I. POLICY

Initial therapy

Eculizumab may be considered medically necessary for patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) to reduce hemolysis when ALL of the following criteria are met:

- Prescribed by a hematologist or nephrologist enrolled in the Soliris REMS program (package insert)
- PNH is documented by flow cytometric analysis of at least 10% PNH cells (establishes the dx)
- Received a meningococcal vaccine administered at least 2 weeks prior to the initiation of therapy (with revaccinations performed according to current guidelines). (package insert)

AND

- One of the following:
  - History of transfusion dependence (at least one blood transfusion in the past 24 months) OR
  - Disabling symptoms (frequent paroxysms of pain, end organ damage) OR
  - Documented history of a major vascular event (MAVE)* from thromboembolism.

*Major Adverse Vascular Events (MAVE)

Venous thrombosis

- Deep vein thrombosis
- Pulmonary embolism
- Hepatic or portal vein thrombosis
- Mesenteric or splenic thrombosis
- Renal vein thrombosis
- Thrombophlebitis
Eculizumab (Soliris®) may be considered medically necessary in patients when used to treat patients with Atypical Hemolytic Uremic Syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy when all of the following indications are met:

- Shiga toxin-related HUS has been ruled out AND
- Members over the age of 9 months have had a meningococcal vaccine administered at least 2 weeks prior to initiation of therapy and revaccinations performed according to current guidelines; pediatric patients should also be immunized for streptococcus pneumonia and Haemophilus influenza type b (Hib); AND
- The prescribing physician is a hematologist or nephrologist enrolled in Soliris REMS program.

**Maintenance Therapy**

Eculizumab (Soliris®) maintenance therapy for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) or atypical hemolytic uremic syndrome (aHUS) may be considered medically necessary when therapy has demonstrated efficacy as evidenced by an improvement in disease activity at twelve weeks and maintenance of at least that improvement at each 6 month re-evaluation as evidenced by the following:

**For patients with PNH all** of the following indications should be met:
- A decrease in the number of transfusions or disabling symptoms
- Stabilization of hemoglobin levels
- Fewer thrombotic events than prior to therapy
- Improvement in fatigue and quality of life

**For patients with aHUS all** of the following indications should be met:
- Decrease in signs of thrombotic microangiopathy (TMA) (normalization of platelet counts and LDH levels, reduction in serum creatinine)
- Decrease in need for plasma exchange (PE) plasma infusion (PI) or dialysis

Eculizumab is considered investigational when the criteria above are not met and for all other indications, including but not limited to treatment of:
- patients under the age of 18 years for the treatment of PNH
- antibody mediated rejection in organ transplantation
- antineutrophil cytoplasmic autoantibody (ANCA) vasculitis
II. PRODUCT VARIATIONS

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

FEP PPO*

*Refer to FEP Medical Policy Manual MP-5.10.11 Soliris. The FEP Medical Policy manual can be found at: www.fepblue.org

III. DESCRIPTION/BACKGROUND

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired genetic blood disorder characterized by hemolytic anemia, thrombosis, impaired bone marrow function and a 3% to 5% risk of developing leukemia. PNH occurs when mutations of the PIG-A gene occur in a bone marrow stem cell resulting in the formation of cells deficient in a class of proteins called GPI-anchored proteins. This lack of protein renders these blood cells defenseless against intravascular hemolysis by the terminal complement mediated immune response.

PNH typically affects people in young adulthood with a median age of 30-40 years. Soliris is a monoclonal antibody that specifically binds to the complement protein, thereby inhibiting generation of the terminal complement complex C5b-9. This mechanism of action allows Soliris to inhibit terminal complement mediated intravascular hemolysis in PNH patients. Previous treatment for PNH was dependent on the severity of patient symptoms, and the only curative therapy is allogenic bone marrow transplantation.
Atypical hemolytic uremic syndrome (aHUS) is a rare and chronic blood disease that can lead to kidney failure and is associated with increased risk of death and stroke. Atypical HUS accounts for 5 to 10 percent of all cases of hemolytic uremic syndrome and disproportionately affects children.

Soliris® (Alexion Pharmaceuticals, Inc., Cheshire, CT is a complement inhibitor indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) age 18 and older to reduce hemolysis and also for patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy. Soliris was approved by the United States Food and Drug Administration (FDA) on March 16, 2007 for the treatment of PNH, and on September 23, 2011 for the treatment of aHUS. Eculizumab (Soliris) binds to complement protein C5 and inhibits its enzymatic cleavage, blocks formation of the terminal complement complex, and thus prevents red cell lysis in paroxysmal nocturnal hemoglobinuria (PNH) and complement-mediated thrombotic microangiopathy in atypical hemolytic uremic syndrome (aHUS).

Soliris includes a boxed warning of life-threatening and fatal meningococcal infections. Additionally, all patients must be vaccinated with a meningococcal vaccine at least 2 weeks prior to receiving their first dose. The safety and effectiveness of Soliris for the treatment of PNH in pediatric patients below the age of 18 years have not been established while for aHUS: safety and effectiveness is similar to adult patients. Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

Dosing

Paroxysmal Nocturnal Hemoglobinuria (PNH)
Eculizumab therapy consists of 600 mg by IV administration every 7 days for the first 4 weeks, followed by 900 mg for the fifth dose 7 days later, then 900 mg every 14 days thereafter.

Atypical Hemolytic Uremic Syndrome (aHUS)
For members 18 years of age and older, eculizumab therapy consists of 900 mg by IV administration every 7 days for the first 4 weeks, followed by 1200 mg for the fifty dose 7 days later, then 1200 mg every 2 weeks thereafter.

For members less than 18 years of age, administer eculizumab based on body weight, according to the following table:

Dosing recommendations in patients less than 18 years of age:

<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>
</tbody>
</table>
Eculizumab has a Black Box Warning as follows (Product Information Label, Soliris 2012):

**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.

Eculizumab is currently being investigated as a potential treatment for other severe, ultra-rare disorders.

**Laboratory Monitoring**

**PNH:** Serum LDH levels increase during hemolysis and may assist in monitoring eculizumab effects, including the response to discontinuation of therapy. In clinical studies, six patients achieved a reduction in serum LDH levels only after a decrease in the eculizumab dosing interval from 14 to 12 days. All other patients achieved a reduction in serum LDH levels with the 14 day dosing interval.

**aHUS:** Early signs of thrombotic microangiopathy (TMA) include a decrease in platelet count, and increases in serum LDH and creatinine levels. Patients should be followed for signs of TMA by monitoring serial platelet counts, serum LDH, and creatinine during eculizumab therapy and following discontinuation of eculizumab.

**Soliris REMS:** Because of the risk of meningococcal infections, eculizumab 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. Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747).
IV. RATIONALE

Paroxysmal Nocturnal Hemoglobinuria
Evidence for the efficacy and safety of eculizumab (Soliris®) was obtained from one comparative clinical trial (TRIUMPH), an open-label, single-arm study (SHEPHERD), and an extension study.

TRIUMPH was a 26-week randomized, placebo-controlled trial conducted in 11 countries in North America, Europe, and Australia. Eligible patients had transfusion-dependent PNH and were not thrombocytopenic. Eighty-eight patients were randomized, but one turned out to be ineligible and was deleted from further analysis. Treatment assignment was stratified based on the number of blood transfusions received within 1 year before trial entry: low stratum, 4–14 units; middle stratum, 15–25 units; high stratum, more than 25 units. Outcome measures included the proportion of patients with hemoglobin levels maintained above an individualized set point (hemoglobin stabilization). The hemoglobin set point was defined as an individual’s lowest hemoglobin level requiring transfusion during the 12 months before trial entry. The set point was the hemoglobin level for any transfusion administered to a symptomatic patient with hemoglobin of 9 g/dL or less or to a symptomatic or asymptomatic patient with hemoglobin of 7 g/dL or less. The median set point was 7.7 g/dL for both treatment groups.

SHEPHERD was an international, 52-week, single-arm study of 97 patients with PNH who were not transfusion-dependent. Patients with thrombocytopenia were included (median platelet count x 109/L [range] 136 [23-355]). The primary outcome measure was reduction in hemolysis as measured by the area under the serum LDH concentration-time curve. A comparison of transfusion requirements 1 year before trial entry and during the 1 year trial was also assessed. Results were stratified by quartiles of baseline serum LDH level and by platelet count (less than or greater than 65 x 109/L). Improvements in LDH and transfusion requirements were greater in patients with higher baseline hemolysis.

Quality of life assessments used in TRIUMPH and SHEPHERD were the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). FACIT-Fatigue is a 13-item self-report questionnaire that measures tiredness, weakness, and difficulty conducting usual activities due to fatigue. Scores range from 0 to 52, with higher scores indicating improvement in fatigue. The minimum clinically meaningful change is 3 points. FACIT-Fatigue has been validated in patients with cancer but not in patients with PNH.

The EORTC QLQ-C30 comprises five functional scales (Physical, Role, Cognitive, Emotional and Social Functioning); three symptom scales (Fatigue, Pain and Nausea/Vomiting); a Global Health Status/QoL scale; and six single item scales (Dyspnea, Insomnia, Loss of Appetite, Constipation, Diarrhea and Financial Difficulties). Scores range from 0 to 100, with higher score indicating a higher (“better”) level of functioning or a higher (“worse”) level of symptoms. EORTC QLQ-C30 has been validated in patients with cancer but not in patients with PNH.
An open-label extension study enrolled 96% of patients who had participated in TRIUMPH, SHEPHERD, or a phase 2 pilot study. The primary outcome was the change in thrombotic event rates before and after treatment. Thrombotic events were determined by the principal investigator; pretreatment events were determined by review of past medical history and adverse events, and pretreatment incidences varied from 18% to 43%. The absolute reduction of thrombotic events was 6.3 events per 100 patient-years (85% relative reduction). In the subgroup of 91 patients receiving anticoagulants, the absolute reduction was 10.82 events per 100 patient-years (94% relative reduction).

The duration of treatment in the extension trial is not stated in the published report. FDA documents indicate that treatment duration ranged from 10 months to 54 months. On-treatment event rates matched those reported during each of the individual trials, suggesting that there were no additional thrombotic events during extended treatment with eculizumab (Soliris®).

Overall Survival with Eculizumab (Soliris®) Treatment
A published report from a single center in England described 79 consecutive transfusion-dependent patients treated with eculizumab (Soliris®). Mean treatment duration was 3.3 years (range: 0 to 8 years). Overall survival in this group was similar to that in age- and sex-matched normal controls (p=0.46 for the difference between Kaplan-Meier survival curves). Five-year survival (95.5% [95% confidence interval (CI): 87.6%, 98.5%]) was greater than that of 30 transfusion-dependent patients treated before the availability of eculizumab (Soliris®; 66.8% [95% CI: 41.4%, 85.1%]).

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Safety
Safety data were available from 236 eculizumab (Soliris®)-treated patients, including 43 patients from TRIUMPH and 193 patients from single-arm clinical studies in PNH. Adverse events were recorded at each dosing visit. Relationship to study drug was investigator-assessed.

Adverse Events

In TRIUMPH, two patients discontinued eculizumab (Soliris®) treatment prematurely, one because of pregnancy (which went on to delivery of a normal infant) and one because traveling to the study center was inconvenient. No patients in TRIUMPH died. Serious adverse events (SAEs) occurred in 4 patients in the eculizumab (Soliris®) group and 9 patients in the placebo group.

Adverse events occurring during TRIUMPH with a frequency of at least 5% in the eculizumab (Soliris®) group. The most common of these were headache (44% vs. 27%), nasopharyngitis (23% vs. 18%), back pain (19% vs. 9%), nausea (16% vs. 11%), cough (12% vs. 9%), and notably, fatigue (12% vs. 2%).

Of 193 PNH patients who received eculizumab (Soliris®) in single-arm studies, serious adverse events that occurred in at least 2 patients were:
- viral infection (2.6%)
- headache (2.1%)
- anemia (1.6%)
- pyrexia (1.6%)
- hemolysis (1.0%)

Four eculizumab (Soliris®) -treated patients died:34
- a 31-year-old man with hemosiderosis who suffered a pulmonary embolus and a hemorrhagic cerebral infarction 31 days after his last dose of eculizumab (Soliris®)
- a 60-year-old female patient with cholecystitis who became septic and died from a cerebrovascular accident approximately 2 months after her last dose of eculizumab (Soliris®)
- a 71-year-old man with myelodysplastic syndrome (MDS) who developed cellulitis, sepsis, and acute renal failure after a fish hook infection and died from progression of his MDS
- a 63-year-old woman who died after 13 months on eculizumab (Soliris®) from pre-existing adenocarcinoma that had metastasized

Review of the narrative descriptions and case report forms of these cases suggested that eculizumab (Soliris®) was unlikely to be related to these deaths.
Infections
Patients taking eculizumab (Soliris®) may be at increased risk of infection with encapsulated bacteria. These include *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *Neisseria meningitidis*. There were 2 cases of *Neisseria meningitidis* in patients receiving eculizumab (Soliris®):34
- a 54 year-old vaccinated female patient who had received eculizumab (Soliris®) for approximately 14 months
- a 24 year-old male vaccinated patient who had received eculizumab (Soliris®) for approximately 12 months

Neither patient died. A third case occurred in an unvaccinated patient who did not have PNH and had received eculizumab (Soliris®) for approximately 7 months. This patient also did not die but developed a complicated course of meningococcemia, with pulmonary embolus, pneumonia, and partial amputation of some digits because of gangrene.

Immunogenicity
Eculizumab (Soliris®) is a humanized monoclonal antibody produced in a murine myeloma cell line. Therefore, it may induce human anti-human antibodies. A direct enzyme-linked immunosorbent assay (ELISA) targeted to the Fab fragment of eculizumab (Soliris®) detected low titers of antibodies in 3/195 PNH patients (2%), including one placebo-treated patient. However, the assay used had not been adequately validated; it may have been unable to detect low titer antibodies due to assay interference by eculizumab (Soliris®). Serum LDH levels were not increased at the time of positive antibody responses, suggesting that the antibodies were not neutralizing. However, a neutralization assay was not performed. Clinical efficacy appears unaffected by the presence of the antibodies.45

**Atypical Hemolytic Uremic Syndrome**

**Summary of Evidence**
Eculizumab (Soliris®) was the subject of two abstracts46, 47, published in conference proceedings, which reported the results of 4 prospective single arm studies the FDA used to determine the safety and efficacy of eculizumab (Soliris®) in adolescents and adults with aHUS37, 45, 48, 49

Each abstract reported a pair of studies that was identical except for the age of the patients (age 12-18 years, and age older than 18 years). One set involved patients with plasma therapy-resistant aHUS (n=17 aged 12 years or older), and the other set involved patients with plasma therapy-sensitive aHUS (n=20 aged 12 years or older). All studies were 26 weeks, with the same dosing protocols (900 mg IV every 7±2 days for 4 weeks, followed by 1,200 mg 7±2 days for week 5, and 1,200 mg every 14 ±2 days for a total of 26 weeks). The comparator for each study was baseline measure (8 week observation period for the plasma therapy-sensitive cohort). Outcomes varied by disease under study, although the major outcome of interest was reduction in the signs of thrombotic microangiopathy (TMA; platelet counts increase, reduction in serum
lactate dehydrogenase levels and serum creatinine levels, and the absence of TMA intervention such as dialysis or plasma exchange). For the plasma therapy-resistant cohort, investigators sought reductions in TMA indicators from baseline (e.g., reduction of serum lactate dehydrogenase levels, increased platelet count, improvements in creatinine clearance). In contrast, where eculizumab (Soliris®) was substituted for plasma therapy in patients who were stable on plasma therapy, outcomes of interest included maintaining corrected levels of TMA indicators (platelet count and serum lactate dehydrogenase levels remain stable compared to baseline).

In patients with plasma therapy resistant aHUS, the mean platelet count (primary endpoint) increased from 109 ± 32 X109/L at baseline to 210 ± 68 X109/L after 26 weeks of therapy The primary endpoint for the cohort with plasma therapy sensitive aHUS was TMA event free status, defined as 12 weeks or more of stable platelet count, no plasma therapy and no new dialysis. The primary endpoint was achieved in 80%, (95% confidence interval [CI], 56%, 94%) of the cohort. In patients with plasma resistant aHUS, four of five patients who required dialysis at baseline were able to discontinue dialysis for the duration of eculizumab (Soliris®) treatment. Another patient developed a new dialysis requirement during the study.

Neither of these studies of eculizumab (Soliris®) treatment of aHUS could be considered for USPSTF grading because they were not randomized controlled trials. The quality of noncomparative studies can be assessed using the measures proposed by Carey and Boden.2 In the absence of published peer-reviewed reports, a combination of Clinicaltrials.gov, the product labeling and the available published abstracts (European Hematology Association Meeting, June 2011) were used to address the quality of the study. Both abstracts46, 47 clearly indicated that one of the study authors was employed by the sponsor, Alexion Pharmaceuticals. The research questions were defined, as was the intervention. The study populations were defined in the ClinicalTrials.gov trial summary; however, the limited space allowed for an abstract and presentation in the product label did not allow an adequate description of the study population.

Patients with known causes of secondary aHUS were excluded (malignancy, HIV infection, some drug exposures, pregnancy, and infections) to reduce confounding.50 The effects of eculizumab (Soliris®) are therefore unknown in this patient population. The product information states that the effects of eculizumab (Soliris®) were similar in patients with and without genetic mutations in both studies. However, neither study (n=17, n=20) was large enough to identify a difference between subpopulations, and the label does not mention differential response to therapy depending on underlying mutation.

The response to eculizumab (Soliris®) therapy was measured using many of the same outcomes used in the plasma therapy, and used an 8-week prospective observation period as a baseline measure for comparison in the plasma therapy-sensitive patients. This was reasonable given the level of morbidity in the patient population. Long-term outcomes such as reduced need for supportive services, transplantation, dialysis, and overall survival were not addressed. In both studies, the TMA event-free status was calculated at each post-dose day of measurement through
week 26 using repeated measures ANOVA. For the change in platelet count over the 26-week study period, the median change from baseline is preferred to the mean, which may be skewed right. Each outcome result was listed or tabulated, but without the background information, the study results could not be considered well described.

Lastly, there was not enough information to assess whether the conclusions were supported by the data. Neither abstract nor product information provided any discussion that considered the place in therapy for eculizumab (Soliris®; it is the only therapy besides plasma therapy, and transplant). Integrating information from several sources improves the understanding of these studies, but only slightly. The long-term effects of eculizumab (Soliris®) and the potentially differing response to therapy by underlying aHUS cause are not clear from the available reports.

In addition to the abstracts detailed above, the available details (results, from product information only) of a retrospective study of eculizumab (Soliris®) for treatment of aHUS in pediatric patients (n=19) are. One abstract details this study.51 This cohort had complement regulatory factor mutation or autoantibody in 53%. No new dialysis was required.

V. DEFINITIONS

N/A

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.
VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

<table>
<thead>
<tr>
<th>HCPCS Code</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-10-CM Diagnosis Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>D59.3</td>
<td>Hemolytic-uremic syndrome</td>
</tr>
<tr>
<td>D59.5</td>
<td>Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]</td>
</tr>
</tbody>
</table>

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

IX. REFERENCES


BCBSA TEC Specialty Pharmacy Report #1- Eculizumab (Soliris®) #1-2012 (Archived).


Rationale references (from BCBSA TEC Specialty Pharmacy Report #1- Eculizumab (Soliris®)


X. POLICY HISTORY

<table>
<thead>
<tr>
<th>Policy Number</th>
<th>CAC Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP 2.178</td>
<td>CAC 7/30/13</td>
<td>New policy. Eculizumab (Soliris®) may be considered medically necessary in patients 18 years of age or older for the treatment of paroxysmal nocturnal hemoglobinuria and the treatment of atypical hemolytic uremic syndrome resistant to plasma exchange/infusion. This drug will require preauthorization. FEP variation added. New policy coded.</td>
</tr>
<tr>
<td>CAC 5/20/14</td>
<td>Minor revision. Policy criteria being revised: for PNH patients, the number of transfusions was reduced from &gt;4 transfusions in 12 months to 1 transfusion in 24 months. The criteria that aHUS patients receive plasma exchange or plasma infusion within the previous 2 weeks has been removed. References updated. No coding changes.</td>
<td></td>
</tr>
<tr>
<td>CAC 6/2/15</td>
<td>Consensus review. No changes to the policy statements. References updated. Codes reviewed.</td>
<td></td>
</tr>
<tr>
<td>Admin updated 12/1/16</td>
<td>Product variation section reformatted.</td>
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</tr>
<tr>
<td>CAC 11/29/16</td>
<td>Minor revision. Added a documented history of a major adverse vascular event (MAVE) from thromboembolism as a new medical necessity indication for treatment of PNH. Additional revisions made to statements for clarification purposes only. References updated. Coding</td>
<td></td>
</tr>
</tbody>
</table>
Health care benefit programs issued or administered by Capital BlueCross and/or its subsidiaries, Capital Advantage Insurance Company®, Capital Advantage Assurance Company® and Keystone Health Plan® Central. Independent licensees of the BlueCross BlueShield Association. Communications issued by Capital BlueCross in its capacity as administrator of programs and provider relations for all companies.