luspatercept-aamt (Reblozyl®)

Policy # 00703
Original Effective Date: 05/11/2020
Current Effective Date: 01/08/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider luspatercept-aamt (Reblozyl®)‡ for the treatment of beta-thalassemia or myelodysplastic syndromes to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for luspatercept-aamt (Reblozyl) will be considered when the following criteria are met:

- Initial Requests:
    - Patient has a diagnosis of beta thalassemia (including beta^{+} thalassemia, beta^{0} thalassemia, and hemoglobin E/beta thalassemia) AND ALL of the following:
        - Patient does NOT have a diagnosis of alpha thalassemia (e.g., Hemoglobin H); AND
        - Patient does NOT have a diagnosis of hemoglobin S (sickle)/beta-thalassemia; AND
          *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility based on clinical trial data and will be denied as not medically necessary** if not met.)*
        - Patient is ≥18 years of age; AND
        - Patient requires regular red blood cell (RBC) transfusion (defined as a requirement of at least 6 units of packed RBCs (PRBCs) over the preceding 6 months with no transfusion-free period >35 days); AND
        - Dose will not exceed 1.25 mg/kg every 3 weeks; OR

- Patient has a diagnosis of a myelodysplastic syndrome with ring sideroblasts OR myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis associated anemia; AND
  - Patient is ≥18 years of age; AND
  - Disease is considered to be very low- to intermediate-risk; AND
  - Patient meets ONE of the following:
    - ❖ Patient has anemia that has not responded to treatment with an erythropoiesis stimulating agent after a trial of at least 3 months; OR
    - ❖ Serum erythropoietin level is greater than 500 mU/L; AND
  - Patient has required 2 or more red blood cell units in the previous 8 weeks; AND
  - Dose will not exceed 1.75 mg/kg every 3 weeks; OR
- Patient has a diagnosis of myelodysplastic syndrome associated anemia; AND
  - Patient is ≥18 years of age; AND
  - Disease is considered to be very low- to intermediate-risk; AND
  - Patient has required 2 or more red blood cell units in the previous 8 weeks; AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Dose will not exceed 1.75 mg/kg every 3 weeks.

- Continuation Requests:
  - Patient received an initial authorization for Reblozyl; AND
  - Patient has experienced and maintained a reduction in transfusion requirements from pretreatment baseline of at least 2 units PRBCs while receiving Reblozyl; AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Dose will not exceed 1.25 mg/kg every 3 weeks for beta thalassemia or 1.75 mg/kg every 3 weeks for myelodysplastic syndromes.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of luspatercept-aamt (Reblozyl) in patients with Hemoglobin S (sickle)/beta thalassemia to be **not medically necessary.****

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Based on review of available data, the Company considers the use of luspatercept-aamt (Reblozyl) in patients with myelodysplastic syndrome associated anemia who do not require regular red blood cell transfusions to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of luspatercept-aamt (Reblozyl) when the patient has not experienced and maintained a reduction in transfusion requirements from pretreatment baseline of at least 2 units PRBCs to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of luspatercept-aamt (Reblozyl) when patient selection criteria are not met (except those denoted as **not medically necessary****) to be **investigational.***

Background/Overview

Reblozyl is an erythroid maturation agent approved to treat anemia in adults with beta-thalassemia who require regular blood transfusions, adults with anemia associated with very low- to intermediate-risk myelodysplastic syndromes (MDS) without previous erythropoiesis stimulating agent (ESA) use, and adults with myelodysplastic syndromes (MDS) with ring sideroblasts or myelodysplastic/myeloproliferative neoplasm (MDS/MPN) with ring sideroblasts and thrombocytosis associated anemia who have failed an ESA. It works by interfering with the signals that suppress red blood cell (RBC) production to improve the manufacture of RBCs and reduce the need for blood transfusions. For all indications, it is administered subcutaneously by a healthcare professional every 3 weeks at a dose of 1 mg/kg and it may be increased to a maximum of 1.25 mg/kg every 3 weeks for beta thalassemia and 1.75 mg/kg every 3 weeks for MDS and MDS/MPN. The hemoglobin level should be assessed prior to each dose (using pre-transfusion levels if an RBC transfusion occurred prior to the dosing). Due to the increased risk of thrombosis at higher hemoglobin levels, the Reblozyl dose should not be administered if the pre-dose hemoglobin is $\geq$11.5 g/dL. It should be delayed until the hemoglobin is $\leq$11 g/dL.

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Beta thalassemia is an inherited blood disorder caused by a mutation of the hemoglobin beta (*HBB*) gene responsible for making the beta-globin protein. When this protein is absent, the disease is referred to as beta-zero (β^0) thalassemia. Whereas if the protein is simply reduced in function, the disease is referred to as beta-plus (β^+) thalassemia. The condition can be further classified by severity. Beta thalassemia major is associated with severe symptoms of anemia diagnosed in childhood while patients with beta thalassemia minor may be asymptomatic or exhibit minor anemia. Thalassemia intermedia has a variable severity with a broad range of symptoms between the minor and major forms. Symptoms of beta thalassemia include shortness of breath, fatigue, weakness, dizziness, jaundice, and/or headaches. Failure to thrive is observed in affected infants. If untreated, bone deformities may develop and overall disease complications lead to a short life span. Even with treatment, severe complications may arise due to iron overload secondary to increased intestinal absorption and frequent blood transfusions.

The main treatment option available for beta thalassemia major is blood transfusion to improve anemia and suppress ineffective erythropoiesis. Transfusions also prevent the majority of skeletal and neurological complications of beta-thalassemia, but are associated with severe complications such as alloimmunization, transmission of infectious disease, and iron overload. Typically, blood transfusions are initiated based on inability of the patient to compensate for low hemoglobin, increases in symptoms from ineffective erythropoiesis, or initial hemoglobin levels <6 g/dL. Transfusions are usually given once every 3-4 weeks and the amount of blood transfused varies based on the pretransfusion hemoglobin levels (typical target is 9-10 g/dL). Additional treatments for this condition include chelation therapy for patients with iron overload (often caused by transfusion), splenectomy for transfusion-dependent patients when hypersplenism increases transfusion requirements, and allogeneic hematopoietic cell transplant (HCT) for patients with an HLA-matched sibling donor for whom benefit outweighs the risks. Hydroxyurea has also been shown to have modest benefit in some patients.

Myelodysplastic syndromes (MDS) are cancers in which cells in the bone marrow do not mature and become healthy blood cells. Patients with MDS with refractory anemia and ring sideroblasts have too few red blood cells in the blood with too much iron inside the cell. Treatment for MDS with refractory anemia and ring sideroblasts includes RBC transfusions and erythropoiesis-stimulating agents (ESAs).

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Myelodysplastic/myeloproliferative neoplasms (MDS/MPN) are diseases of the blood and bone marrow with features of myelodysplastic syndromes as well as myeloproliferative neoplasms (e.g., a greater than normal number of blood stem cells become one or more types of blood cells and the total number of blood cells slowly increases).

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Reblozyl was approved in November 2019 for the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell transfusions. In April 2020, Reblozyl received the additional indication of treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis. In August 2023, Reblozyl received a third indication for the treatment of anemia without previous erythropoiesis stimulating agent use in adult patients with very low- to intermediate-risk myelodysplastic syndromes who may require regular red blood cell transfusions.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Beta Thalassemia

The efficacy of Reblozyl was evaluated in adult patients with beta thalassemia in the BELIEVE trial, a multicenter, randomized, double-blind, placebo-controlled trial. Patients (n=336) included in the trial had a diagnosis of beta thalassemia and required regular red blood cell transfusions (6-20 RBC units in prior 24 weeks) with no transfusion-free period greater than 35 days. Patients were randomized 2:1 to receive Reblozyl subcutaneously every 3 weeks (n=224) or placebo (n=112). Reblozyl treatment was continued 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. Patients with hemoglobin S/beta thalassemia or alpha-thalassemia or who had major organ damage were excluded from the study. Additionally, patients with recent deep vein thrombosis or stroke or recent use of erythropoiesis stimulating agents, immunosuppressants, or hydroxyurea were also excluded.

The primary endpoint in BELIEVE was the proportion of patients achieving RBC transfusion burden reduction defined as a ≥33% reduction from baseline with a reduction of at least 2 units from week 13 to week 24. In the Reblozyl group, 48% of patients met this endpoint vs. 5% in the placebo group ($p<0.0001$).

Myelodysplastic Syndromes with Ring Sideroblasts or Myelodysplastic/Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis Associated Anemia in ESA-refractory or intolerant Patients

The efficacy of Reblozyl in patients with myelodysplastic syndromes (n=229) was evaluated in the MEDALIST trial, a multi-center, randomized, double-blind, placebo-controlled trial. Patients included had very low, low, or intermediate-risk (as defined by international prognostic scoring system-revised [IPSS-R]) myelodysplastic syndromes with ring sideroblasts and requiring red blood cell transfusions (2 or more RBC units over 8 weeks). Patients were required to have had an inadequate response to prior treatment with an erythropoiesis-stimulating agent, be intolerant of ESAs, or have a serum erythropoietin >200 U/L. Patients with deletion 5q, white blood cell count >14 GI/L, neutrophils <0.5 Gi/L, platelets <50 Gi/L, or with prior use of a disease modifying agent for treatment of MDS were excluded from the trial.

Patients were randomized 2:1 to Reblozyl (n=153) or placebo (n=76) and treatment was started at 1 mg/kg subcutaneously every 3 weeks with dose increase permitted after completion of the first 2 cycles if the patient had at least one RBC transfusion in the prior 6 weeks. Two dose level increases were allowed (to 1.33 mg/kg and to 1.75 mg/kg). Doses were held and subsequently reduced for adverse reactions, reduced if the hemoglobin increased by ≥2 g/dL from the prior cycle, and held if the pre-dose hemoglobin was ≥11.5 g/dL. All patients received best supportive care including RBC transfusions as needed. The primary efficacy assessment was conducted after completion of 24 weeks on study drug and based on the proportion of patients who were red blood cell transfusion independent (RBC-TI) defined as the absence of any RBC transfusion during any consecutive 8-week period occurring entirely within weeks 1 through 24. A statistically significantly higher

percentage of patient in the Reblozyl group (37.9%) achieved RBC-TI compared to the placebo group (13.2%).

Myelodysplastic Syndromes with Associated Anemia in ESA-naïve Patients
The efficacy of Reblozyl was evaluated in the COMMANDS trial, a multi-center, open-label, randomized active-controlled trial comparing Reblozyl to epoetin alfa in patients with anemia due to IPSS-R very low, low, or intermediate-risk myelodysplastic syndromes or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis in ESA-naïve patients who require regular red blood cell transfusions. For eligibility, patients were required to have had 2 to 6 RBC units/8 weeks confirmed for a minimum of 8 weeks immediately preceding randomization.

The COMMANDS trial included 356 patients randomized 1:1 to Reblozyl (n=178) or epoetin alfa (n=178). Randomization was stratified by RBC transfusion burden, RS status, and endogenous serum erythropoietin (sEPO) level at baseline. Treatment was started at 1 mg/kg subcutaneously every 3 weeks. Two dose level increases were allowed (to 1.33 mg/kg and to 1.75 mg/kg). Doses were held and subsequently reduced for adverse reactions, reduced if the hemoglobin increased by ≥2 g/dL from the prior cycle, and held if the redoes hemoglobin was ≥12 g/dL

All patients received best supportive care, which included RBC transfusions as needed. Patients were treated for 24 weeks and were assessed for efficacy at that time point. Treatment beyond 24 weeks was optional based upon response to treatment and absence of disease progression. The efficacy of Reblozyl was established based upon the proportion of patients at the time of interim efficacy analysis who experienced both red blood cell transfusion independence (defined as the absence of any RBC transfusion during any consecutive 12-week period) and an associated concurrent mean improvement in hemoglobin by at least 1.5 g/dL for any consecutive 12 week period during Weeks 1-24. Of the 147 patients in the Reblozyl arm, 86 (58.5%) met this definition of response compared to 48 (31.2%) in the Epoetin Alfa arm. This result was statistically significant with a p-value <0.0001.

References

1. Reblozyl [package insert]. Celgene Corporation. Summit, New Jersey. Updated August 2023.
2. Reblozyl Drug Evaluation. Express Scripts. Updated November 2019.

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3. Reblozyl Prior Authorization Policy. Express Scripts. Updated April 2020.

Policy History

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04/02/2020	Medical Policy Committee review
04/08/2020	Medical Policy Implementation Committee approval. New policy.
11/05/2020	Medical Policy Committee review
11/11/2020	Medical Policy Implementation Committee approval. Updated criteria and background information to include coverage for new FDA-approved indication of myelodysplastic syndromes.
11/04/2021	Medical Policy Committee review
11/10/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/03/2022	Medical Policy Committee review
11/09/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/07/2023	Medical Policy Committee review
12/13/2023	Medical Policy Implementation Committee approval. Updated criteria and background information to include new indication for low- to intermediate-risk myelodysplastic syndrome-associated anemia in adult patients without previous erythropoiesis stimulating agent use.

Next Scheduled Review Date: 12/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is

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intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J0896 Delete codes effective 01/01/2023: C9399, J3490, J3590
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or

diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.