UnitedHealthcare®

UnitedHealthcare® Community Plan
Medical Benefit Drug Policy

REBLOZYL® (LUSPATERCEPT-AAMT)

Policy Number: 2020D0084A **Effective Date: TBD**

Instructions for Use ⓘ

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Commercial Policy

- REBLOZYL® (LUSPATERCEPT-AAMT)

COVERAGE RATIONALE

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, beta^{0} 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 Therapy

- **Diagnosis of beta thalassemia including beta^{+} thalassemia, beta^{0} 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**
- **The treatment of myelodisplastic syndromes with or without ring siderobalsts; 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 and Coverage Determination Guidelines 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 myocardiopathy, 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 (beta^{0}) 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.

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, beta^{0} 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 >33% was achieved in 23 patients (72%), and >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)

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.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for Reblozyl® (luspatercept-aamt). Local Coverage Determinations (LCDs) do not exist at this time.

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals. (Accessed November 13, 2019)

REFERENCES

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
TBD	New Policy

INSTRUCTIONS FOR USE

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug 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.