Cigna Medical Coverage Policy

Subject: Eculizumab (Soliris®)

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Effective Date................................. 1/15/2013
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INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna companies including plans formerly administered by Great-West Healthcare, which is now a part of Cigna. Coverage Policies are intended to provide guidance in interpreting certain standard Cigna benefit plans. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supercedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of Cigna. Copyright ©2013 Cigna

Coverage Policy

Cigna covers eculizumab (Soliris®) as medically necessary for EITHER of the following indications:

- paroxysmal nocturnal hemoglobinuria (PNH) when EITHER of the following has been met:
  - at least one transfusion related to anemia secondary to PNH
  - occurrence of a thromboembolic event
- atypical hemolytic uremic syndrome (aHUS)

NOTE: Unless contraindicated, a meningococcal vaccine must be administered at least two (2) weeks prior to the initiation of eculizumab (Soliris®) therapy.

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to eculizumab (Soliris®).

Cigna does NOT cover eculizumab (Soliris®) for Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS) because it is considered experimental, investigational and unproven (this list may not be all-inclusive).

FDA Approved Indications

Paroxysmal Nocturnal Hemoglobinuria (PNH)
Soliris is indicated for the treatment of patients with PNH to reduce hemolysis.
Atypical Hemolytic Uremic Syndrome (aHUS)
Soliris is indicated for the treatment of patients with aHUS to inhibit complement-mediated thrombotic microangiopathy. The effectiveness of Soliris in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function. Prospective clinical trials in additional patients are ongoing to confirm the benefit of Soliris in patients with aHUS. Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

FDA Recommended Dosing
Patients must be administered a meningococcal vaccine at least two weeks prior to initiation of Soliris therapy and revaccinated according to current medical guidelines for vaccine use.

PNH
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. Soliris should be administered at the recommended dosage regimen time points, or within two days of these time points.

aHUS
For patients 18 years of age and older, Soliris therapy consists of 900 mg weekly for the first 4 weeks, followed by 1200 mg for the fifth dose 1 week later, then 1200 mg every 2 weeks thereafter.

For patients less than 18 years of age, administer Soliris based upon body weight in the following table:

<table>
<thead>
<tr>
<th>Patient Body Weight</th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 kg and over</td>
<td>900 mg weekly x 4 doses</td>
<td>1200 mg at week 5; then 1200 mg every 2 weeks</td>
</tr>
<tr>
<td>30 kg to less than 40 kg</td>
<td>600 mg weekly x 2 doses</td>
<td>900 mg at week 3; then 900 mg every 2 weeks</td>
</tr>
<tr>
<td>20 kg to less than 30 kg</td>
<td>600 mg weekly x 2 doses</td>
<td>600 mg at week 3; then 600 mg every 2 weeks</td>
</tr>
<tr>
<td>10 kg to less than 20 kg</td>
<td>600 mg weekly x 1 dose</td>
<td>300 mg at week 2; then 300 mg every 2 weeks</td>
</tr>
<tr>
<td>5 kg to less than 10 kg</td>
<td>300 mg weekly x 1 dose</td>
<td>300 mg at week 2; then 300 mg every 3 weeks</td>
</tr>
</tbody>
</table>

Black Box Warning
WARNING: SERIOUS MENINGOCOCCAL INFECTIONS
Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies. Immunize patients with a meningococcal vaccine at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risks of developing a meningococcal infection. Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected. Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS prescribers must enroll in the program.

Drug Availability
Soliris (eculizumab) is supplied as 300 mg single-use vials containing 30 mL of 10 mg/mL sterile, preservative-free Soliris solution per vial.

Because of the risk of meningococcal infections, Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS, prescribers must enroll in the program. Prescribers must counsel patients about the risk of meningococcal infection, provide the patients with the REMS educational materials, and ensure patients are vaccinated with a meningococcal vaccine.
**General Background**

**Pharmacology/Disease Overview**

Eculizumab is a recombinant humanized IgG monoclonal antibody used to reduce hemolysis in patients with PNH. Patients with PNH produce abnormal red blood cells (RBCs) because of a genetic mutation. These abnormal RBCs are overly sensitive to hemolysis by complement. Eculizumab prevents erythrocyte lysis by inhibiting the terminal complement complex. Eculizumab is an option for patients whose current hemolysis prevention therapy is limited by medication toxicity or inconsistent efficacy.

HUS is characterized by hemolytic anemia, thrombocytopenia, and renal failure caused by platelet thrombi in the microcirculation of the kidney and other organs. Typical (acquired) HUS is triggered by infectious agents such as strains of E. coli that produce powerful Shiga-like exotoxins, whereas aHUS can be genetic, acquired, or idiopathic. Onset of atypical HUS ranges from prenatal to adulthood.

aHUS is considered genetic when two or more members of the same family are affected by the disease at least six months apart and exposure to a common triggering infectious agent has been excluded, or when a disease-causing mutation(s) is identified in one of the nine genes in which mutations are known to be associated with aHUS, irrespective of familial history.

**Guidelines**

**American Society of Hematology (ASH)**

The ASH recommends eculizumab for the treatment of PNH. It is a well tolerated long-term (> 8 years) therapy that shows improvement in PNH associated symptoms, a reduction in transfusion requirements and a higher proportion of transfusion independent patients than previously seen in other therapies. There is a significant reduction in the development of thromboembolism on eculizumab therapy and most importantly, patients have been able to stop primary prophylaxis with warfarin without any thrombotic complications.

**Clinical Efficacy**

**PNH**

Clinical experience with eculizumab is limited to three case reports, an open-label pilot study, a 52-week extension of the pilot study, and one randomized, double-blind, placebo-controlled, multicenter trial. Eculizumab was well tolerated and increased quality of life in all of these studies. In the 26-week experimental trial, stabilization of hemoglobin concentrations was established in 49% of eculizumab patients compared to no patients in the placebo group, and the median number of units of RBCs transfused was zero units in the eculizumab group versus 10 units in the placebo group.

Hillmen et. al. (2004) evaluated the safety and efficacy of eculizumab in 11 transfusion-dependent patients with PNH in a 12-week, open-label, pilot study. Mean transfusion rates decreased from 2.1 units/patient/month to 0.6 units/patient/month (p=not reported), and median transfusion rates decreased from 1.8 units/patient/month to zero units/patient/month (p=0.003). Hemoglobinuric episodes decreased by 96% (p<0.001) while quality of life measurements improved significantly (global health status: p=0.02; physical functioning: p<0.001; emotional functioning: p=0.001; cognitive functioning: p=0.002; fatigue: p<0.001; dyspnea: p=0.002; insomnia: p=0.049). A reduction in mean lactate dehydrogenase concentrations from 3111 units/L to 594 units/L (p=0.002), and an increase in the mean percentage of PNH type III blood cells from 36.7% (of the total erythrocytes) to 59.2% (p=0.005) were also observed.

These same PNH patients were monitored further to assess the long-term safety and efficacy of eculizumab in a 52-week, open-label, extension study (Hill et al., 2005). Patients maintained the results achieved in all parameters at 12 weeks throughout the additional 52-week study period. Improvements in the role functioning (p=0.003) and pain (p=0.023) domains of the quality of life measurements were also reported at the end of this study. However, the constipation domain increased significantly (p<0.001).

Hillmen et. al. (2006) evaluated the efficacy of eculizumab in 87 PNH patients with hemolysis in a 26-week, randomized, double-blind, placebo-controlled, multicenter trial. Primary endpoints included the number of patients achieving hemoglobin stabilization and the number of RBC units transfused. Secondary endpoints evaluated transfusion independence, change in level of fatigue, and hemolysis. Prespecified exploratory analyses included Quality of Life, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLC-C30), change in LDH concentrations from baseline to week 26, median time to first transfusion, and change in proportion of PNH type III blood cells from baseline to week 26. Eculizumab...
significantly reduced hemolysis, increasing hemoglobin stabilization and decreasing RBC transfusion requirements compared to placebo (p<0.001). Eculizumab was also superior to placebo in all secondary and prespecified exploratory analyses outcomes. The most common adverse reactions associated with eculizumab therapy were headache, nasopharyngitis, and back pain. There were no significant differences in adverse reactions between the two groups.

**aHUS**

In aHUS Study 2, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins. Reduction in terminal complement activity was observed in all patients after commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. Platelet counts were maintained at normal levels despite the elimination of PE/PI. Renal function, as measured by median eGFR, was maintained during Soliris therapy. No patient required new dialysis with Soliris.

The efficacy results for the aHUS retrospective study were generally consistent with results of the two prospective studies. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline. A total of 19 pediatric patients (ages 2 months to 17 years) received Soliris in aHUS Study 3. The median duration of Soliris therapy was 16 weeks (range 4 to 70 weeks) for children < 2 years of age (n=5), 31 weeks (range 19 to 63 weeks) for children 2 to <12 years of age (n=10), and 38 weeks (range 1 to 69 weeks) for patients 12 to 17 years of age (n=4). Fifty three percent of pediatric patients had an identified complement regulatory factor mutation or auto-antibody. Overall, the efficacy results for these pediatric patients appeared consistent with what was observed in patients enrolled in aHUS Studies 1 and 2. No pediatric patient required new dialysis during treatment with Soliris.

**Adverse Reactions**

In addition to the Black Box Warning, the most frequently reported adverse reactions in the PNH are headache, nasopharyngitis, back pain, and nausea. The most frequently reported adverse reactions in aHUS are hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leucopenia. Eculizumab is contraindicated in patients with unresolved serious Neisseria meningitidis infections and in patients who are not currently vaccinated against Neisseria meningitidis.

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**Coding/Billing Information**

**Note:** This list of codes may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

**Covered when medically necessary:**

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>J1300</td>
<td>Injection, eculizumab, 10 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-9-CM Diagnosis Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>283.2</td>
<td>Hemoglobinuria due to hemolysis from external causes</td>
</tr>
<tr>
<td>283.11</td>
<td>Hemolytic-uremic syndrome</td>
</tr>
</tbody>
</table>

**Experimental/Investigational/Unproven/Not Covered when used for Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS):**

<table>
<thead>
<tr>
<th>ICD-9-CM Diagnosis Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>041.41-041.49</td>
<td>Escherichia coli [E. Coli]</td>
</tr>
<tr>
<td>283.11</td>
<td>Hemolytic-uremic syndrome</td>
</tr>
</tbody>
</table>
References


