BlueCross BlueShield of North Carolina

An independent licensee of the Blue Cross and Blue Shield Association

Corporate Medical Policy

Luspatercept-aamt (Reblozyl®)

File Name:	luspatercept_reblozyl
Origination:	2/2020
Last CAP Review:	11/2020
Next CAP Review:	11/2021
Last Review:	11/2020

Description of Procedure or Service

Luspatercept-aamt (Reblozyl®) is an erythroid maturation agent that is indicated for the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions. It is also indicated for the treatment of anemia in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T), who are failing an erythropoiesis stimulating agent (ESAs) and requiring 2 or more RBC units over 8 weeks.

Beta thalassemia is an inherited hematologic disorder characterized by reduced hemoglobin production, resulting in a decrease in oxygen transported to cells throughout the body. Clinical manifestations of beta thalassemia include hemolytic anemia and impaired iron handling. Supportive treatment for beta thalassemia patients often consists of lifelong chronic blood transfusions for survival, together with treatment for iron overload caused by frequent transfusions.

Luspatercept-aamt (Reblozyl) is a recombinant fusion protein that was approved by the U.S. Food and Drug Administration (FDA) in November 2019 for the treatment of anemia in patients with beta thalassemia requiring regular RBC transfusions. It was FDA approved in April 2020 for the treatment of anemia associated with MDS-RS and MDS/MPN-RS-T. Luspatercept induces erythroid maturation by binding several endogenous TGF-β superfamily ligands, thus diminishing Smad2/3 signaling. In beta thalassemia, decreasing abnormally elevated Smad2/3 signaling is thought to improve hematology parameters associated with ineffective erythropoiesis.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for luspatercept-aamt (Reblozyl) when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit

design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Luspatercept-aamt (Reblozyl) is covered

BETA THALASSEMIA
Initial Therapy

Luspatercept-aamt (Reblozyl) may be considered medically necessary for the treatment of anemia in adult patients (≥18 years old) with beta thalassemia when the following criteria are met:

1. The patient has a confirmed diagnosis of beta thalassemia (including Hemoglobin E/beta thalassemia and beta thalassemia with mutation and/or multiplication of alpha globin); AND
2. The patient requires regular red blood cell (RBC) transfusions (defined as at least 6 RBC units within the 24 weeks prior to initiation and no transfusion-free period ≥35 days during that time); AND
3. Luspatercept is prescribed by or in consultation with a hematologist or specialist in treating beta thalassemia; AND
4. The patient does not have a diagnosis of Hemoglobin (sickle) S/beta thalassemia or alpha thalassemia (e.g., Hemoglobin H); AND
5. The patient does not have major organ damage (e.g., liver disease, heart disease, lung disease, or renal insufficiency)

Initial authorization: 6 months

Continuation Therapy

Continuation of treatment with luspatercept-aamt (Reblozyl) beyond 6 months after initiation of therapy, and every 12 months thereafter, may be considered medically necessary for the treatment of beta thalassemia when the following criteria are met:

1. The patient is currently receiving luspatercept for beta thalassemia and continues to meet initial criteria; AND
2. The patient has demonstrated a reduction in RBC transfusion burden following luspatercept treatment

MYELODYSPLASTIC SYNDROMES
Initial Therapy

Luspatercept-aamt (Reblozyl) may be considered medically necessary for the treatment of adult patients (≥18 years old) with symptomatic anemia associated with a myelodysplastic syndrome or myelodysplastic/myeloproliferative neoplasm when the following criteria are met:

1. The patient has a confirmed diagnosis of one of the following:
    a. Myelodysplastic syndrome with ring sideroblasts (MDS-RS), or
    b. Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T); AND
2. The patient has very low- to intermediate-risk disease based on prognostic risk stratification; AND
3. The patient has ring sideroblasts ≥ 15% OR ≥ 5% with an *SF3B1* mutation; AND
4. The patient requires regular red blood cell (RBC) transfusions (defined as at least 2 RBC units within the 8 weeks prior to initiation); AND
5. The patient has one of the following:

   a. An inadequate response to prior treatment with an erythropoiesis stimulating agent (ESA), or
   b. A contraindication / intolerance to ESAs, or
   c. Inability to receive ESA treatment as defined by a serum erythropoietin level > 200 U/L; AND
6. Luspatercept is prescribed by or in consultation with a hematologist, oncologist, or other specialist in treating myelodysplastic syndromes

Initial authorization: 6 months

Continuation Therapy

Continuation of treatment with luspatercept-aamt (Reblozyl) beyond 6 months after initiation of therapy, and every 12 months thereafter, may be considered medically necessary for the treatment of anemia associated with myelodysplastic syndromes when the following criteria are met:

1. The patient is currently receiving luspatercept for anemia associated with MDS-RS or MDS/MPN-RS-T and continues to meet initial criteria; AND
2. The patient has demonstrated a reduction in RBC transfusion burden following luspatercept treatment

When Luspatercept-aamt (Reblozyl) is not covered

Luspatercept-aamt (Reblozyl) is considered **investigational** and therefore not covered when the above criteria are not met.

Luspatercept-aamt is considered **investigational** and therefore not covered when used as a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anemia.

Luspatercept-aamt is considered **investigational** and therefore not covered for any other diagnoses, including Hemoglobin (sickle) S/beta thalassemia and alpha thalassemia (e.g., Hemoglobin H).

Policy Guidelines

The recommended starting dose of Reblozyl is 1 mg/kg given as a subcutaneous injection once every 3 weeks. Reblozyl should be administered by a healthcare professional. Hemoglobin (Hgb) should be assessed and reviewed prior to each administration. If a red blood cell (RBC) transfusion occurred prior to dosing, dosing considerations should be based on the pretransfusion Hgb. If the pre-dose Hgb is ≥ 11.5 g/dL and the Hgb is not influenced by recent transfusion, the Reblozyl dose should be delayed until the Hgb is ≤ 11 g/dL.

For patients with beta thalassemia, if a reduction in RBC transfusion burden is not achieved after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose, the Reblozyl dose should be increased to, but not exceeding, the maximum dose of 1.25 mg/kg. If a patient experiences a response followed by a lack of or lost response to Reblozyl, the patient should be assessed for causative factors (e.g., a bleeding event).

For anemia of MDS-RS or MDS/MPN-RS-T, if the patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose, the Reblozyl dose should be

increased to 1.33 mg/kg. If the patient is not transfusion-free after at least 2 consecutive doses (6 weeks) at the 1.33 mg/kg dose, the Reblozyl dose should be increased to, but not exceeding, the maximum dose of 1.75 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, or if unacceptable toxicity occurs at any time.

According to the manufacturer's safety information for Reblozyl, the most common adverse reactions (>10% incidence) include headache, bone pain, arthralgia, fatigue, cough, abdominal pain, diarrhea, and dizziness. Patients with beta thalassemia have an increased risk of thrombosis/thromboembolism, thus patients receiving Reblozyl should be monitored for signs and symptoms of thromboembolic events and treatment initiated promptly in these events. Hypertension may develop in patients receiving Reblozyl treatment. Blood pressure should be monitored during treatment and anti-hypertensive therapy initiated if needed. Reblozyl may cause fetal harm, and females of reproductive potential receiving Reblozyl should use effective contraception.

Clinical Trial Evidence

Beta Thalassemia

The efficacy and safety of luspatercept was assessed in a randomized, multicenter, double-blind, placebo-controlled, multicenter trial of 336 adult patients with beta thalassemia (including Hemoglobin E/beta thalassemia and beta thalassemia with mutation and/or multiplication of alpha globin) requiring regular RBC transfusions (6-20 RBC units per 24 weeks) with no transfusion-free period greater than 35 days during the 24-week period (BELIEVE trial; NCT02604433). Patients were randomized 2:1 to receive luspatercept (n=224) or placebo (n=112) subcutaneously once every 3 weeks as long as a reduction in transfusion requirement was observed or until unacceptable toxicity. All patients within the trial were permitted to receive best supportive care, including RBC transfusions; iron-chelating agents; 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 (liver disease, heart disease, lung disease, renal insufficiency) were excluded from the trial. Other exclusion criteria included patients with recent deep vein thrombosis or stroke, or recent use of ESAs, immunosuppressants, or hydroxyurea therapy. The primary efficacy endpoint was based on the proportion of patients achieving a reduction in RBC transfusion burden (≥33% reduction from baseline) with at least a 2-unit reduction from week 13 to week 24. Luspatercept compared with placebo significantly increased the proportion of patients with a 33% or greater reduction in RBC transfusion burden (with a reduction of at least 2 units) from weeks 13 to 24 (21.4% vs 4.5%; $p<0.0001$).

The following information is derived from FDA prescribing information, as peer reviewed published trial results have not been identified.

Myelodysplastic Syndromes

The efficacy of luspatercept was assessed in the MEDALIST trial (NCT02631070), a multicenter, double-blind, randomized, placebo-controlled trial evaluating patients with very low, low, or intermediate-risk myelodysplastic syndromes who have ring sideroblasts and require RBC transfusions (at least 2 RBC units over 8 weeks). Patients included in the trial were required to have had an inadequate response to previous treatment with an ESA, have intolerance to ESAs, or have a serum erythropoietin > 200 U/L. Patients were randomized 2:1 to receive luspatercept (n=153) or placebo (n=76). The primary efficacy endpoint was assessed as transfusion independence for 8 weeks or longer during weeks 1 through 24. During weeks 1 through 24 of treatment, 38% of patients receiving luspatercept compared to 13% of patients receiving placebo met the primary endpoint of transfusion independence for 8 weeks or longer ($p<0.001$).

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: *J0896*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Celgene Corporation. Reblozyl (luspatercept-aamt) for injection, for subcutaneous use. Highlights of prescribing information. November 2019. Available at: https://media.celgene.com/content/uploads/reblozyl-pi.pdf. Last accessed February 2020.

U.S. Food and Drug Administration. FDA approves first therapy to treat patients with rare blood disorder. November 2019. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-therapy-treat-patients-rare-blood-disorder. Last accessed February 2020.

Rund D and Rachmilewitz E. β-Thalassemia. N Engl J Med 2005;353:1135-46.

Medical Director review 2/2020

Celgene Corporation. Reblozyl (luspatercept-aamt) for injection, for subcutaneous use. Highlights of prescribing information. April 2020. Available at: https://media.celgene.com/content/uploads/reblozyl-pi.pdf. Last accessed July 2020.

Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. MEDALIST Study. N Engl J Med 2020;382:140-151.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Myelodysplastic Syndromes, version 2.2020. Revised February 28, 2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf. Accessed July 2020.

Medical Director review 7/2020

Specialty Matched Consultant Advisory Panel review 11/2020

Policy Implementation/Update Information

2/11/20 New policy developed. Reblozyl is considered medically necessary for the treatment of anemia in adult patients (≥18 years old) with beta thalassemia when specified medical criteria and guidelines are met. Added HCPCS codes C9399, J3490, and J3590 to Billing/Coding section. References added. Medical Director review 2/2020. (krc)

6/30/20 Added HCPCS code J0896 to Billing/Coding section effective 7/1/2020 and deleted codes C9399, J3490, J3590 termed 6/30/2020. (krc)

9/22/20 New indication added to "When Covered" section for anemia associated with MDS-RS and MDS/MPN-RS-T. Updated "Description" and "Policy Guidelines" sections to include this indication. References added. Medical Director review 7/2020. (krc)

1/12/21 Specialty Matched Consultant Advisory Panel review 11/18/2020. No change to policy statements. (krc)