Introduction

Beta thalassemia is an inherited blood disorder. Due to a change in one or more genes, the body doesn’t make enough hemoglobin. Hemoglobin is a protein in red blood cells that carries oxygen to the body. When the body does not make enough hemoglobin or red blood cells, it causes a condition called anemia. Anemia leads to fatigue and weakness and can be mild, moderate, or severe. Treatment of anemia from beta thalassemia is meant to increase the number of healthy red blood cells. This policy describes when drugs called erythroid maturation agents used to treat anemia may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
### Drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
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</thead>
</table>
| Reblozyl® (luspatercept-aamt) SC | Reblozyl® (luspatercept-aamt) may be considered medically necessary for the treatment of anemia in adult patients when the following criteria are met:  
  • Patient is 18 years of age or older  
  AND  
  • Patient has beta thalassemia  
  AND  
  • Patient has received a minimum of 6 red blood cell (RBC) units in the past 6 months  
  AND  
  • Patient has no transfusion-free period >30 days during the past 6 months  
  AND  
  • Reblozyl® is not being used as a substitute for RBC transfusions in patients who require immediate correction of anemia  
  AND  
  • Reblozyl® is prescribed by or in consultation with a hematologist |

### Drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reblozyl® (luspatercept-aamt)</td>
<td>All other uses of Reblozyl® (luspatercept-aamt) for conditions not outlined in this policy are considered investigational.</td>
</tr>
</tbody>
</table>

### Length of Approval

<table>
<thead>
<tr>
<th>Approval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial authorization</td>
<td>Reblozyl® (luspatercept-aamt) may be approved up to 6 months.</td>
</tr>
<tr>
<td>Re-authorization criteria</td>
<td>Future re-authorization of Reblozyl® (luspatercept-aamt) may be approved up to 1 year as long as the drug-specific coverage criteria are met and chart notes demonstrate at the time of re-authorization a reduction in RBC transfusion burden from baseline.</td>
</tr>
</tbody>
</table>
Documentation Requirements

The patient's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis, relevant history, physical evaluation and RBC transfusion history

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>J0896</td>
<td>Injection, luspatercept-aamt, 0.25 mg (Reblozyl®)</td>
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</table>

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Related Information

Consideration of Age

The ages stated in this policy for which Reblozyl® (luspatercept-aamt) is considered medically necessary are based on the ages approved in the FDA labeling.

Benefit Application

This policy is managed through both the Pharmacy and Medical benefit.
Background

β-thalassemia is a hereditary red blood cell disorder caused by mutations in the β-globin gene that can causes anemia and associated comorbidities such as bone deformities, ulcers, splenomegaly and treatment related sequelae such as iron overload. β-thalassemia is more common in Mediterranean countries, Central Asia and Southeast Asia. β-thalassemia can result in a range of phenotypes that include asymptomatic individuals to patients with severe anemia. The cause of β-thalassemia is from a gene mutation which impacts the hemoglobin subunits and can be classified into categories such as β-thalassemia minor, β-thalassemia intermedia and β-thalassemia major. Blood transfusion is the current standard of care for adult patients with β-thalassemia who require RBC transfusion. With blood transfusion therapy supportive care in the form of iron chelation agents may be prescribed.

The burden of β-thalassemia in the US is approximately 1 in 100,000 and varies by region based on immigration patterns. The economic impact of β-thalassemia can be profound over time as patients with β-thalassemia major may be dependent on life-long blood transfusion regimens. The quality of life of subjects with β-thalassemia may diminish as treatment management modalities often require monitoring of symptoms, blood counts and iron levels but more importantly can be impacted by the negative side effects of blood transfusions such as iron overload and infusion related reactions.

β-thalassemia’s are genetic disorders of hemoglobin synthesis characterized by deficient (β⁺) or absent (β⁰) synthesis of the β-globin subunit of hemoglobin that can result in anemia. The majority of patients inherit their disorder as a mendelian recessive trait which can impart varying levels of phenotypic expression and disease conditions. Heterozygous individual may be asymptomatic or exhibit light symptoms such as with mild anemia being labeled as β-thalassemia minor and homozygous individuals have more severe anemia of varying degrees and are labeled as β-thalassemia major or intermedia.

Luspatercept is a recombinant fusion protein comprised of the modified extracellular domain of the human activin receptor type IIB linked to the fragment crystallizable region (Fc) domain of human immunoglobin G1 which binds several endogenous TGF-β-superfamily ligands that diminishes Smad2/3 signaling. In mice models, luspatercept promoted erythroid maturation through differentiation of late-stage erythroid precursors (normoblasts). These models revealed that luspatercept decreased abnormally elevated Smad2/3 signaling and improved hematology parameters associated with ineffective erythropoiesis. Luspatercept activity in binding to and inhibiting Smad 2/3 ligands GDF11 and activin corrected anemia and ineffective erythropoiesis. In patients with low RBC transfusion burden hemoglobin levels increased in 7 days of initiating
treatment and correlated with the increase in luspatercept C<sub>MAX</sub> and the greatest increase in hemoglobin was seen after the first dose.

**Summary of Evidence**

**Efficacy**

Luspatercept had consistent efficacy in decreasing transfusion burden compared to those receiving placebo as reported in the randomized, double-blind, placebo-controlled, Phase III BELIEVE Trial. Patients being managed for transfusion dependent β-thalassemia requiring 3 units of blood every 3 weeks for life adds a significant burden to treatment management. Luspatercept achieved reduction in transfusion burden across any 12- or 24-week period in the BELIEVE Trial demonstrating wide efficacy. 48/224 (21.4%) achieved the primary end point of a ≥33% reduction in RBC transfusion burden with a reduction of ≥2 RBC units from baselines during weeks 13-24 vs 5/112 (4.5%) of patients in placebo. 158/224 (70.5%) of subjects achieved a greater than 33% reduction in RBC transfusion requirements during any consecutive 12 weeks of treatments vs 33/112 (29.5%) of placebo treated subjects. There were statistically significant findings that favored luspatercept for other secondary endpoints including:

- ≥33% reduction in transfusion burden at weeks 37-48: 19.6% (n=44 of 224 luspatercept-treated patients) vs. 3.6% (n=4 of 112 placebo-treated patients; p<0.001)
- ≥50% reduction in transfusion burden at weeks 13-24: 7.6% (n=17/224) vs. 1.8% (n=2/112; p=0.03)
- ≥50% reduction in transfusion burden at weeks 37-48: 10.3% (n=24/224) vs. 0.9% (n=1/112; p=0.002)

**Safety**

The safety profile of luspatercept was generally tolerable as the most common adverse events were mild to moderate and manageable without dose modification, delay or discontinuation. Common adverse events included bone pain, headache, and injection site reactions. Safety analyses by demographic subgroups did not reveal any significant differences from overall safety findings. The most common serious adverse events from clinical trials included anemia, DVT, fever, infection and septic shock. These side effects are commonly associated with the side effects related to the use of hematologic factors and subcutaneous injection site related
Reactions. Relevant warnings and precautions associated with luspatercept include thromboembolic events (TEE) which were reported in 8/223 (3.6%) of subjects and included DVT and stroke followed by hypertension in 61/571 (10.7%) of subjects. There is limited data regarding pediatric patients and the use of luspatercept. A warning label for embryo-fetal toxicity is stated. Pregnant and lactating women were excluded from the clinical study populations and throughout clinical development. Animal reproductive data was collected which resulted in adverse developmental outcomes. Outcomes included increased embryo-fetal mortality, alterations to growth, and structural abnormalities which occurred at levels higher than the maximum recommended human dose of 1.25 mg/kg.

References


**History**

<table>
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<tr>
<th>Date</th>
<th>Comments</th>
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<tr>
<td>04/01/20</td>
<td>New policy, approved March 10, 2020, effective for dates of service on or after July 2, 2020, following 90-day provider notification. Add to Prescription Drug section. Reblozy (luspatercept-aamt) may be considered medically necessary for the treatment of anemia in adult patients with beta thalassemia when criteria are met. Coverage criteria for Reblozy (luspatercept-aamt) (HCPCS code J3590) becomes effective for dates of service on or after July 2, 2020.</td>
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</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2020 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)


Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action before a date to keep your health insurance or benefits.

You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Arabic (Arabic):
بيحوي هذا الإشعار معلومات هامة. قد يحيح هذا الإشعار معلومات هامة في نفس اللغة أو اللغة العربية. في هذه الأوراق، يمكن أن يحتوي إشعار على توثيق المعلومات المتعلقة بالعافية أو الخدمات المقدمة في هذه الأوراق. يرجى إلقاء نظرة على هذه المعلومات قبل تقديم أي استفسارات أو استفسارات.
Call 800-722-1471 (TTY: 800-842-5357) for help.

中文 (Chinese):
本通知有重要的讯息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保障的重要訊息。本通知可能有重要的日期。您可能需要在截止日期之前採取行動。以保留您的健康保險或愛費補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).

Oromo (Cushite):

Deutsche (German):

Italiano (Italian):
Este Aviso contiene información importante. Es posible que esté contenido información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas claves en este aviso. Es importante que se tome nota de los plazos para mantener su cobertura de salud o ayuda de

Γαλλέζικα (Français):
Les informations contenues dans ce document sont importantes. Il est possible que certaines informations importantes soient contenues dans ce document. Il est important de prendre note des délais pour la conservation de votre assurance ou de l'aide.

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas claves en este aviso. Es importante que se tome nota de los plazos para mantener su cobertura de salud o ayuda.

Tagalog (Tagalog):
Ang Pagawa na ito ay naglalarawan ng mahahalagang impormasyon. Ang pagawa na ito ay naglalarawan ng mahahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaaring mabahagi o mabahagi ngayon ang utang na loob o iibahagi ang karanasan sa iyong mga kaibigan.

Український (Ukrainian):
Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані в цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб забезпечити Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дозвоніть нас за номером телефону 800-722-1471 (TTY: 800-842-5357).