09-J3000-61

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Revised: 01/01/25

Subject: Luspatercept-aamt (Reblozyl®) Injection

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Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Luspatercept-aamt (Reblozyl) is an erythroid maturation agent first approved by the Food and Drug Administration (FDA) in November 2019 for "the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions". In April 2020, the FDA approved an additional indication of "treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more RBC units over 8 weeks 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)". In August 2023, the FDA approved a third indication of "treatment of anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular RBC transfusions". The product labeling includes a "Limitations of Use" statement that luspatercept-aamt is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia. Prior to FDA approval, luspatercept-aamt was granted orphan designation for the treatment of beta thalassemia (March 2013) and treatment of myelodysplastic syndrome (MDS) (March 2013). Luspatercept-aamt is a recombinant fusion protein that binds several endogenous TGF-β (Transforming Growth Factor-Beta) superfamily ligands (a ligand trap) resulting in reduced aberrant Smad2/3 signaling and enhanced late-stage erythropoiesis. By interfering with the signals that suppress RBC production, the drug improves patients' ability to manufacture their own RBCs, therefore reducing the need for transfusions.

Beta thalassemia is an inherited disorder characterized by absent (B0) or reduced (B+) production of the β-globin chains in hemoglobin. The reduced synthesis of β-globin leads to an imbalance in the alpha/beta-globin chain ratio and the excess of unpaired alpha-globin chains leads to premature death of RBCs and their precursors in the bone marrow. Ineffective erythropoiesis leads to anemia and various subsequent complications including hemolysis, hypercoagulability, transfusional iron overload secondary to frequent RBC transfusions, heart disease, and hepatic cirrhosis. Over 200 different mutations that affect the β-globin gene, most often point mutations, have been described in patients

with beta thalassemia. Patient genotypes may be either homozygous (e.g., B+/B+, B0/B0) or compound heterozygous (e.g., B0/B+). Persons with only one defective β-globin gene (e.g., B/B+, B/B0) are typically asymptomatic and are known as beta thalassemia carriers (also called thalassemia minor, beta thalassemia trait, and heterozygous beta thalassemia). Phenotypic findings range widely in non-carrier patients and are categorized as beta thalassemia major (lack of or very minimal β-globin production; a.k.a., Cooley's anemia and Mediterranean anemia) or beta thalassemia intermedia (some residual β-globin production). Individuals with thalassemia major become severely symptomatic in the first two years of life and require regular RBC transfusions to survive. Thalassemia intermedia includes patients who present later and often do not require regular transfusion; however, transfusion needs are highly variable in this group. There are also beta thalassemias associated with other Hb anomalies, such as beta-thalassemia and hemoglobin E (HbE) (e.g., BE/B+, BE/B0). Diagnosis of beta thalassemia is based on an assessment of various clinical signs and symptoms. Typical laboratory tests include a complete blood count (CBC), peripheral blood smear, iron studies, and qualitative and quantitative hemoglobin analysis (typically by electrophoresis or chromatography). In patients with beta thalassemia major or intermedia, hemoglobin analysis will find low levels of adult hemoglobin (HbA) and high level of fetal hemoglobin (HbF). Molecular genetic testing can also be done to determine the exact genotype of the patient. Prior to luspatercept-aamt there were no approved FDA drugs to treat anemia secondary to beta thalassemia. Current treatment options for beta thalassemia are extremely limited. Packed red blood cell (RBC) and iron chelation therapy (ICT) are the mainstays of treatment. Stem cell transplantation is one of two curative treatments currently; however, many patients are ineligible and there is a high degree of risks and complications. The gene therapy, betibeglogene autotemcel (Zynteglo), approved in August 2022 is also a potentially curative treatment; however, long-term durability is still being determined.

The safety and efficacy of luspatercept-aamt leading to initial FDA approved 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 patients with beta thalassemia requiring regular red blood cell transfusions (6 to 20 RBC units per 24 weeks) with no transfusion-free period greater than 35 days during that period were randomized 2:1 to luspatercept-aamt (n=224) or placebo (n=112). Luspatercept-aamt 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. Patients were excluded if they had hemoglobin S/β-thalassemia or alpha-thalassemia, had major organ damage (liver disease, heart disease, lung disease, renal insufficiency), recent deep vein thrombosis or stroke, or recent use of ESA, immunosuppressant, or hydroxyurea therapy. The median age was 30 years (range of 18 to 66), the diagnosis breakdown was 74.1 to 77.7% beta-thalassemia, 13.8 to 18.8% HbE/beta thalassemia, and 7.1 to 8% beta thalassemia combined with alpha-thalassemia, the median baseline transfusion burden 12 weeks prior to randomization was 6.12 to 6.27, the gene mutation grouping was 30 to 31% B0/B0 and 69 to 70% B0/non-B0, approximately 58% of patients had a splenectomy, and the median age patients started regular transfusions was 2 years old. The efficacy was established based upon the primary endpoint of the proportion of patients achieving RBC transfusion burden reduction (≥33% reduction from baseline) with a reduction of at least 2 units from Week 13 to Week 24. Results are show in Table 1 below.

Table 1

Endpoint	Luspatercept-aamt (n=224)	Placebo (n=112)	Risk Difference (95% CI)	P-value
≥33% Reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks				
Week 13 to Week 24 (Primary Endpoint)	48 (21.4%)	5 (4.5%)	17.0 (10.4, 23.6)	<0.0001
Week 37 to Week 48	44 (19.6%)	4 (3.6%)	16.1 (9.8, 22.4)	<0.0001
≥50% Reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks				
Week 13 to Week 24	17 (7.6%)	2 (1.8%)	5.8 (1.6, 10.1)	0.0303
Week 37 to Week 48	23 (10.3%)	1 (0.9%)	9.4 (5, 13.7)	0.0017

The safety and efficacy of luspatercept-aamt leading to FDA approval in ESA-refractory or -intolerant patients with certain myelodysplastic syndromes was evaluated in the MEDALIST trial (NCT02631070), a multi-center, randomized, double-blind, placebo-controlled trial in patients with IPSS-R very low, low, or intermediate-risk myelodysplastic syndromes who have ring sideroblasts and require red blood cell transfusions (2 or more RBC units over 8 weeks). For eligibility, patients were required to have had an inadequate response to prior treatment with an erythropoiesis-stimulating agent (ESA), be intolerant of ESAs, or have a serum erythropoietin >200 U/L. Patients were randomized 2:1 to luspatercept-aamt (n=153) or placebo (n=76). Randomization was stratified by baseline RBC transfusion burden and baseline IPSS-R. All patients received best supportive care, which included RBC transfusions as needed. The primary efficacy assessment was conducted after completion of 24 weeks on study drug. Patients with a decrease in transfusion requirement or increase in hemoglobin could continue on blinded study drug thereafter until unacceptable toxicity, loss of efficacy, or disease progression. The median age was 71 years (range 26 to 95), 63% were male and 69% were White. The primary efficacity endpoint was the proportion of patients who were RBC 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. Results are show in Table 2 below.

Table 2

Endpoint	Luspatercept-aamt (n=153) (95% CI)	Placebo (n=76) (95% CI)	Common Risk Difference (95% CI)	P-value
RBC-TI ≥8 weeks during Weeks 1-24	58 (37.9%) (30.2, 46.1)	10 (13.2%) (6.5, 22.9)	24.6 (14.5, 34.6)	<0.0001
RBC-TI ≥12 weeks during Weeks 1-24	43 (28.1%) (21.1, 35.9)	6 (7.9%) (3.0, 16.4)	20.0 (10.9, 29.1)	0.0002
RBC-TI ≥12 weeks during Weeks 1-48*	51 (33.3%) (25.9, 41.4)	9 (11.8%) (5.6, 21.3)	21.4 (11.2, 31.5)	0.0003

*The median (range) duration of treatment was 49 weeks (6 to 114 weeks) on the REBLOZYL arm and 24 weeks (7 to 89 weeks) on the placebo arm.

The safety and efficacy of luspatercept-aamt leading to FDA approval in ESA-naïve patients with myelodysplastic syndromes was evaluated in the COMMANDS trial (NCT03682536), a multi-center, open-label, randomized active-controlled trial comparing luspatercept-aamt versus epoetin alfa in patients with anemia due to IPSS-R very low, low, or intermediate-risk MDS or with MDS/MPN RS-T in

ESA-naïve patients (with endogenous sEPO levels of <500 U/L) who require regular red blood cell transfusions. For eligibility, patients were required to have <5% blasts in bone marrow and had 2 to 6 RBC units/8 weeks confirmed for a minimum of 8 weeks immediately preceding randomization. The trial included 356 patients randomized 1:1 to luspatercept-aamt (n=178) or epoetin alfa (n=178). Randomization was stratified by RBC transfusion burden, ring sideroblasts (RS status, and endogenous serum erythropoietin (sEPO) level at baseline. 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 median age was 74 years (range 33 to 93 years), 56% were male, and 79.5% were White. Efficacy was established at the time of the interim efficacy analysis based upon the proportion of patients who experienced both RBC-TI, 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 to 24. At the time of the interim efficacy analysis, 301 subjects were included in the analysis (about 85% of the total information). The key efficacy results are shown in Table 3 below.

Table 3

Endpoint	Luspatercept-aamt (n=147) (95% CI)	Epoetin Alfa (n=154) (95% CI)	Common Risk Difference (95% CI)	P-value
RBC-TI for ≥12 weeks + concurrent mean Hgb increase of ≥1.5 g/dL (Weeks 1-24)	86 (58.5%) (50.1, 66.6)	48 (31.2%) (24.0, 39.1)	26.6 (15.8, 37.4)	<0.0001
Mean Hgb increase ≥1.5 g/dL (Weeks 1-24)	106 (72.1%) (64.1, 79.2)	75 (48.7%) (40.6, 56.9)	23.2 (12.2, 34.1)	--
HI-E per IWG ≥8 weeks (Weeks 1-24)	109 (74.1%) (66.3, 81.0)	79 (51.3%) (43.1, 59.4)	22.3 (11.8, 32.8)	<0.0001
RBC-TI for 24 weeks (Weeks 1-24)	70 (47.6%) (39.3, 56.0)	45 (29.2%) (22.2, 37.1)	17.0 (6.7, 27.2)	0.0012
RBC-TI for ≥12 weeks (Weeks 1-24)	98 (66.7%) (58.4, 74.2)	71 (46.1%) (38.1, 54.3)	19.1 (8.6, 29.6)	0.0003

HI-E = Hematologic Improvement – Erythroid Response; NE = Not Estimable; RBC-TI = red blood cell transfusion independence

The National Comprehensive Cancer Network (NCCN) Guidelines for Myelodysplastic Syndromes (Version 1.2025) list luspatercept-aamt as a Category 1 recommendation for the treatment of lower risk MDS [lower risk defined as IPSS-R (Very Low, Low, Intermediate)] associated with symptomatic anemia with no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts ≥15% (or ring sideroblasts ≥5% with an SF3B1 mutation) as a single agent or following no response to or relapse after imetelstat (Rytelo). It is also a Category 2A recommendation for the treatment of lower-risk MDS associated with symptomatic anemia with no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts <15% (or ring sideroblasts <5% with an SF3B1 mutation) with serum erythropoietin ≤500 mU/mL as a single agent or following no response to or relapse after an erythropoiesis-stimulating agent (ESA) alone (despite adequate iron stores). The guidelines also include a Category 2A recommendation to consider luspatercept for MDS/MPN with SF3B1 mutation and thrombocytosis (MDS/MPN-T-SF3B1) as a single agent option for treatment of anemia. The NCCN Guidelines for Myeloproliferative Neoplasms (Version 2.2024) also include a 2A recommendation for the use of luspatercept for management of myelofibrosis-associated symptomatic anemia. If the patient has

presence of symptomatic splenomegaly and/or constitutional symptoms, luspatercept is recommended to be used in combination with ruxolitinib (Jakafi).

POSITION STATEMENT:

Initiation of luspatercept-aamt (Reblozyl) **meets the definition of medical necessity** when **ANY** of the following criteria are met ("1", "2", or "3"):

1. **ALL** of the following ("a" to "e"):
    a. Member has **EITHER** of the following diagnoses ("i" or "ii") – medical record documentation confirming the member's diagnosis must be submitted:
        i. Myelodysplastic Syndromes (MDS) [including MDS subtypes such as MDS with ring sideroblasts (MDS-RS), MDS with single lineage dysplasia (MDS-SLD), MDS with multilineage dysplasia (MDS-MLD)], **AND BOTH** of the following:
            - The member has **LESS THAN** 5% blasts in bone marrow
            - The member does **NOT** have a chromosome 5q deletion [i.e., MDS with del(5q)]
        ii. Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) with Ring Sideroblasts (RS) and Thrombocytosis (T) (MDS/MPN-RS-T) [also known as MDS/MPN with SF3B1 mutation and thrombocytosis, or MDS/MPN-T-SF3B1] – member must have a documented platelet count greater than or equal to 450,000/mcL.
    b. The member has lower risk MDS* defined as **ANY** of the following - medical record documentation of the member's IPSS, IPSS-R, or WPSS score must be submitted:
        - MDS is classified as low- or intermediate-1 (INT-1) risk disease based on an International Prognostic Scoring System (IPSS) score of 1 or less
        - MDS is classified as very low-, low-, or intermediate-risk (3.5 score only) disease based on a revised International Prognostic Scoring System (IPSS-R) score of 3.5 or less
        - MDS is classified as very low-, low-, or intermediate-risk disease based on a WHO-based Prognostic Scoring System (WPSS) score of 2 or less

        **The lower-risk requirement does NOT apply to members with MDS/MPN-RS-T*
    c. **EITHER** of the following ("i" or "ii"):
        i. **ALL** of the following ("1" to "4") – medical record documentation of the member's current hemoglobin level (within the past 90 days) **AND** risk factor(s) for increased blood transfusion complications must be submitted:
            1. Member has symptomatic anemia
            2. Member has a hemoglobin level **LESS** than 8 g/dL
            3. Luspatercept-aamt is being given in an attempt to avoid blood transfusion
            4. Member has one or more risk factors for increased blood transfusion complications
        ii. Member has symptomatic anemia requiring transfusion of **two or more** total units of packed red blood cells (RBCs) in the previous 8 weeks – medical record documentation of the member's transfusion history for at least the past 8 weeks, and occurring prior to any luspatercept-aamt treatment, must be submitted

d. Luspatercept-aamt is prescribed by, or in consultation with, a hematologist/oncologist

e. Dosage of luspatercept-aamt does not exceed 1 mg/kg every 3 weeks for the first two doses, 1.33 mg/kg every 3 weeks for the next two doses, and then 1.75 mg/kg every 3 weeks for subsequent doses

2. **ALL** of the following ("a" to "d"):

   a. Member has a documented diagnosis of beta-thalassemia (may include hemoglobin E/beta thalassemia and beta-thalassemia with mutation and/or multiplication of alpha globin) as evidence by beta globin (HBB) gene analysis showing pathogenic variants on **BOTH** genes - laboratory or medical record documentation of the genetic testing results must be submitted

   b. Member requires regular red blood cell (RBC) transfusions as defined by **BOTH** of the following criteria ("a" and "b") – medical record documentation of the member's transfusion history for at least the past 24 weeks, and occurring prior to any luspatercept-aamt treatment, must be submitted:

      i. Member required transfusion of **six or more** total units of packed RBCs in the previous 24 weeks

      ii. There was no transfusion-free period greater than 35 consecutive days in the previous 24 weeks

   c. Luspatercept-aamt is prescribed by, or in consultation with, a hematologist or other specialist with expertise in the treatment of beta thalassemia

   d. Dosage of luspatercept-aamt does not exceed 1 mg/kg every 3 weeks for the first two doses, and then 1.25 mg/kg every 3 weeks for subsequent doses

3. **ALL** of the following ("a" to "e"):

   a. Member has a documented diagnosis of myelofibrosis [a subtype of myeloproliferative neoplasms (MPN)] - medical record documentation confirming the member's diagnosis must be submitted

   b. The member has symptomatic anemia as a result of their myelofibrosis

   c. If the member has presence of symptomatic splenomegaly and/or constitutional symptoms, luspatercept-aamt will be used in combination with ruxolitinib (Jakafi)

   d. Luspatercept-aamt is prescribed by, or in consultation with, a hematologist/oncologist

   e. Dosage of luspatercept-aamt does not exceed 1 mg/kg every 3 weeks for the first two doses, 1.33 mg/kg every 3 weeks for the next two doses, and then 1.75 mg/kg every 3 weeks for subsequent doses

Approval duration: 6 months

Continuation of luspatercept-aamt (Reblozyl) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "4"):

1. An authorization or reauthorization for luspatercept-aamt has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of anemia due to beta thalassemia, MDS, MDS/MPN-RS-T, or myelofibrosis (if another health plan, documentation of a health plan-paid claim for luspatercept-aamt during the 90 days immediately before the authorization request must be submitted); **OR** the member has previously met **ALL** indication-specific criteria

2. Member meets **EITHER** of the following depending on the duration of treatment and indication for use with luspatercept-aamt ("a" or "b"):
    a. Less than 12 months of treatment:
        i. MDS, MDS/MPN-RS-T, or myelofibrosis - member has had a reduction in transfusion requirements **OR** an increase in hemoglobin levels as compared to their pretreatment baseline - medical record documentation of the member's reduced transfusion requirements or increase in hemoglobin levels must be submitted
        ii. Beta-thalassemia - member has had a reduction in transfusion requirements as compared to their pretreatment baseline - medical record documentation of the member's transfusion history supporting the reduction must be submitted
    b. 12 or more months of treatment:
        i. MDS, MDS/MPN-RS-T, or myelofibrosis - provider attestation that the member continues to maintain a beneficial reduction in transfusion requirements or a sustained increase in hemoglobin levels as compared to before treatment with luspatercept-aamt
        ii. Beta-thalassemia - provider attestation that the member continues to maintain a beneficial reduction in transfusion requirements as compared to before treatment with luspatercept-aamt
3. Luspatercept-aamt is prescribed by, or in consultation with, a hematologist/oncologist or, for members with beta thalassemia, other specialist with expertise in the treatment of beta thalassemia
4. **EITHER** of the following depending on the indication for use:
    a. Beta-thalassemia - dosage of luspatercept-aamt does not exceed 1.25 mg/kg every 3 weeks
    b. MDS, MDS/MPN-RS-T, or myelofibrosis - dosage of luspatercept-aamt does not exceed 1.75 mg/kg every 3 weeks

Approval duration: 12 months

Luspatercept-aamt (Reblozyl) **does NOT meet the definition of medical necessity** for any other thalassemias or hemoglobinopathies, including, but not limited to, the following:

- Alpha thalassemia without concomitant beta thalassemia
- Sickle cell beta thalassemia [also known as hemoglobin S (HbS)-beta-thalassemia disease]

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- For the treatment of:

- Anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions. Limitations of Use: Luspatercept-aamt is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.
- Anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions
- Anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell (RBC) units over 8 weeks 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)

- Beta Thalassemia - the recommended starting dose is 1 mg/kg once every 3 weeks by subcutaneous injection. Assess and review hemoglobin (Hgb) results and transfusion record 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 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 there is an increase in hemoglobin greater than 2 g/dL within 3 weeks (and in the absence of transfusions), the dosage should be reduced in accordance with the package labeling information. 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 dose to 1.25 mg/kg. Do not increase the dose beyond the maximum dose of 1.25 mg/kg. Discontinue 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.
- Myelodysplastic Syndromes Associated Anemia - the recommended starting dose is 1 mg/kg once every 3 weeks by subcutaneous injection. Assess and review hemoglobin (Hgb) results and transfusion record 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 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 there is an increase in hemoglobin greater than 2 g/dL within 3 weeks (and in the absence of transfusions), the dosage should be reduced in accordance with the package labeling information. If a patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose, increase the dose to 1.33 mg/kg. If a patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1.33 mg/kg dose, increase the dose to 1.75 mg/kg. Do not increase the dose beyond the maximum dose of 1.75 mg/kg. Discontinue 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.
- Luspatercept-aamt should be reconstituted and administered by a healthcare professional. Refer to the product labeling for directions on reconstitution and administration.

Dose Adjustments

- Renal impairment - No dosage adjustment appears needed in patients with mild to moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2) based on pharmacokinetic (PK) studies. The effect of severe renal impairment (eGFR <29 mL/min/1.73 m^2) on luspatercept PK is unknown.
- Hepatic impairment - No dosage adjustment appears is needed for patients with mild to severe hepatic impairment based on PK studies.
- Adverse events - For beta thalassemia, no dosage adjustments are recommended in the product labeling for adverse events. Adverse events are managed by interruption or discontinuation of treatment. For myelodysplastic syndromes, adverse events are managed by interruption or discontinuation of treatment; however, the treatment is restarted at the next lower dose level. Refer to the product labeling.

Drug Availability

- 25 mg single-use vial as lyophilized powder (reconstituted with 0.68 mL sterile water for injection to create a 25 mg/0.5 mL concentration)
- 75 mg single-use vial as lyophilized powder (reconstituted with 1.6 mL sterile water for injection to create a 75 mg/1.5 mL concentration)
- Store vials refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- **Thrombosis/Thromboembolism** - Thromboembolic events (TEE) were reported in 8/223 (3.6%) of luspatercept- treated patients. Reported TEEs included deep vein thromboses, pulmonary embolus, portal vein thrombosis, and ischemic strokes. Patients with known risk factors for thromboembolism, e.g., splenectomy or concomitant use of hormone replacement therapy, may be at further increased risk of thromboembolic conditions. Consider thromboprophylaxis in patients with beta thalassemia at increased risk of TEE. Monitor patients for signs and symptoms of thromboembolic events and institute treatment promptly.
- **Hypertension** - Hypertension was reported in 11.4% (63/554) of luspatercept- treated patients. Across clinical studies, the incidence of grade 3-4 hypertension ranged from 2% to 9.6%. In adult patients with beta thalassemia with normal baseline blood pressure, 13 (6.2%) patients developed systolic blood pressure (SBP) ≥130 mmHg and 33 (16.6%) patients developed diastolic blood pressure (DBP) ≥80 mmHg. In ESA-refractory or -intolerant adult patients with MDS with normal baseline blood pressure, 26 (30%) patients developed SBP ≥130 mm Hg and 23 (16%) patients developed DBP ≥80 mm Hg. In ESA-naïve adult patients with MDS with normal baseline blood pressure, 23 (36%) patients developed SBP ≥140 mm Hg and 11 (6%) patients developed DBP ≥80 mm Hg. Monitor blood pressure prior to each administration. Manage new-onset hypertension or exacerbations of preexisting hypertension using anti-hypertensive agents.
- **Extramedullary Hematopoietic Masses (EMH)** - In adult patients with transfusion dependent beta thalassemia, EMH masses were observed in 3.2% of luspatercept-treated patients, with spinal cord compression symptoms due to EMH masses occurring in 1.9% of patients (BELIEVE and REBLOZYL long-term follow-up study). In a study of adult patients with non-transfusion dependent beta thalassemia, a higher incidence of EMH masses was observed in 6.3% of luspatercept-treated patients vs. 2% of placebo-treated patients in the double-blind phase of the study, with spinal cord compression due to EMH masses occurring in 1 patient with a prior history of EMH. Luspatercept is not indicated for use in patients with non-transfusion dependent beta-thalassemia. Possible risk factors for the development of EMH masses in patients with beta thalassemia include history of EMH masses, splenectomy, splenomegaly, hepatomegaly, or low baseline hemoglobin (<8.5 g/dL). Signs and symptoms may vary depending on the anatomical location. Monitor patients with beta thalassemia at initiation and

during treatment for symptoms and signs or complications resulting from the EMH masses and treat according to clinical guidelines. Discontinue treatment in case of serious complications due to EMH masses. Avoid use in patients requiring treatment to control the growth of EMH masses.

- **Embryo-Fetal Toxicity** - Based on findings from animal reproductive studies, luspatercept-aamt may cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of luspatercept-aamt to pregnant rats and rabbits during organogenesis resulted in adverse developmental outcomes including increased embryo-fetal mortality, alterations to growth, and structural abnormalities at exposures (based on area under the curve [AUC]) above those occurring at the maximum recommended human dose of 1.25 mg/kg. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment and for at least 3 months after the final dose

BILLING/CODING INFORMATION:

HCPCS Coding

J0896	Injection, luspatercept-aamt, 0.25 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

C93.10	Chronic myelomonocytic leukemia not having achieved remission
C94.40 – C94.42	Acute panmyelosis with myelofibrosis
C94.6	Myelodysplastic disease, not elsewhere classified
D46.0	Refractory anemia without ring sideroblasts, so stated
D46.1	Refractory anemia with ring sideroblasts
D46.20	Refractory anemia with excess of blasts, unspecified
D46.21	Refractory anemia with excess of blasts 1
D46.4	Refractory anemia, unspecified
D46.9	Myelodysplastic syndrome, unspecified
D46.A	Refractory cytopenia with multilineage dysplasia
D46.B	Refractory cytopenia with multilineage dysplasia and ringed sideroblasts
D46.C	Myelodysplastic syndrome with isolated del(5q) chromosomal abnormality
D46.Z	Other myelodysplastic syndromes
D47.1	Chronic myeloproliferative disease
D47.4	Osteomyelofibrosis
D56.1	Beta thalassemia
D56.5	Hemoglobin E-beta thalassemia
D75.81	Myelofibrosis

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT.**

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the late review date.

DEFINITIONS:

None

RELATED GUIDELINES:

Allogeneic Bone Marrow and Stem Cell Transplantation, 02-38240-01

Betibeglogene Autotemcel (Zynteglo) IV Infusion, 09-J4000-35

Chelation Therapy, 01-99000-07

OTHER:

International Prognostic Scoring System (IPSS)

	Score Value				
Prognostic variable	0	0.5	1	1.5	2
Marrow blasts (%)	<5	5 to 10	--	>10 to 20	>20 to 30
Karyotype	Good	Intermediate	Poor	--	--
Cytopenia*	0 or 1	2 or 3			
• Low: score of 0 • INT-1: score of 0.5 or 1 • INT-2: score of 1.5 or 2 • High: score of 2.5 or greater					

*Neutrophil count <1,800/mcL, platelets <100,000/mcL, Hb <10 g/dL

Revised International Prognostic Scoring System (IPSS)

	Score Value						
Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetic	Very good	--	Good	--	Intermediate	Poor	Very poor
Marrow blasts (%)	<2	--	>2 to <5	--	5 to 10	>10	--
Hemoglobin (g/dL)	≥10	--	8 to <10	<8	--	--	--

Platelets (per mcL)	≥100,000	50,000 to <100,000	<50,000				
ANC (per mcL)	≥800	<800					

- Very low: score of ≤1.5
- Low: score of >1.5 to 3
- Intermediate: score of >3 to 4.5
- High: score of >4.5 to 6
- Very High: score of >6

Website to calculator tool: http://www.ipss-r.com/

WHO-based Prognostic Scoring System (WPSS)

Variable	Variable scores			
	0	1	2	3
WHO category	RCUS, RARS, MDS with isolated del(5q)	RCMD	RAEB-1	RAEB-2
Karyotype	Good	Intermediate	Poor	-
Severe anemia (Hg <9 g/dl in biological males or <8 mg/dL in biological females)	Absent	Present	-	-

- Very low: score of 0
- Low: score of 1
- Intermediate: score of 2
- High: score of 3 or 4
- Very High: score of 5 or 6

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 12/11/24.

GUIDELINE UPDATE INFORMATION:

03/15/20	New Medical Coverage Guideline.
06/15/20	Revision to guideline consisting of updating the description section, position statement, dosage/administration, precautions, billing/coding, other section, and references based on a new FDA-approved indication for MDS.
07/01/20	Revision: Added HCPCS code J0896 and deleted code J3590.
1/15/22	Review and revision to guideline consisting of updating the description section, position statement, and references.
01/15/23	Review and revision to guideline consisting of updating the description section, position statement, warnings/precautions, related guidelines, and references. Diagnosis of beta-thalassemia must be confirmed via genetic testing.
10/15/23	Revision to guideline consisting of updating the description section, position statement, dosage/administration, precautions, billing/coding, and references based on a new FDA-approved indication for ESA-naïve adult patients with MDS.
01/15/24	Review and revision to guideline consisting of updating the description section (NCCN info), position statement, and references. Added requirement for MDS that the member does not have a chromosome 5q deletion.
01/15/25	Review and revision to guideline consisting of updating the description section (NCCN info), position statement, billing/coding, and references. Added new indication of myelofibrosis-associated symptomatic anemia per NCCN. Added an allowance that member's with MDS or MDS/MPN-RS-T can qualify for treatment prior to transfusion when certain requirements are met.