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PHARMACY / MEDICAL POLICY – 5.01.614

Erythroid Maturation Agents

Effective Date:	May 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Apr. 21, 2025	None
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Beta thalassemia is an inherited blood disorder. Due to a change in one or more genes, the body doesn't make enough hemoglobin. Hemoglobin is a protein in red blood cells that carries oxygen to the body. When the body does not make enough hemoglobin or red blood cells, it causes a condition called anemia. Anemia leads to fatigue and weakness and can be mild, moderate, or severe. Treatment of anemia from beta thalassemia is meant to increase the number of healthy red blood cells. This policy describes when drugs called erythroid maturation agents used to treat anemia may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Reblozyl (luspatercept-aamt) SC	**Reblozyl (luspatercept-aamt) may be considered medically necessary for the treatment of anemia in adult individuals with beta thalassemia when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has beta thalassemia **AND** • Has received a minimum of 6 red blood cell (RBC) units in the past 6 months **AND** • Has no transfusion-free period >30 days during the past 6 months **AND** • Reblozyl is not being used as a substitute for RBC transfusions in individuals who require immediate correction of anemia **AND** • Reblozyl is prescribed by or in consultation with a hematologist **Reblozyl (luspatercept-aamt) may be considered medically necessary for the treatment of anemia in adult individuals failing an erythropoiesis stimulating agent (ESA) when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has tried and failed or had intolerance to one ESA (e.g., epoetin alfa, darbepoetin) **AND** • Has very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPNRS-T) **AND** • Has received a minimum of 2 red blood cell (RBC) units in the past 8 weeks **AND** • Reblozyl is prescribed by or in consultation with a hematologist

Drug	Medical Necessity
	Reblozyl (luspatercept-aamt) may be considered medically necessary for the treatment of anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult individuals when the following criteria are met: • The individual is aged 18 years or older **AND** • Has very low- to intermediate-risk myelodysplastic syndromes (MDS) **AND** • Has received a minimum of 2 red blood cell (RBC) units in the past 8 weeks **AND** • Reblozyl is prescribed by or in consultation with a hematologist

Drug	Investigational
Reblozyl (luspatercept-aamt)	**All other uses of Reblozyl (luspatercept-aamt) for conditions not outlined in this policy are considered investigational.** **The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for Reblozyl (luspatercept-aamt) may be approved up to 12 months.** **All other reviews for Reblozyl (luspatercept-aamt) may be approved up to 6 months.**
Re-authorization criteria	**Non-formulary exception reviews and all other reviews for Reblozyl (luspatercept-aamt) may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate at the time of re-authorization a reduction in RBC transfusion burden from baseline.**

Documentation Requirements

The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis, relevant history, physical evaluation, and RBC transfusion history

Coding

Code	Description
HCPCS	
J0896	Injection, luspatercept-aamt (Reblozyl), 0.25 mg

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Consideration of Age

The ages stated in this policy for which Reblozyl (luspatercept-aamt) is considered medically necessary are based on the ages approved in the FDA labeling.

Benefit Application

This policy is managed through the medical benefit.

Evidence Review

Background

β-thalassemia is a hereditary red blood cell disorder caused by mutations in the β-globin gene that can cause anemia and associated comorbidities such as bone deformities, ulcers, splenomegaly and treatment related sequelae such as iron overload. β-thalassemia is more common in Mediterranean countries, Central Asia and Southeast Asia. β-thalassemia can result in a range of phenotypes that include asymptomatic individuals to individuals with severe anemia. The cause of β-thalassemia is from a gene mutation which impacts the hemoglobin subunits and can be classified into categories such as β-thalassemia minor, β-thalassemia intermedia and β-thalassemia major. Blood transfusion is the current standard of care for adult individuals with β-thalassemia who require RBC transfusion. With blood transfusion therapy supportive care in the form of iron chelation agents may be prescribed.

The burden of β-thalassemia in the US is approximately 1 in 100,000 and varies by region based on immigration patterns. The economic impact of β-thalassemia can be profound over time as individuals with β-thalassemia major may be dependent on life-long blood transfusion regimens. The quality of life of subjects with β-thalassemia may diminish as treatment management modalities often require monitoring of symptoms, blood counts and iron levels but more importantly can be impacted by the negative side effects of blood transfusions such as iron overload and infusion related reactions.

β-thalassemia's are genetic disorders of hemoglobin synthesis characterized by deficient (β^{+}) or absent (β^{0}) synthesis of the β-globin subunit of hemoglobin that can result in anemia. The majority of individuals inherit their disorder as a mendelian recessive trait which can impart varying levels of phenotypic expression and disease conditions. Heterozygous individuals may be asymptomatic or exhibit light symptoms such as with mild anemia being labeled as β-thalassemia minor and homozygous individuals have more severe anemia of varying degrees and are labeled as β-thalassemia major or intermedia.

Luspatercept is a recombinant fusion protein comprised of the modified extracellular domain of the human activin receptor type IIB linked to the fragment crystallizable region (Fc) domain of human immunoglobin G1 which binds several endogenous TGF-β-superfamily ligands that diminishes Smad2/3 signaling. In mice models, luspatercept promoted erythroid maturation through differentiation of late-stage erythroid precursors (normoblasts). These models revealed that luspatercept decreased abnormally elevated Smad2/3 signaling and improved hematology parameters associated with ineffective erythropoiesis. Luspatercept activity in binding to and inhibiting Smad 2/3 ligands GDF11 and activin corrected anemia and ineffective erythropoiesis. In individuals with low RBC transfusion burden hemoglobin levels increased in 7 days of

initiating treatment and correlated with the increase in luspatercept C_{MAX} and the greatest increase in hemoglobin was seen after the first dose.

Summary of Evidence

Efficacy

Luspatercept had consistent efficacy in decreasing transfusion burden compared to those receiving placebo as reported in the randomized, double-blind, placebo-controlled, Phase III BELIEVE Trial. Individuals being managed for transfusion dependent β-thalassemia requiring 3 units of blood every 3 weeks for life adds a significant burden to treatment management. Luspatercept achieved reduction in transfusion burden across any 12- or 24-week period in the BELIEVE Trial demonstrating wide efficacy. 48/224 (21.4%) achieved the primary end point of a ≥33% reduction in RBC transfusion burden with a reduction of ≥2 RBC units from baselines during weeks 13-24 vs 5/112 (4.5%) of individuals in placebo. 158/224 (70.5%) of subjects achieved a greater than 33% reduction in RBC transfusion requirements during any consecutive 12 weeks of treatments vs 33/112 (29.5%) of placebo treated subjects. There were statistically significant findings that favored luspatercept for other secondary endpoints including:

- ≥33% reduction in transfusion burden at weeks 37-48: 19.6% (n=44 of 224 luspatercept-treated individuals) vs. 3.6% (n=4 of 112 placebo-treated individuals; p<0.001)
- ≥50% reduction in transfusion burden at weeks 13-24: 7.6% (n=17/224) vs. 1.8% (n=2/112; p=0.03)
- ≥50% reduction in transfusion burden at weeks 37-48: 10.3% (n=24/224) vs. 0.9% (n=1/112; p=0.002)

The expanded approval is based on interim results from the Phase 3 COMMANDS trial, which compared luspatercept with another ESA, epoetin alfa. Luspatercept demonstrated superior efficacy of concurrent RBC transfusion independence (RBC-TI) and hemoglobin (Hb) increase compared with epoetin alfa, regardless of ring sideroblast status. The trial randomized individuals with very low-, low- or intermediate-risk MDS who were RBC transfusion independent and ESA-naïve to receive either subcutaneous luspatercept once every 3 weeks or epoetin alfa weekly. Of the individuals who received luspatercept, 58.5% (n=86) achieved the primary endpoint of RBC-TI of at least 12 weeks with a mean Hb increase of at least 1.5 g/dL within the first 24 weeks, compared with 31.2% (n=48) of individuals treated with epoetin alfa.

Safety

The safety profile of luspatercept was generally tolerable as the most common adverse events were mild to moderate and manageable without dose modification, delay or discontinuation. Common adverse events included bone pain, headache, and injection site reactions. Safety analyses by demographic subgroups did not reveal any significant differences from overall safety findings. The most common serious adverse events from clinical trials included anemia, DVT, fever, infection and septic shock. These side effects are commonly associated with the side effects related to the use of hematologic factors and subcutaneous injection site related reactions. Relevant warnings and precautions associated with luspatercept include thromboembolic events (TEE) which were reported in 8/223 (3.6%) of subjects and included DVT and stroke followed by hypertension in 61/571 (10.7%) of subjects. There is limited data regarding pediatric individuals and the use of luspatercept. A warning label for embryo-fetal toxicity is stated. Pregnant and lactating women were excluded from the clinical study populations and throughout clinical development. Animal reproductive data was collected which resulted in adverse developmental outcomes. Outcomes included increased embryo-fetal mortality, alterations to growth, and structural abnormalities which occurred at levels higher than the maximum recommended human dose of 1.25 mg/kg.

In the Phase 3 COMMANDS trial, the most common (>10%) all-grade adverse reactions were diarrhea, fatigue, hypertension, peripheral edema, nausea, and dyspnea.

2021 Update

Reviewed Reblozyl (luspatercept-aamt) prescribing information and conducted a literature search on the management of anemia for thalassemias and myelodysplastic syndromes. No new information was identified that would result in changes to policy statements.

2022 Update

Reviewed Reblozyl (luspatercept-aamt) prescribing information. The prescribing information was updated in July 2022 and included information to discontinue Reblozyl for individuals with extramedullary hematopoietic (EMH) masses causing serious complications along with a warning regarding the risk for the development of EMH in individuals with beta thalassemia. No new information was identified that would result in changes to policy statements.

2023 Update

Reviewed Reblozyl (luspatercept-aamt) prescribing information. The prescribing information was updated in August 2023 and included new indication for the treatment of anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult individuals with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions. No new information was identified that would result in changes to policy statements.

2024 Update

Reviewed Reblozyl (luspatercept-aamt) prescribing information. Removed coverage from the pharmacy benefit to align with current benefit coverage.

2025 Update

Reviewed Reblozyl (luspatercept-aamt) prescribing information. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

References

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History

Date	Comments
04/01/20	New policy, approved March 10, 2020, effective for dates of service on or after July 2, 2020, following 90-day provider notification. Add to Prescription Drug section. Reblozyl (luspatercept-aamt) may be considered medically necessary for the treatment of anemia in adult individuals with beta thalassemia when criteria are met. Coverage criteria for Reblozyl (luspatercept-aamt) (HCPCS code J3590) becomes effective for dates of service on or after July 2, 2020.
07/01/20	Coding update. Added code J0896. Removed code J3590.

Date	Comments
11/01/20	Interim Review, approved October 13, 2020. Added a new indication to Reblozyl (luspatercept-aamt) for the treatment of anemia in adults with MDS-RS or with MDS/MPN-RS-T who failed an ESA.
12/01/21	Annual Review, approved November 18, 2021. No changes to policy statements.
01/01/23	Annual Review, approved December 23, 2022. No changes to policy statements. Changed the wording from "patient" to "individual" throughout the policy for standardization.
11/01/23	Annual Review, approved October 10, 2023. Added a new indication to Reblozyl (luspatercept-aamt) for the treatment of anemia in ESA-naïve adults with very low- to intermediate-risk MDS.
06/01/24	Annual Review, approved May 24, 2024. No changes to policy statement. Removed coverage from the pharmacy benefit to align with current benefit coverage.
05/01/25	Annual Review, approved April 21, 2025. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.