at least two cell lineages** (e.g., RBCs and WBCs) to establish the diagnosis of PNH.[11]

Patients with PNH have a median survival of ten years after diagnosis.[7] Eculizumab is the only therapy specifically developed for PNH. Studies have found eculizumab treatment results in significantly reduced hemolysis resulting in improvements in anemia as indicated by increased hemoglobin stabilization and reduced need for RBC transfusions compared to placebo.[1] Patients report less fatigue and improved health-related quality of life when treated with eculizumab compared to treatment with placebo.[1]

Eculizumab Safety[1]
Eculizumab has a boxed warning for an increased risk of meningococcal infections. It is contraindicated in patients with unresolved serious *Neisseria meningitidis* infection and patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection. All patients without a history for meningococcal vaccination should receive the vaccine at least two weeks prior to receiving the first dose of eculizumab.

Eculizumab Efficacy
aHUS
The efficacy of eculizumab in aHUS patients was evaluated in 3 single-arm studies (two prospective and 1 retrospective). In all three trials the endpoints evaluated include platelet count change from baseline, hematologic normalization (maintenance of normal platelet counts and LDH levels for at least 4 weeks), complete TMA response (hematologic normalization plus at least a 25% reduction in serum creatinine for a minimum of 4 weeks), TMA-event free status (absence for at least 12 weeks of a decrease in platelet count of >25% from baseline, plasma exchange or plasma infusion and new dialysis requirement), and daily TMA intervention rate (number of plasma exchange or plasma infusion interventions (PE/PI) and the number of new dialysis required per patient per day).[1,5]

Study 1 enrolled 17 patients with aHUS resistant to PE/PI. Patients were treated for a minimum of 26 weeks (mean was 38 weeks). Eculizumab reduced signs of complement-mediated TMA activity shown by an increase from 109 ± 32 $x10^9$/L at baseline to 169 ± 72$x10^9$/L by one week with the effect maintained through 26 weeks. Study 2 enrolled 20 patients with aHUS sensitive to PE/PI who were treated with eculizumab for a minimum of 26 weeks (mean was 40 weeks). Eculizumab reduced signs of complement mediated TMA in this study as well. Platelet counts were maintained at normal levels despite elimination of PE/PI. The mean platelet count was 229 ± 78$x10^9$/L at baseline and 233 ± 69$x10^9$/L at week 26. The retrospective study 3 of 19 pediatric patients was conducted for a mean duration range of 16 to 38 weeks depending on age range. Efficacy results were consistent with results of Study 1 and 2. Eculizumab reduced signs of complement-mediated TMA shown by an increase in mean platelet count of 171 ± 83$x10^9$/L at baseline to 233 ± 109$x10^9$/L one week after therapy. The effect was maintained through 26 weeks. Mean platelet count at week 26 was 254 ± 79$x10^9$/L.[1,5]

PNH

One randomized, double-blind, placebo-controlled 26-week study (TRIUMPH) evaluated eculizumab in the treatment of PNH (n=87). Primary endpoints were stabilization of hemoglobin above level required for transfusion and number of packed red blood cells transfused during the study period. Secondary efficacy measures included hemolysis, change in level of fatigue as measured by FACIT-fatigue score, and proportion of patients with transfusion independence. Stabilization of hemoglobin levels occurred in 49% of eculizumab treated patients compared to zero in the placebo group ($p<0.001$). The median number of packed red blood cells infused was zero in the eculizumab group compared to ten in the placebo group ($p<0.001$). Transfusion independence was achieved by 51% of patients treated with eculizumab compared to zero for placebo ($p<0.001$). Fatigue scores were improved with eculizumab (+6.4 points) versus placebo (-4 points) ($p<0.001$). Hemolysis was also reduced with eculizumab therapy compared to placebo ($p<0.001$).[8]

Generalized myasthenia gravis:

A 26-week, phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter study (REGAIN) was conducted to determine the safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalized myasthenia gravis. Eligible patients (N=125) were at least 18 years old, had a positive serological test for anti-acetylcholine receptor antibodies, had a Myasthenia Gravis-Activities of Daily Living (MG-ADL) score of 6 or more, a Myasthenia Gravis Foundation of America (MGFA) clinical classification class II-IV disease, vaccination against *Neisseria meningitides*, and previous failed treatment with at least 2 immunosuppressive therapies or one immunosuppressive therapy and chronic intravenous immunoglobulin or plasmapheresis/plasma exchange given at least four times per year, for 12 months without symptom control. The primary efficacy endpoint was the change from baseline to week 26 in MG-ADL total score, as measured by the worst-rank ANCOVA. The primary analysis showed no significant difference between eculizumab and placebo (least squares mean rank 56.6 [SEM 4.5] vs 68.3 [4.5]; rank-based treatment difference -11.7, 95% CI -24.3 to 0.96; $p=0.0698$). However, there was a statistically significant difference in the change in MG-ADL score from baseline to week 26 between eculizumab and placebo in a pre-specified sensitivity repeated-measures model analysis with immunosuppressive treatments as covariates, (least squares mean -4.2 (SEM 0.49) vs. -2.3 (0.48); least squares mean difference of change in score with eculizumab relative to placebo -1.9, 95% CI -3.3 to -0.6; $p=0.006$).[1,4] The REGAIN trial discussion notes, "using the repeated-measures analyses, the benefit of eculizumab compared with placebo occurred within the first 4 weeks of treatment, with most of the effect achieved by 12 weeks."[4]

MGFA Clinical Classification[9]

Class	Features
I	Any ocular muscle weakness; may have weakness of eye closure; All other muscles are normal
II	Mild weakness affecting muscles other than the ocular muscles; may also have ocular muscle weakness of any severity
	IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
	IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
III	Moderate weakness affecting muscles other than the ocular muscles; may also have ocular muscle weakness of any severity
	IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
	IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
IV	severe weakness affecting muscles other than the ocular muscles; may also have ocular muscle weakness of any severity
	IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser

	involvement of oropharyngeal muscles.
	IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
V	Intubation with or without mechanical ventilation (exception: intubation for routine perioperative management). The use of a feeding tube without intubation places a patient in class IVb.

CODING

There is no specific HCPCS code for this drug, claims must be filed with an unlisted drug code such as J3490 and the NDC number.

RELATED POLICIES

None

PUBLISHED

Provider Update, April 2018

REFERENCES:

1. Soliris prescribing information. Alexion. October 2017
2. National Institute of Neurological Disorders and Stroke. Myasthenia Gravis Fact Sheet. NIH Publication No. 17-768. May 2017.
3. UpToDate. Diagnosis of myasthenia gravis. Literature review current through: Oct 2017; last updated: Aug 23, 2017.
4. Howard JF Jr, Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalized myasthenia gravis (REGAIN): a phase randomized, double-blind, placebo-controlled, multicentre study. Lancet Neurol. 2017 Oct 20. pii: S1474-4422(17)30369-1. [Epub ahead of print].
5. NEJM 2013; 368 (23): 2169-81.
6. Am J Kidney Dis. 2014;63(1):40-48
7. Blood 2005; 106(12):3699-3709.
8. N Engl J Med 2006; 355(12):1233-1243
9. Myasthenia Gravis Foundation of America. Myasthenia Gravis: A Manual for the Health Care Provider (PDF). 2010. Accessed 11/17/2017. http://www.myasthenia.org/LinkClick.aspx?fileticket=TPIgma-npRI%3D&tabid=125
10. UpToDate. Atypical hemolytic uremic syndrome. Literature review current through Oct 2017.
11. UpToDate. Clinical manifestations and diagnosis of paroxysmal nocturnal hemoglobinuria. Literature review current through Oct 2017.
12. National Organization for Rare Disorders. Atypical Hemolytic Uremic Syndrome. Accessed Nov 2017.