Medical Policy Bulletin

Title:
Luspatercept–aamt (Reblozyl®)
Policy #:
MA08.110e

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

In the absence of coverage criteria from applicable Medicare statutes, regulations, NCDs, LCDs, CMS manuals, or other Medicare coverage documents, this policy uses internal coverage criteria developed by the Company in consideration of peer-reviewed medical literature, clinical practice guidelines, and/or regulatory status.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

MEDICALLY NECESSARY

β-THALASSESMIA
Initial Therapy for β-thalassemia

Luspatercept-aamt (Reblozyl) is considered medically necessary and, therefore, covered for the treatment of anemia in adult individuals with β-thalassemia who require regular red blood cell (RBC) transfusions, when all of the following criteria, including dosing and frequency, are met:

- Documented diagnosis of β-thalassemia, hemoglobin E/β-thalassemia, or β-thalassemia combined with α-thalassemia confirmed by one of the following tests:
  - Molecular genetic testing that reveals pathogenic variation(s) in the *HBB* gene causing β-thalassemia
  - Hemoglobin electrophoresis
- Individual has a baseline hemoglobin (Hgb) level 11 g/dL or less.
- There is documentation the individual is transfusion-dependent, requiring regular RBC transfusions (i.e., at least six units of RBC in the previous 24 weeks and no transfusion-free period for ≥35 days during that period).
- Treatment will not be combined with a gene therapy used to treat β-thalassemia.
- Dosing and frequency: 1 mg/kg as a subcutaneous injection every 3 weeks. If a reduction in RBC transfusion burden is not achieved after at least two consecutive doses (6 weeks), luspatercept-aamt (Reblozyl) will be covered up to a maximum dose of 1.25 mg/kg every 3 weeks.

Continuation Therapy for β-thalassemia

Continuation of luspatercept-aamt (Reblozyl) is considered medically necessary and, therefore, covered for individuals who have demonstrated a documented reduction in the number of transfusions compared to baseline.

MYELODYSPLASTIC SYNDROMES (MYELODYSPLASTIC NEOPLASMS) (MDS)

Myelodysplastic Syndromes (Myelodysplastic Neoplasms) (MDS) and Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN)

Initial Therapy for MDS

Luspatercept-aamt (Reblozyl) is considered medically necessary and, therefore, covered for the treatment of anemia in adult individuals with myelodysplastic syndromes (myelodysplastic neoplasms) (MDS) and myelodysplastic/myeloproliferative neoplasms (MDS/MPN) when all of the following criteria, including dosing and frequency, are met:

- Individual has presence of the long arm of chromosome 5 (i.e., no del [5q])
- Individual has documented diagnosis of one of the following:
    - Lower risk MDS (defined as International Prognostic Scoring System [IPSS-R] Very Low, Low, Intermediate) with or without other cytogenetic abnormalities and one of the following:
        - Ring sideroblasts (RS) 15% or greater (or RS ≥5% with an SF3B1 mutation) with one of the following:
            - as a single agent (National Comprehensive Cancer Network [NCCN]-preferred regimen)
            - following no response to or relapse after imetelstat (Rytelo) (NCCN-preferred regimen)
        - RS less than 15% (or RS <5% with an SF3B1 mutation) when serum erythropoietin levels are 500 mU/mL or less
            - Following no response to or relapse after ESAs* alone, despite adequate iron stores (unless contraindication(s) or intolerance(s) to ESAs) (NCCN-preferred regimen)
    - Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPNs) Overlap Neoplasms with SF3B1 mutation and thrombocytosis (i.e., platelets ≥ 450 x109/L), as a single agent
- Individual has a baseline hemoglobin (Hgb) level 11 g/dL or less
- There is documentation that the individual is transfusion-dependent, requiring regular RBC transfusions (i.e., ≥ two units every 8 weeks)
    - Exception if there is documentation that the individual can't receive regular blood transfusions (e.g., religious reasons, blood shortages)
- Dosing and frequency: 1 mg/kg as a subcutaneous injection every 3 weeks. If individual is not RBC transfusion-free after at least two consecutive doses, an increased dose of 1.33 mg/kg every 3 weeks will be covered. If individual is still not RBC transfusion-free after at least two more consecutive doses, an increased maximum dose of 1.75 mg/kg every 3 weeks will be covered.

*NOTE: ESA failure defined as lack of ≥1.5 gm/dL rise in hemoglobin or lack of a decrease in RBC transfusion requirement by 6 to 8 weeks of treatment (per NCCN).

Continuation Therapy for MDS

Continuation of luspatercept-aamt (Reblozyl) is considered medically necessary and, therefore, covered for individuals who have demonstrated at least one of the following, compared to baseline:

- Increase in RBC transfusion independence (transfusion-free period)
- Increase in hemoglobin levels
- Reduction in transfusion burden (the amount of units required with each red cell transfusion)

Myelofibrosis

Initial Therapy for Myelofibrosis

Luspatercept-aamt (Reblozyl) is considered medically necessary and, therefore, covered for the treatment of myelofibrosis-associated anemia when all of the following criteria, including dosing and frequency, are met:

- The individual has documentation of one of the following features:
    - Splenomegaly and constitutional symptoms (e.g., fever, night sweats, itching, bone pain, and weight loss) well controlled on current JAK inhibitor, in combination JAK inhibitor
    - Ongoing symptomatic splenomegaly and/or constitutional symptoms, in combination with ruxolitinib
    - No splenomegaly or constitutional symptoms
- Individual has a baseline hemoglobin (Hgb) level 11 g/dL or less
- Dosing and frequency: 1 mg/kg as a subcutaneous injection every 3 weeks. If individual is not RBC transfusion-free after at least two consecutive doses, an increased dose of 1.33 mg/kg every 3 weeks will be covered. If individual is still not RBC transfusion-free after at least two more consecutive doses, an increased maximum dose of 1.75 mg/kg every 3 weeks will be covered.

Continuation Therapy for Myelofibrosis

Continuation of luspatercept-aamt (Reblozyl) is considered medically necessary and, therefore, covered for individuals who have demonstrated at least one of the following, compared to baseline:

- Increase in RBC transfusion independence (transfusion-free period)
- Increase in hemoglobin levels
- Reduction in transfusion burden (the amount of units required with each red cell transfusion)

NOT MEDICALLY NECESSARY

Continuation therapy with luspatercept-aamt (Reblozyl) in individuals with β-thalassemia is considered not medically necessary and, therefore, not covered for individuals who do not experience a decrease in transfusion burden after five doses (two doses at 1 mg/kg and three doses at 1.25 mg/kg). The available published peer-reviewed literature does not support its use in the treatment of this disease.

Continuation therapy with luspatercept-aamt (Reblozyl) in individuals with MDS, MDS/MPN, or myelofibrosis is considered not medically necessary and, therefore, not covered for individuals who do not experience a decrease in transfusion burden after at least three consecutive doses of the maximum dosage of 1.75 mg/kg administered at 3-week intervals. The available published peer-reviewed literature does not support its use in the treatment of this disease.

When molecular genetic testing reveals established benign variation(s) or wild-type genotype in the *HBB* gene, luspatercept-aamt (Reblozyl) is considered not medically necessary and, therefore, not covered because the available published peer-reviewed literature does not support its use in the treatment of this disease.

EXPERIMENTAL/INVESTIGATIONAL

All other uses for luspatercept-aamt (Reblozyl), including those listed below, are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

- Individuals with hemoglobin S/β-thalassemia or α-thalassemia
- Individuals with non-transfusion–dependent β-thalassemia
- As a substitute for RBC transfusions in those who require immediate correction of anemia

When molecular genetic testing reveals a likely pathogenesis, or variations of unknown significance (VUS), in the *HBB* gene, the use of luspatercept-aamt (Reblozyl) is considered experimental/investigational and, therefore, not covered because the safety and/or effectiveness of this service cannot be established by review of the available published peer-reviewed literature.

DOSING AND FREQUENCY REQUIREMENTS

The Company reserves the right to modify the Dosing and Frequency Requirements listed in this policy to ensure consistency with the most recently published recommendations for the use of luspatercept-aamt (Reblozyl). Changes to these guidelines are based on a consensus of information obtained from resources such as, but not limited to: the US Food and Drug Administration (FDA), Company-recognized authoritative pharmacology compendia, or published peer-reviewed clinical research. The professional provider must supply supporting documentation (i.e., published peer-reviewed literature) in order to request coverage for an amount of luspatercept-aamt (Reblozyl) outside of the Dosing and Frequency Requirements listed in this policy. For a list of Company-recognized pharmacology compendia, view our policy on off-label coverage for prescription drugs and biologics.

Accurate member information is necessary for the Company to approve the requested dose and frequency of this drug. If the member's dose, frequency, or regimen changes (based on factors such as changes in member weight or incomplete therapeutic response), the provider must submit those changes to the Company for a new approval based on those changes as part of the utilization management activities. The Company reserves the right to conduct post-payment review and audit procedures for any claims submitted for luspatercept-aamt (Reblozyl).

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the service.

When coverage of luspatercept-aamt (Reblozyl) is requested outside of the Dosing and Frequency Requirements listed in this policy, the prescribing professional provider must supply documentation (i.e., published peer-reviewed literature) to the Company that supports this request.

Guidelines

There is no Medicare coverage determination addressing luspatercept-aamt (Reblozyl); therefore, the Company policy is applicable.

DRUG INFORMATION

Luspatercept-aamt (Reblozyl) for individuals with β-thalassemia is administered as a subcutaneous injection every 3 weeks. Per prescribing information: Assess and review hemoglobin (Hb) results prior to each dose. If a red blood cell (RBC) transfusion occurred prior to dosing, use the pretransfusion hemoglobin for dose evaluation. In the absence of transfusions, if hemoglobin increase is greater than 2 g/dL within 3 weeks or the predose Hb is 11.5 g/dL or higher, reduce the dose or interrupt treatment.

Luspatercept-aamt (Reblozyl) for individuals with myelodysplastic syndrome (MDS) is administered as a subcutaneous injection every 3 weeks. Per prescribing information: Prior to each dose, review the individual's hemoglobin (Hb) and transfusion record. In the absence of transfusions, if Hb increase is greater than 2 g/dL within 3 weeks or if the predose Hb is 11.5 g/dL or higher, reduce the dose or interrupt treatment. If, upon dose reduction, the individual loses response (i.e., requires a transfusion) or hemoglobin concentration drops by 1 g/dL or more in 3 weeks in the absence of transfusion, increase the dose by one dose level. Wait a minimum of 6 weeks between dose increases.

PROGNOSTIC SCORING SYSTEMS FOR MDS

There are three prognostic scoring systems for MDS that use several factors to calculate a risk score to categorize the disease as either lower-risk MDS (milder disease with slower progression) or higher-risk MDS (more aggressive disease). Factors may include the following: percent of blast cells in bone marrow, chromosome changes, number of low blood counts, hemoglobin levels, platelets and neutrophil counts, and presence of severe anemia.

Lower-risk disease is defined in one of the following scoring systems:

- International Prognostic Scoring System (IPSS): low or intermediate-1 risk
- Revised International Prognostic Scoring System (IPSS-R): very low, low, or intermediate risk
- WHO-Based Prognostic Scoring System (WPSS): very low, low, or intermediate risk

Higher-risk disease is defined in one of the following scoring systems:

- International Prognostic Scoring System (IPSS): intermediate-2 or high risk
- Revised International Prognostic Scoring System (IPSS-R): high or very high risk
- WHO-Based Prognostic Scoring System (WPSS): high or very high risk

BENEFIT APPLICATION

Subject to the applicable Evidence of Coverage, luspatercept-aamt (Reblozyl) is covered under the medical benefits of the Company's Medicare Advantage products when the medical necessity criteria and Dosing and Frequency Requirements listed in this medical policy are met.

For Medicare Advantage members, certain drugs are available through either the member's medical benefit (Part B benefit) or pharmacy benefit (Part D benefit), depending on how the drug is prescribed, dispensed, or administered. This medical policy only addresses instances when luspatercept-aamt (Reblozyl) is covered under a member's medical benefit (Part B benefit). It does not address instances when luspatercept-aamt (Reblozyl) is covered under a member's pharmacy benefit (Part D benefit).

However, services that are identified in this policy as experimental/investigational or not medically necessary are not eligible for coverage or reimbursement by the Company.

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

Luspatercept-aamt (Reblozyl) was approved by the FDA on November 8, 2019, for the treatment of anemia in adult individuals with β-thalassemia who require RBC transfusions. (Limitations of use: Luspatercept-aamt (Reblozyl) is not indicated for use as a substitute for RBC transfusions in individuals who require immediate correction of anemia). Supplemental approvals for luspatercept-aamt (Reblozyl) have since been issued by the FDA.

The safety and effectiveness of luspatercept-aamt (Reblozyl) in pediatric individuals have not been established; based on findings in juvenile animals, luspatercept-aamt (Reblozyl) is not recommended for use in the pediatric population.

Description

LUSPATERCEPT-AAMT (REBLOZYL)

Luspatercept-aamt (Reblozyl) was approved by the US Food and Drug Administration (FDA) on November 8, 2019, for the treatment of anemia in adult individuals with β-thalassemia who require regular red blood cell (RBC) transfusions. Luspatercept-aamt (Reblozyl) is not indicated for use as a substitute for RBC transfusions in individuals who require immediate correction of anemia. A supplemental approval was granted on April 3, 2020, for the treatment of anemia failing an erythropoiesis-stimulating agent (ESA) and requiring two or more RBC units over 8 weeks in adults 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). Supplemental approval was also granted on August 28, 2023, for the treatment of anemia in ESA-naïve adults with very low- to intermediate-risk MDS who may require regular RBC transfusions.

Luspatercept-aamt (Reblozyl) is a recombinant fusion protein that causes erythroid maturation. Luspatercept-aamt (Reblozyl) binds to and inhibits several endogenous transforming growth factor (TGF)-β superfamily ligands involved in late-stage erythropoiesis, thereby diminishing abnormally elevated Smad2/3 signaling and enhancing RBC production and preventing anemia.

β-THALASSEMIA

β-thalassemia is a relatively rare inherited blood disorder in the United States, but its incidence of symptomatic cases is estimated to be approximately one in 100,000 individuals in the general population. Many states in the United States diagnose infants with a hemoglobin disorder through newborn screenings, although most states do not routinely test for thalassemia. β-thalassemia is caused by variations in the *HBB* gene (usually in an autosomal recessive pattern) that provides instructions for making the β-globin protein, a component (subunit) of hemoglobin. A lack of β-globin leads to a shortage of functional hemoglobin, the iron-containing protein in RBCs that carries oxygen to cells throughout the body, creating a shortage of mature RBC. This shortage of mature RBCs leads to anemia and other associated health problems, such as organ damage or abnormal blood clots, in those with β-thalassemia.

β-thalassemia has three main forms: minor, intermedia, and major, which indicate the severity of the disease. Individuals with β-thalassemia minor (trait) are usually asymptomatic, and individuals often are unaware that they have the condition. Individuals with thalassemia intermedia are typically diagnosed later in life, exhibit a wide variability in symptoms and severity (less severe phenotype than thalassemia major), and may only require periodic

blood transfusions (non-transfusion–dependent thalassemia). The most severe form of β-thalassemia is thalassemia major (also known as Cooley anemia), diagnosed within the first 2 years of life, and requires life-long, regular blood transfusions to replenish their RBC supply. In β-thalassemia major, there is minimal to no β-globin chain production and consequently little to no adult hemoglobin (HbA). β-thalassemia major is caused by homozygosity or compound heterozygosity for β0 thalassemia mutations or, in rare cases, β+ thalassemia mutations with extremely low production of β-globin chains. The other major cause is compound heterozygosity for hemoglobin E (i.e., HbE/β-thalassemia); HbE is a β+ type of mutation. Worldwide, individuals with HbE/β-thalassemia represent approximately 50% of those affected with severe β-thalassemia.

Over time, an influx of iron-containing hemoglobin from chronic blood transfusions can lead to a build-up of iron in the body, resulting in liver, heart, and hormone problems. Individuals are required to undergo chelation therapy to remove the excess iron from the body. The only available curative option is a hematopoietic stem cell transplant. Betibeglogene autotemcel [Beti-Cel (Zynteglo)], an autologous hematopoietic stem cell–based gene therapy, is another option for the treatment of adult and pediatric individuals with β-thalassemia who require regular RBC transfusions.

PEER-REVIEWED LITERATURE
Summary

The safety and efficacy of luspatercept-aamt (Reblozyl) were evaluated in a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial (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) in adults (n=336) with a documented diagnosis of β-thalassemia (77% of participants), hemoglobin E/β-thalassemia, or β-thalassemia combined with α-thalassemia who required regular RBC transfusions (six to 20 RBC units in the 24 weeks prior to randomization and no transfusion-free period for ≥35 days during that period). Participants were randomly assigned 2:1 to luspatercept-aamt (Reblozyl) 1 mg/kg subcutaneously every 21 days plus best supportive care (BSC) (n=224) or placebo plus BSC (n=112) administered subcutaneously once every 21 days, as long as a reduction in transfusion requirement was observed or until unacceptable toxicity resulted. All participants 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 those with hemoglobin S/β-thalassemia or α-thalassemia or who had major organ damage (liver disease, heart disease, lung disease, renal insufficiency). Those with recent deep vein thrombosis or stroke or recent use of an ESA, immunosuppressant, or hydroxyurea therapy were also excluded.

The baseline transfusion burden 12 weeks prior to randomization was approximately a median of 6.12 transfusions (minimum 3, maximum 14). The primary outcome of this trial was the proportion of participants achieving RBC transfusion burden reduction (≥33% reduction from baseline), with a reduction of at least two units from Week 13 to Week 24. Twenty-one percent of those who were in the luspatercept-aamt (Reblozyl) group achieved at least a 33% reduction in transfusions compared to 4.5% of the individuals who received a placebo (P<0.0001). Thromboembolic events were reported more frequently in those treated with luspatercept-aamt (Reblozyl) (3.6%) compared to placebo (0.9%).

MYELODYSPLASTIC SYNDROMES

Myelodysplastic syndromes (MDS) (also known as myelodysplastic neoplasms) are a group of cancers caused by variation(s) in gene(s) and are characterized by ineffective hematopoiesis and progressive cytopenias. The hematopoietic stem cells become abnormal and either stop replicating, or they create defective (e.g., dysplasia, die early) new blood cells. The defective cells overcrowd the bone marrow causing even fewer healthy blood cells to be created or survive and enter the bloodstream. MDS affects all three lines of blood cells, causing symptomatic anemia (dyspnea, fatigue, weakness), infection, and bleeding. MDS predominantly affects the elderly male population and has the risk of progression to an aggressive cancer, acute myeloid leukemia. There are many types of MDS classified by the following features: percent of blast cells in bone marrow, chromosome changes, number of low blood counts, hemoglobin levels, platelets and neutrophil counts, and presence of severe anemia.

The only curative option for MDS is an allogeneic hematopoietic cell transplantation (HCT). Other treatment options for MDS, depending on genetic and other hematologic factors, may include ESA therapy, red-cell transfusions with iron chelation therapy, lenalidomide, or hypomethylating agents (e.g., azacitidine, decitabine). Individuals with anemia and lower risk MDS in whom ESA therapy is not effective (serum EPO levels >200 U/L) generally become dependent on red-cell transfusions. Treatment goals for those with lower risk MDS include transfusion independence, improvement in hemoglobin levels, and maintenance of or improvement in quality of life.

MDS SUBTYPES
Advances in molecular technology and the development of next-generation sequencing provides a greater understanding of the molecular genetic background of MDS. Lower risk MDS can be subdivided into certain cytogenetic, morphologic, and clinical characteristics used to direct therapeutic implications.

Del(5q)
Lower risk MDS with an isolated deletion in the long arm of chromosome 5 (del[5q]) is generally considered a good prognostic variable; however, three or more chromosome anomalies—of which del(5q) could be included—are considered a complex karyotype and associated with poor prognosis. MDS with isolated del(5q) is highly responsive to lenalidomide that acts through karyotype-dependent pathways mediated by haploinsufficient genes. Individuals without the del(5q) do not respond as favorably, but have demonstrated greater outcomes to alternative treatments such as luspatercept-aamt (Reblozyl) or ESAs. Identifying the specific cytogenetic profile will aid in clinical decision-making.

SF3B1
The majority of MDS individuals exhibit at least one somatic mutation in the spliceosome gene with the most frequent mutation occurring in splicing factor 3B subunit 1A (SF3B1). Although there is documentation of a variety of other mutated genes, only mutations in SF3B1 have been associated with a more favorable prognosis; thus, the mutational status of SF3B1 is an essential predictor of treatment response. Of note, individuals with an SF3B1 mutation have demonstrated a greater and lasting erythroid response to luspatercept-aamt (Reblozyl) over standard ESAs.

RING SIDEROBLASTS
Ring sideroblasts (RS) are erythroid precursors with iron-laden mitochondria forming a perinuclear ring. The mitochondrial iron retention prevents iron from incorporating into heme, leading to low RBC production. Typically, the presence of 15% RS or greater—or 5% RS or greater with an SF3B1 mutation—is a positive predictor of luspatercept-aamt (Reblozyl) response. Determining the percentage of RS is a key assessment for treatment recommendation in lower risk MDS populations.

SERUM EPO
Erythropoietin (EPO) is a glycoprotein hormone produced by the peritubular cells of the kidney to stimulate RBC production, with greater serum EPO (sEPO) levels indicating impaired red blood cell production. Generally, individuals with sEPO levels less than or equal to 500 mU/mL are indicated for luspatercept-aamt (Reblozyl) or ESAs, while greater sEPO levels are indicated for immunosuppressants or chemotherapy.

PEER-REVIEWED LITERATURE
Summary

Myelodysplastic Syndromes with Ring Sideroblasts or Myelodysplastic/Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis Associated Anemia in ESA-Refractory or -Intolerant Individuals

The safety and efficacy of luspatercept-aamt (Reblozyl) to decrease the severity of anemia were evaluated in a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial (A Study of Luspatercept [ACE-536] to Treat Anemia Due to Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes) (MEDALIST) by Fenaux et al. 2020 in adults (n=229) with a documented diagnosis of MDS with ring sideroblasts according to World Health Organization criteria (i.e., with either ≥15% ring sideroblasts or ≥5% ring sideroblasts if an *SF3B1* variation was present, and with <5% bone marrow blasts). About 87% of participants had MDS with ring sideroblasts (MDS-RS), while the remainder were categorized as MDS/MPN-RS-T. Participants had disease defined according to the Revised International Prognostic Scoring System (IPSS-R) as being of very low (10% of participants), low (72% of participants), or intermediate risk (17% of participants) MDS. Participants required regular RBC transfusions (≥ two units per 8 weeks during the 16 weeks before randomization), and had an inadequate response to prior treatment with an ESA, be intolerant of ESAs, or have a serum EPO greater than 200 U/L. The study excluded individuals with MDS with deletion 5q (del 5q), white blood cell count greater than 13 G/L, neutrophils lower than 0.5 Gi/L, platelets lower than 50 Gi/L, or with prior use of a disease-modifying agent for treatment of MDS. The median age was 71 years (range, 26–95). Ninety-one percent of individuals had a variation in the *SF3B1* gene.

In the double-blind primary phase of the MEDALIST trial, participants were randomly assigned (2:1) to receive luspatercept-aamt (Reblozyl) or placebo, administered subcutaneously every 3 weeks for 24 weeks with no crossover allowed. The starting dose of luspatercept was 1 mg/kg. If a new transfusion was necessary after the individuals were considered to have transfusion independence, they could continue receiving luspatercept-aamt (Reblozyl), with adjustment to a dose of 1.33 mg/kg, and then to 1.75 mg/kg. At Week 25, disease was assessed and those without clinical benefit discontinued luspatercept or placebo and entered follow-up. Those who had clinical benefit without disease progression could enter the double-blind Extension Phase (n=126) and continue receiving

luspatercept-aamt (Reblozyl) or placebo until they had unacceptable toxic effects or disease progression, withdrew consent, or met discontinuation criteria. Follow-up will continue for at least 3 years following the last dose.

The primary end point of RBC transfusion independence (RBC-TI) for 8 weeks or longer during weeks 1 through 24, was seen in 58 individuals (38%) who received luspatercept-aamt (Reblozyl) versus 10 individuals (13%) who received placebo (*P*<0.001). The results showed that there was a greater reduction in the severity of anemia in transfusion-dependent individuals with lower risk MDS-RS who received luspatercept-aamt (Reblozyl) . The most common luspatercept-associated adverse events (of any grade) included fatigue, diarrhea, asthenia, nausea, and dizziness.

Treatment of Myelodysplastic Syndromes with Associated Anemia in ESA-Naïve Individuals

The safety and efficacy of luspatercept-aamt (Reblozyl) were evaluated in an open-label, randomized active-controlled trial comparing luspatercept-aamt (Reblozyl) versus epoetin alfa in 356 individuals with anemia due to IPSS-R very low, low, or intermediate-risk MDS or with MDS/MPN RS-T in ESA-naïve individuals (endogenous sEPO levels of < 500 U/L) who require regular RBC transfusions (two to six RBC units per 8 weeks confirmed for a minimum of 8 weeks immediately preceding randomization). IPSS-R risk classification at baseline was 9.3% very low, 72.2% low, 17.4% intermediate, 0.3% high, and 0.8% missing. The efficacy of luspatercept-aamt (Reblozyl) was established at the time of the interim efficacy analysis based on the proportion of individuals 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. Individuals who received luspatercept-aamt (Reblozyl) had a higher response rate than those who received epoetin alfa, 58.5% compared to 31.2%. The most common adverse reactions included fatigue, diarrhea, and hypertension.

OFF-LABEL INDICATION

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless

otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)
N/A

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)

D46.1 Refractory anemia with ring sideroblasts
D46.9 Myelodysplastic syndrome, unspecified
D56.1 Beta thalassemia
D56.5 Hemoglobin E-beta thalassemia

HCPCS Level II Code Number(s)

J0896 Injection, luspatercept-aamt, 0.25 mg

Revenue Code Number(s)
N/A

Policy History

Revisions From MA08.110e:

06/18/2026	This version of the policy will become effective 06/18/2026. This policy was updated to communicate the Company's coverage position for luspatercept-aamt (Reblozyl) in consideration of the changes to the National Comprehensive Cancer Network (NCCN) Compendia for Myelodysplastic Syndromes. For individuals with Ring sideroblasts (RS) 15% or greater (or RS ≥5% with an SF3B1 mutation), coverage for luspatercept-aamt (Reblozyl) is Medically Necessary as a single agent, or following no response to or relapse after imetelstat (Rytelo). For individuals with RS less than 15% (or RS <5% with an SF3B1 mutation), in addition to following no response to ESAs, coverage for luspatercept-aamt (Reblozyl) is Medically Necessary when there has also been "relapse after ESAs* alone", despite adequate iron stores (unless contraindication(s) or intolerance(s) to ESAs). A definition of ESA failure, per NCCN was added: *NOTE: ESA failure defined as lack of ≥1.5 gm/dL rise in hemoglobin or lack of a decrease in RBC transfusion requirement by 6 to 8 weeks of treatment (per NCCN). All of the ICD-10 CM codes have been removed from this policy. Report the most appropriate diagnosis code in support of medically necessary criteria as listed in the policy.

Revisions From MA08.110d:

03/28/2025	This version of the policy will become effective 03/28/2025. This policy was updated to communicate the Company's coverage position for luspatercept-aamt

	(Reblozyl) for the treatment of myelodysplastic syndromes (MDS), in consideration of the US Food and Drug Administration, the National Comprehensive Cancer Network (NCCN), and clinical trials. Additionally, coverage was clarified **for individuals with MDS-related anemia** who are negative for ring sideroblast. New criteria were added for myelofibrosis and myelodysplastic/myeloproliferative neoplasms (MDS/MPN), in alignment with the National Comprehensive Cancer Network (NCCN). The following ICD-10 CM codes have been added to this policy: • C94.40 Acute panmyelosis with myelofibrosis not having achieved remission • C94.42 Acute panmyelosis with myelofibrosis, in relapse • C94.6 Myelodysplastic disease, not elsewhere classified • D46.0 Refractory anemia without ring sideroblasts, so stated • D46.20 Refractory anemia with excess of blasts, unspecified • D46.21 Refractory anemia with excess of blasts 1 • D46.22 Refractory anemia with excess of blasts 2 • D46.A Refractory cytopenia with multilineage dysplasia • D46.B Refractory cytopenia with multilineage dysplasia and ring sideroblasts • D46.4 Refractory anemia, unspecified • D46.Z Other myelodysplastic syndromes • D47.1 Chronic myeloproliferative disease • D47.4 Osteomyelofibrosis • D75.81 Myelofibrosis --- *Note*: On December 4, 2024, this policy in Notification was updated to incorporate changes to the Policy Section for the treatment of lower risk MDS, in alignment with the FDA and NCCN. • FROM: Ring sideroblasts (RS) 15% or greater (or RS ≥5% with an SF3B1 mutation) and erythropoiesis-stimulating agent (ESA)-naïve • TO: Ring sideroblasts (RS) 15% or greater (or RS ≥5% with an SF3B1 mutation) with or without prior erythropoiesis-stimulating agent (ESA) therapy

Revisions From MA08.110c:

05/07/2024	This policy has been reissued in accordance with the Company's annual review process.
08/21/2023	This version of the policy will become effective 08/21/2023. This policy was updated to communicate the Company's coverage position for β-thalassemia and myelodysplastic syndromes, in alignment with US Food and Drug Administration (FDA) prescribing information and the National Comprehensive Cancer Network (NCCN). Baseline hemoglobin (Hgb) level of less than or equal to 11 g/dL was added as a criterion for β-thalassemia and myelodysplastic syndromes. Serum erythropoietin levels were added as criteria for lower risk (defined as International Prognostic Scoring System [IPSS-R] Very Low, Low, Intermediate) myelodysplastic syndromes

Revisions From MA08.110b:

06/29/2022	**This policy has been reissued in accordance with the Company's annual review process.**
05/19/2021	**This policy has been reissued in accordance with the Company's annual review process.**
07/01/2020	This policy has been identified for the HCPCS code update, effective 07/01/2020. The following NOC codes have been **removed** from this policy and are replaced by the following HCPCS code: **REMOVED:** C9399 Unclassified drugs or biologicals

	J3590 Unclassified biologics **REPLACED WITH:** J0896 Injection, luspatercept-aamt, 0.25 mg

Revisions From MA08.110a:

06/08/2020	This version of the policy will become effective 06/08/2020. This policy was updated to communicate the Company's coverage position for the new indication of Myelodysplastic Syndromes (MDS), represented by the following ICD-10 codes: D46.1 Refractory anemia with ring sideroblasts D46.9 Myelodysplastic syndrome, unspecified

Revisions From MA08.110:

03/09/2020	The following new policy has been developed to communicate the Company's coverage criteria for luspatercept–aamt (Reblozyl®).

Version Effective Date:
06/18/2026
Version Issued Date:
06/18/2026
Version Reissued Date:
N/A