

REBLOZYL® (LUSPATERCEPT-AAMT)

Policy Number: PHARMACY 322.1 T2

Effective Date: February 1, 2020

[Instructions for Use](#) ⓘ

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Related Policy
<ul style="list-style-type: none"> Provider Administered Drugs – Site of Care Review at Launch for New to Market Medications

CONDITIONS OF COVERAGE

Applicable Lines of Business/Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General Benefits Package
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	No ¹
Precertification with Medical Director Review Required	No
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	Office ² , Outpatient ⁴ , Home ³
Special Considerations	<p>¹Precertification is not required, however it is strongly recommended for Reblozyl. While no penalty will be imposed for failure to request a pre-service review, if one is not requested, a medical necessity review will be conducted post-service to determine coverage. It is the referring physician’s responsibility to provide medical documentation to demonstrate clinical necessity for the medication. As of Jul. 1, 2020, precertification will be required. Refer to the Clinical Policy titled Review at Launch for New to Market Medications.</p> <p>²Participating providers in the office setting: Precertification is required for services performed in the office of a participating provider. Non-participating/out-of-network providers in the office setting: Precertification is not required, but encouraged for out-of-network services performed in the office. If precertification is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered.</p> <p>³Home infusion of Reblozyl requires additional precertification for the home care services.</p> <p>⁴Additional precertification requirements apply to requests for hospital outpatient facility infusion of</p>

COVERAGE RATIONALE

See [Benefit Considerations](#) ⓘ

Reblozyl has been added to the Review at Launch program. Some members may not be eligible for coverage of this medication at this time. Refer to the Clinical Policy titled [Review at Launch for New to Market Medications](#) for additional details.

Reblozyl is proven and/or medically necessary for the treatment of anemia in adult patients with beta thalassemia who meet ALL of the following criteria:¹⁻⁴

Initial Therapy

- Diagnosis of beta thalassemia including beta⁺ thalassemia, beta⁰ thalassemia, and hemoglobin E/beta thalassemia; **and**
- Patient is 18 years of age or older; **and**
- Patient is transfusion dependent as evidenced by **both** of the following in the previous 24 weeks:
 - Has required regular transfusion of at least six units of packed red blood cells (PRBC); **and**
 - No transfusion free period greater than 35 days**and**
- Reblozyl is prescribed by, or in consultation with, a hematologist, or other specialist with expertise in the diagnosis and management of beta thalassemia; **and**
- Reblozyl dosing is in accordance with the United States Food and Drug Administration approved labeling: starting dose of 1 mg/kg every 3 weeks by subcutaneous injection, with maximum dose of 1.25 mg/kg every 3 weeks; **and**
- Initial authorization will be for no more than 6 months.

Continuation of Therapy

- Diagnosis of beta thalassemia including beta⁺ thalassemia, beta⁰ thalassemia, and hemoglobin E/beta thalassemia; **and**
- Reblozyl is prescribed by, or in consultation with, a hematologist, or other specialist with expertise in the diagnosis and management of beta thalassemia; **and**
- Patient has experienced a reduction in transfusion requirements from pretreatment baseline of at least 2 units PRBC while receiving Reblozyl; **and**
- Reblozyl dosing is in accordance with the United States Food and Drug Administration approved labeling: starting dose of 1 mg/kg every 3 weeks by subcutaneous injection, with maximum dose of 1.25 mg/kg every 3 weeks; **and**
- Reauthorization will be for no more than 12 months.

Reblozyl is not proven or medically necessary for:

- The treatment of non-transfusion dependent beta thalassemia; or
- The treatment of beta thalassemia in pediatric patients; or
- The treatment of sickle beta thalassemia (hemoglobin S [HbS]/beta thalassemia); or
- The treatment of alpha thalassemia; or
- The treatment of myelodysplastic syndromes with or without ring sideroblasts; or
- The treatment of myeloproliferative neoplasm (MPN)-associated myelofibrosis.

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

HCPCS Code	Description
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics

ICD-10 Diagnosis Code	Description
D56.1	Beta thalassemia
D56.5	Hemoglobin E-beta thalassemia

BACKGROUND

Beta-thalassemias are a group of hereditary blood disorders characterized by anomalies in the synthesis of the beta chains of hemoglobin resulting in variable phenotypes ranging from severe anemia to clinically asymptomatic individuals. The total annual incidence of symptomatic individuals is estimated at 1 in 100,000 throughout the world and 1 in 10,000 people in the European Union. Three main forms have been described: thalassemia major, thalassemia intermedia and thalassemia minor. Individuals with thalassemia major usually present within the first two years of life with severe anemia, requiring regular red blood cell (RBC) transfusions. Findings in untreated or poorly transfused individuals with thalassemia major, as seen in some developing countries, are growth retardation, pallor, jaundice, poor musculature, hepatosplenomegaly, leg ulcers, development of masses from extramedullary hematopoiesis, and skeletal changes that result from expansion of the bone marrow. Regular transfusion therapy leads to iron overload related complications including endocrine complication (growth retardation, failure of sexual maturation, diabetes mellitus, and insufficiency of the parathyroid, thyroid, pituitary, and less commonly, adrenal glands), dilated cardiomyopathy, liver fibrosis and cirrhosis). Patients with thalassemia intermedia present later in life with moderate anemia and do not require regular transfusions. Main clinical features in these patients are hypertrophy of erythroid marrow with medullary and extramedullary hematopoiesis and its complications (osteoporosis, masses of erythropoietic tissue that primarily affect the spleen, liver, lymph nodes, chest and spine, and bone deformities and typical facial changes), gallstones, painful leg ulcers and increased predisposition to thrombosis. Thalassemia minor is clinically asymptomatic but some subjects may have moderate anemia. Beta-thalassemias are caused by point mutations or, more rarely, deletions in the beta globin gene on chromosome 11, leading to reduced (beta⁺) or absent (beta⁰) synthesis of the beta chains of hemoglobin. Transmission is autosomal recessive; however, dominant mutations have also been reported. Diagnosis of thalassemia is based on hematologic and molecular genetic testing. Treatment of thalassemia major includes regular RBC transfusions, iron chelation and management of secondary complications of iron overload. In some circumstances, spleen removal may be required. Bone marrow transplantation remains the only definitive cure currently available. Individuals with thalassemia intermedia may require splenectomy, folic acid supplementation, treatment of extramedullary erythropoietic masses and leg ulcers, prevention and therapy of thromboembolic events. Prognosis for individuals with beta-thalassemia has improved substantially following recent medical advances in transfusion, iron chelation and bone marrow transplantation therapy. However, cardiac disease remains the main cause of death in patients with iron overload.

BENEFIT CONSIDERATIONS

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Clinical Policy titled: Acquired Rare Disease Drug Therapy Exception Process.

CLINICAL EVIDENCE

The efficacy of Reblozyl was evaluated in adult patients with beta thalassemia in the BELIEVE trial (NCT02604433). BELIEVE is a multicenter, randomized, double-blind, placebo-controlled trial in which (n=336) patients with beta thalassemia (including beta⁺ thalassemia, beta⁰ thalassemia, and hemoglobin E/beta thalassemia; beta thalassemia with mutation and/or multiplication of alpha globin was also allowed) requiring regular red blood cell transfusions (6-20 RBC units per 24 weeks) with no transfusion-free period greater than 35 days during that period were randomized 2:1 to Reblozyl (n=224) or placebo (n=112). In BELIEVE, Reblozyl was administered subcutaneously once every 3 weeks as long as a reduction in transfusion requirement was observed or until unacceptable toxicity. All patients were eligible to receive best supportive care, which included RBC transfusions; iron-chelating agents; use of antibiotic, antiviral, and antifungal therapy; and/or nutritional support, as needed.

The BELIEVE trial excluded patients with hemoglobin S/beta-thalassemia or alpha-thalassemia or who had major organ damage (liver disease, heart disease, lung disease, renal insufficiency). Patients with recent deep vein thrombosis or stroke or recent use of ESA, immunosuppressant, or hydroxyurea therapy were also excluded. The median age was 30 years (range: 18-66).

The primary efficacy outcome measure was the proportion of patients achieving RBC transfusion burden reduction from baseline of at least 33%, with a reduction of at least 2 units from week 13 to week 24. Of the patients who

received Reblozyl, 21.4% (n=48) achieved the primary endpoint compared with 4.5% (n=5) of those who received placebo (risk difference 17.0; 95% CI 10.4, 23.6; p<0.0001). Secondary outcome measures included the proportion of patients achieving RBC transfusion burden reduction from baseline of at least 33%, with a reduction of at least 2 units from week 37 to 48 and the proportion of patients achieving RBC transfusion burden reduction from baseline of at least 50%, with a reduction of at least 2 units for 12 consecutive weeks from week 13 to week 24 and from week 37 to 48. Of the patients who received Reblozyl, 19.6% (n=44) achieved a 33% reduction and 2 unit reduction in transfusion burden from week 37 to 48 compared to 3.6% (n=4) with placebo (risk difference 16.1; 95% CI 9.8, 22.4; p<0.0001). 7.6% (n=17) and 10.3% (n=23) of patients receiving Reblozyl experienced a 50% reduction in transfusion burden with a 2 unit reduction for 12 consecutive weeks compared to 1.8% (n=2) and 0.9% (n=1) from week 13 to 24 and from week 37 to week 48 respectively (p<0.05 for both comparisons).

The efficacy of Reblozyl was evaluated in a phase 2 open-label, nonrandomized, uncontrolled study in 32 patients with transfusion dependent (requiring >4 RBC units per 8 weeks) received Reblozyl ranging from 0.6 to 1.25 mg/kg every 3 weeks. The median age was 38.5 years (range: 20-62). The primary endpoint in the transfusion-dependent population was a 20% reduction in transfusion burden over a 12 week interval. Transfusion dependence was defined as those who received an average of >4 RBC units every 8 weeks over the 6-month period before study initiation. Twenty-six (81%) of patients receiving Reblozyl achieved a 20% reduction in transfusion over any 12 weeks on study compared with the 12 weeks before baseline. RBC transfusion burden reduction of $\geq 33\%$ was achieved in 23 patients (72%), and $\geq 50\%$ reduction was achieved in 20 patients (63%) while receiving Reblozyl. An additional secondary endpoint included changes in liver iron concentration (LIC) measured using magnetic resonance imaging. Of 9 patients with transfusion dependence with baseline LIC >3 mg/g dry weight who were treated for >4 months, 5 (56%) achieved a decrease in LIC >2 mg/g dry weight. Mean LIC (+/- SD) for transfusion dependent patients at the end of the initial stage of treatment was -0.27 mg/g dry weight (+/- 1.64), compared with 5.03 mg/g (+/- 5.32) at baseline. All LIC responders were receiving ongoing concomitant iron chelation therapy.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Reblozyl (luspatercept-aamt) is an erythroid maturation agent indicated for the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions.

Limitations of Use

Reblozyl is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

The recommended starting dose of Reblozyl is 1 mg/kg once every 3 weeks by subcutaneous injection. Hemoglobin (Hgb) should be assessed prior to each administration. If an RBC transfusion occurred prior to dosing, the pretransfusion Hgb must be considered for dosing purposes. If the pre-dose hemoglobin (Hgb) is greater than or equal to 11.5 g/dL and the Hgb level is not influenced by recent transfusion, delay dosing until the Hgb is less than or equal to 11 g/dL. If a patient does not achieve a reduction in RBC transfusion burden after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose, increase the Reblozyl dose to 1.25 mg/kg. Reblozyl should be discontinued if a patient does not experience a decrease in transfusion burden after 9 weeks of treatment (administration of 3 doses) at the maximum dose level or if unacceptable toxicity occurs at any time.

REFERENCES

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare Pharmacy, Clinical Pharmacy Program that was researched, developed and approved by the UnitedHealth Group National Pharmacy & Therapeutics Committee. [2020D0084A]

1. Reblozyl [package insert]. Summit, NJ: Celgene Corporation, November 2019.
2. Galanello R, Origa R. Beta-thalassemia. Orphanet Journal of Rare Diseases. 2010; 5:11
3. Piga A, Perrotta S, Gamberini MR, et al. Luspatercept improves hemoglobin levels and blood transfusion requirements in a study of patients with beta-thalassemia. Blood. 2018; 133(12):1279-89.
4. An Efficacy and Safety Study of Luspatercept (ACE-536) Versus Placebo in Adults Who Require Regular Red Blood Cell Transfusions Due to Beta (β) Thalassemia (BELIEVE). Clinicaltrials.gov website <https://clinicaltrials.gov/ct2/show/NCT02604433?term=luspatercept&draw=2&rank=6>. Accessed November 8, 2019.
5. Origa R. Beta-thalassemia. Genet Med. 2017;19(6):609-19.

6. A Safety and Efficacy Study to Evaluate Luspatercept in Subjects With Myeloproliferative Neoplasm-associated Myelofibrosis Who Have Anemia With and Without Red Blood Cell-transfusion Dependence. Clinicaltrials.gov website <https://clinicaltrials.gov/ct2/show/NCT03194542?term=luspatercept&draw=2&rank=2>. Accessed November 8, 2019.
7. A Study of Luspatercept (ACE-536) to Treat Anemia Due to Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes (MEDALIST). Clinicaltrials.gov website <https://clinicaltrials.gov/ct2/show/NCT02631070?term=luspatercept&draw=2&rank=9>. Accessed November 8, 2019.
8. Efficacy and Safety Study of Luspatercept (ACE-536) Versus Epoetin Alfa for the Treatment of Anemia Due to IPSS-R Very Low, Low or Intermediate Risk Myelodysplastic Syndromes (MDS) in ESA Naïve Subjects Who Require Red Blood Cell Transfusions (COMMANDS). Clinicaltrials.gov website <https://clinicaltrials.gov/ct2/show/NCT03682536?term=luspatercept&draw=2&rank=10>. Accessed November 8, 2019.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
03/01/2020	<ul style="list-style-type: none"> • Added language pertaining to the Review at Launch program for Reblozyl
02/01/2020	<ul style="list-style-type: none"> • New Clinical Policy

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare Oxford reserves the right to modify its Policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice.

The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Oxford Clinical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.