Reblozyl (luspatercept-aamt)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the criteria is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication

1. Treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions.
2. Treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).

Limitations of Use: Reblozyl is not indicated for use as a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anemia.

POLICY

Required Documentation

A. Anemia with Beta Thalassemia

Submission of the following information is necessary to initiate the prior authorization review:

1. Initial therapy requests
   a. Pretreatment or pretransfusion hemoglobin (Hgb) level
   b. Hemoglobin electrophoresis or high-performance liquid chromatography (HPLC) results
2. Continuation of therapy requests: Current or recent pretransfusion Hgb level

B. Anemia of Myelodysplastic Syndrome or Myelodysplastic/Myeloproliferative Neoplasm

Submission of the following information is necessary to initiate the prior authorization review:

1. Initial therapy requests
    a. Pretreatment or pretransfusion hemoglobin (Hgb) level
    b. Pretreatment ring sideroblasts level
    c. *SF3B1* mutation status (if pretreatment ring sideroblasts are greater than or equal to 5% and less than 15%)
    d. Pretreatment serum erythropoietin levels
2. Continuation of therapy requests: Current or recent pretransfusion Hgb level

Exclusions

Anemia with Beta Thalassemia

Coverage will not be provided for members with any of the following exclusions:

A. Members with hemoglobin S/β-thalassemia or alpha-thalassemia
B. Members with recent (defined as less than or equal to 24 weeks prior to initiation of Reblozyl therapy) deep vein thrombosis or stroke
C. Members with platelet count greater than 1000 x 10^9 per liter

Criteria for Initial Approval

A. Anemia with Beta Thalassemia

Authorization of 16 weeks may be granted for treatment of anemia with beta thalassemia when all of the following criteria are met:

1. The member has symptomatic anemia evidenced by a pretreatment or pretransfusion Hgb level less than or equal to 11 grams per deciliter
2. The member has a diagnosis of beta thalassemia (β-thalassemia) or hemoglobin E/β-thalassemia (β-thalassemia with mutation and/or multiplication of alpha globin is allowed) confirmed by hemoglobin electrophoresis or high performance liquid chromatography (HPLC)
3. The member required at least 6 red blood cell (RBC) units to be transfused in the previous 24 weeks
4. The member has had no transfusion free period greater than 35 days in the previous 24 weeks
5. Reblozyl is prescribed by, or in consultation with, a hematologist, or other specialist with expertise in the diagnosis and management of beta thalassemia

Note: If a red blood cell (RBC) transfusion occurred prior to dosing, the pretransfusion hemoglobin (Hgb) level must be considered for dosing purposes.

B. Anemia of Myelodysplastic Syndrome or Myelodysplastic/Myeloproliferative Neoplasm

Authorization of 24 weeks may be granted for the treatment of very low- to intermediate-risk myelodysplastic syndrome or myelodysplastic/myeloproliferative neoplasm when all of the following criteria are met:

1. The member has symptomatic anemia evidenced by a pretreatment or pretransfusion Hgb level less than or equal to 11 grams per deciliter.
2. Other causes of anemia (e.g., gastrointestinal bleeding, hemolysis, renal disease, nutritional deficiency, etc.) have been ruled out and/or addressed
3. The member has been receiving regular red blood cell (RBC) transfusions
4. The member meets either of the following:
    a. Ring sideroblasts are greater than or equal to 15%
    b. Ring sideroblasts are greater than or equal to 5% and less than 15% and the patient has an *SF3B1* mutation.
5. The member meets either of the following:
    a. Pretreatment serum erythropoietin levels greater than 500 mU/mL
    b. Pretreatment serum erythropoietin levels less than or equal to 500mU/mL following no response to the combination of an erythropoiesis-stimulating agent (ESA) and granulocyte-colony stimulating factor (G-CSF)
6. Reblozyl is prescribed by, or in consultation with, a hematologist, oncologist, or other specialist with expertise in the diagnosis and management of myelodysplastic syndromes

Continuation of Therapy

Authorization of 6 months may be granted for continued treatment in members requesting authorization for an indication listed in the Criteria for Initial Approval section when all of the following criteria are met:

A. The member must achieve or maintain a reduction in red blood cell transfusion burden

B. The member must not experience an unacceptable toxicity from Reblozyl
C. The member must have a pre-dose Hgb level less than or equal to 11 grams per deciliter. If the Hgb level is greater than 11 grams per deciliter, the prescriber agrees to hold the dose until the level falls to 11 grams per deciliter
D. Reblozyl is prescribed by, or in consultation with, a hematologist, oncologist, or other specialist with expertise in the diagnosis and management of the indication that is being treated

Dosage and Administration
Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

CLINICAL RATIONALE

Reblozyl (luspatercept-aamt) is indicated for the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions. It is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia. Reblozyl (luspatercept-aamt) is the first agent indicated for the treatment of beta thalassemia.

Efficacy
The efficacy of Reblozyl (luspatercept-aamt) for the treatment of anemia in adult patients with beta thalassemia was evaluated in the BELIEVE trial, which was a multicenter, randomized, double-blind, placebo-controlled trial (N = 336). Patients were included in the trial if they were adults diagnosed with beta thalassemia or hemoglobin E/beta thalassemia who require regular transfusions of 6 to 20 RBC units in the 24 weeks prior to randomization, with no transfusion-free period greater than 35 days. However, patients were excluded if they had had a deep vein thrombosis or stroke or recent use of erythropoietin-stimulating agents, immunosuppressants, or hydroxyurea. The median age of patients who were included was 30 years, with patients receiving a median of 6 RBC units/12 weeks. In addition, 57.8% of patients had previously undergone a splenectomy and 69% of patients were heterozygous for a gene mutation that results in no beta globin production. Patients were randomized in a 2:1 ratio to receive either Reblozyl (luspatercept-aamt) 1 mg/kg (which could be uptitrated to 1.25 mg/kg) subcutaneously every 3 weeks or placebo for at least 48 weeks. Of note, patients could also receive best supportive care, which included RBC transfusions and iron-chelating agents. The primary endpoint was the proportion of patients achieving RBC transfusion burden reduction (defined as ≥ 33% reduction from baseline) with a reduction of at least 2 RBC units from week 13 to week 24, and the secondary endpoint was the proportion of patients who had ≥ 50% reduction from baseline in RBC transfusion burden with a reduction of ≥ 2 RBC units at different time intervals. Of the patients who received Reblozyl, 21.4% (n=48) achieved the primary endpoint compared with 4.5% (n=5) of those who received placebo (risk difference 17.0; 95% CI 10.4, 23.6; p<0.0001). Of the patients who received Reblozyl, 19.6% (n=44) achieved a 33% reduction and 2 unit reduction in transfusion burden from week 37 to 48 compared to 3.6% (n=4) with placebo (risk difference 16.1; 95% CI 9.8, 22.4; p<0.0001). 7.6% (n=17) and 10.3% (n=23) of patients receiving Reblozyl experienced a 50% reduction in transfusion burden with a 2 unit reduction for 12 consecutive weeks compared to 1.8% (n=2) and 0.9% (n=1) from week 13 to 24 and from week 37 to week 48 respectively (p<0.05 for both comparisons). Most patients (80.4%) in the Reblozyl group who had a reduction in the transfusion burden of at least 33% from baseline during any 12-week interval had at least two distinct episodes of response, and 51.3% had at least four episodes of response. Similarly, 68.9% of the patients in the Reblozyl group who had at least a 50% reduction in the transfusion burden in any 12-week interval had at least two distinct responses and 33.3% had at least four responses. Reductions in the transfusion burden of at least 33% and at least 50% from baseline were estimated to avoid the need for approximately 7 and 8 red-cell units, respectively, per patient over 6 months. In terms of safety, treatment-emergent adverse events leading to dose delay or reduction were similar between the two treatment arms.

The efficacy and safety of Reblozyl (luspatercept-aamt) for the treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with

myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) was evaluated for this indication in the double-blind, placebo-controlled, phase III MEDALIST trial, which demonstrated that Reblozyl (luspatercept-aamt) significantly increased the proportion of patients who experienced RBC transfusion independence for at least 8 weeks. Among the 229 participants in the study who were refractory to an erythropoiesis-stimulating agent, 38% of those randomized to Reblozyl achieved transfusion independence for at least 8 weeks during the first 24 weeks of treatment versus 13% of those assigned to placebo (P<0.001). A higher percentage of patients in the Reblozyl group than in the placebo group met the key secondary end point (28% vs. 8% for weeks 1 through 24, and 33% vs. 12% for weeks 1 through 48; P<0.001 for both comparisons). The most common Reblozyl-associated adverse events included fatigue, diarrhea, asthenia, nausea, and dizziness. The incidence of adverse events decreased over time.

Reblozyl (luspatercept-aamt) is also listed in the National Comprehensive Cancer Network (NCCN) Drug and Biologics Compendium with a Category of Evidence and Consensus 2A for the very low to intermediate-risk myelodysplastic syndrome-associated anemia.

Safety

Reblozyl (luspatercept-aamt) is associated with thromboembolism and hypertension. In adult patients with beta thalassemia, thromboembolic events were reported in 3.6% of Reblozyl (luspatercept-aamt)-treated patients. Reported events included deep vein thrombosis, pulmonary embolism, portal vein thrombosis, and ischemic strokes. Hypertension was reported in 10.7% of patients who received Reblozyl (luspatercept-aamt). Across the clinical trials, the incidence of grade 3 to 4 hypertension ranged from 1.8% to 8.6% of patients.

The most common adverse events (i.e., ≥ 10%) reported in clinical trials were headache, bone pain, arthralgia, fatigue, abdominal pain, cough, diarrhea, dizziness, and liver function test abnormalities.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- J0896 Injection, luspatercept-aamt, 0.25 mg

REFERENCES

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- Cappellini MD, Viprakasit V, Taher A et al. The BELIEVE trial: results of a phase 3, randomized, double-blind, placebo-controlled study of luspatercept in adult beta-thalassemia patients who require regular red blood cell (RBC) transfusions. Blood. 2018; 132 (supplement 1): 163.
- Fenaux P, Platzbecker U, Mufti GJ et al. The MEDALIST trial: results of a phase 3, randomized, double-blind, placebo-controlled study of luspatercept to treat patients with very low-, low-, or intermediate-risk myelodysplastic syndromes (MDS) associated anemia with ring sideroblasts (RS) who require red blood cell (RBC) transfusions. 2018 December. URL: http://acceleronpharma.com/wp-content/uploads/2018/12/MEDALIST-ASH-Oral-Presentation-2-Dec-2018-FINAL-FOR-UPLOAD.pdf. Available from Internet. Accessed 2021 Septemberr 29.
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- Fenaux P., Platzbecker U, Mufti GJ, et.al. Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes. N Engl J Med 2020;382:140-51.
- Cappellini MD, Viprakasit V, A.T. Taher AT, et al. A Phase 3 Trial of Luspatercept in Patients with Transfusion-Dependent β-Thalassemia. N Engl J Med 2020;382:1219-31.

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POLICY HISTORY

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