PART B DRUG MEDICAL/PHARMACY			
	ASPIRE HEALTH	**Effective Date:** 12/15/2024	
	Reblozyl (luspatercept-aamt)	**Policy #** Reblozyl (luspatercept-aamt)	
		Last Review Date	**Applicable to:**
		08/27/2024	☑ Medicare Advantage ☐ Commercial ☐ Elevance Health HMO ☐ Blue Shield Trio
	Approver's Name & Title QI & UM Drug Subcommittee		

Aspire Health Plan (AHP) applies medical drug clinical criteria as a reference for medical policy information only. Federal and state laws or requirements, contract language, and Plan benefit may take precedence over the application of these clinical criteria. Please consult the applicable certificate or contract for benefit details. This policy is subject to revision at the discretion of the Plan and is therefore subject to change. Refer to the disclaimer section below for more information.

POLICY

This policy addresses the use of Reblozyl (luspatercept), an erythroid maturation agent, for the treatment of anemia in adults with beta thalassemia (β-thalassemia) and myelodysplastic syndrome (MDS) or myelodysplastic / myeloproliferative neoplasms (MDS / MPN) requiring regular red blood cell transfusions.

APPLICABLE HCPCS

J0896: Injection, luspatercept-aamt, 0.25 mg: 1 billable unit = 0.25 mg

Available as: Lyophilized powder for injection: 25 mg/vial, 75 mg/vial.

CLINICAL CRITERIA

The requested oncology drug may be authorized when ALL of the following have been met with *documentation.*Medical record documentation by the prescriber or administering physician should substantiate the medical necessity for the use of the requested drug by clearly indicating the relevant clinical signs and symptoms related to the medical condition for which this drug is being prescribed. The documentation must also include all prior treatment regimens and the member's response to each drug or therapy.*

I. INITIAL CRITERIA

A. PRESCRIBER SPECIALTY: Prescribed by, or in consultation with, a hematologist or other specialist with expertise in the diagnosis and management of myelodysplastic syndromes. *If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests.* **AND**

B. DIAGNOSIS: Member has ONE of the following diagnosis:

1. **Anemia in beta-thalassemia who require regular RBC transfusions**

   Documented diagnosis of β-thalassemia or Hemoglobin E / β-thalassemia (Excludes Sickle beta thalassemia (Hemoglobin S / β-thalassemia) or alpha thalassemia)

or

2. **Anemia in Myelodysplastic Syndrome (MDS)**

   Documented diagnosis of:

   a. MDS, **or**

   b. Myelodysplastic / myeloproliferative neoplasms (MDS / MPN) with ring sideroblasts and thrombocytosis

AND

C. DOCUMENTATION REQUIRED:

1. Member has *symptomatic* anemia evidenced by a pretreatment or *pretransfusion Hgb level less than or equal to 11 g/dL. Pretreatment or pretransfusion hemoglobin (Hgb) level required.

   *If an RBC transfusion occurred prior to dosing, the pretransfusion Hb must be considered for dosing purposes. Lab values are obtained within 7 days of the date of administration.

2. Member is considered transfusion dependent as evidenced by ONE of the following:

   a. Anemia with beta thalassemia: Requiring at least 6 red blood cell (RBC) units to be transfused in the previous 24 weeks; **or**

   b. Anemia of MDS or MDS / MPN: Member has been receiving regular RBC transfusions as defined by greater than or equal to 2 units per 8 weeks.

3. Member's current weight (within the last 30 days) must be provided at time of request for weight-based dosing.

AND

D. EXCLUSIONS

Reblozyl is not proven or medically necessary for the treatment of:

1. Alpha thalassemia;

2. Non-transfusion dependent β-thalassemia;

3. Sickle beta thalassemia [Hemoglobin S / β-thalassemia].

II. REAUTHORIZATION / CONTINUATION OF THERAPY CRITERIA

Applicable to AHP members who have previously received authorization of treatment for the requested drug product OR newly enrolled members established on the requested product within the previous year.

Reblozyl (luspatercept-aamt) may be authorized for continuation of therapy when initial criteria have been met **AND** there is documentation of beneficial response from previous course of treatment:

A. Member is currently receiving therapy with Reblozyl; **AND**

B. Reblozyl is being used to treat an FDA approved indication and meets the initial therapy criteria as stated above; **AND**

C. Positive response to therapy as evidenced by achieving or maintaining RBC transfusion burden reduction. NOTE: In the case of new starts, allowing for improvement after dose changes are being made is considered.

Clinical Reviewer: Response is defined as a decrease in transfusion burden. If there is no response after 9 weeks of treatment (3 doses) at the maximum dose level (1.75 mg/kg every 3 weeks), Reblozyl should be discontinued. (Prescribing Information, 2023).

D. Prescriber attests to, or clinical reviewer has found, no evidence of intolerable adverse effects or unacceptable toxicity from Reblozyl (examples of unacceptable toxicity include thromboembolic events, severe hypertension, extramedullary hematopoietic masses in patients with beta thalassemia, etc.).

STEP THERAPY

Step therapy criteria do not apply for members who are currently being treated with the requested medications. Step therapy is only applied for members that are new to therapy (have not received the requested drug in the last 365 days.

No Step Therapy Required.

DOSAGE AND AUTHORIZATION TIMEFRAMES

1. Recommended Dosage: Reblozyl dosing is in accordance with the FDA approved labeling.
    a. Anemia due to beta thalassemia: Max dose 1.25 mg/kg once every 3 weeks
    b. Anemia due to myelodysplastic syndromes: Max dose 1.75 mg/kg once every 3 weeks
2. Quantity Limit
    a. Reblozyl 25 mg single-dose vial: 2 vials every 21 days
    b. Reblozyl 75 mg single-dose vial: 2 vials every 21 days
3. Authorization Period
    a. Initial Authorization: Coverage will be provided initially for 9 weeks (3 initial doses) and may be renewed annually thereafter.
    b. Continuation of Authorization: May authorize for up to 12 months.

    Discontinue therapy if there is no decrease in transfusion burden after 9 weeks of treatment (administration of 3 doses) at the maximum dose (Prescribing Information).

4. Reauthorization: Reassess every 6 months to determine the need for continued therapy; therapy should be discontinued if the member does not respond to therapy, as defined in the Continuation of Therapy section.

5. Authorization is limited to the submitted request that was reviewed. Any modifications to the diagnosis or prescribed indication necessitates a new prior authorization request.

DRUG INFORMATION

PHARMACOLOGIC CATEGORY: Activin Receptor Ligand Trap; Hematopoietic Agent

PRODUCTS: Reblozyl

ROUTE OF ADMINISTRATION: Subcutaneous; Reblozyl should be reconstituted and administered by a healthcare professional.

FDA-APPROVED INDICATIONS

Beta Thalassemia: Anemia in adult patients with beta thalassemia who require regular blood cell transfusions.

Myelodysplastic Syndromes Associated Anemia: Anemia without previous erythropoiesis stimulating agent (ESA) use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes who may require regular blood cell transfusions

Myelodysplastic syndromes with ring sideroblasts (MDS-RS) or myelodysplastic / myeloproliferative neoplasm with ring sideroblasts (MDS/MPN-RST) and thrombocytosis associated anemia: Anemia failing an ESA and requiring 2 or more RBC units over eight 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).

LIMITATION: Reblozyl is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

COMPENDIAL APPROVED (OFF-LABELED) USES: None

CONTRAINDICATIONS: There are no contraindications listed in the manufacturer's US labeling.

MONITORING PARAMETERS:

Assess and review Hb results prior to each administration; if an RBC transfusion occurred prior to dosing, use pretransfusion Hb for dose evaluation.

The American Society of Clinical Oncology hepatitis B virus (HBV) screening and management provisional clinical opinion (ASCO [Hwang 2020]) recommends HBV screening with hepatitis B surface antigen, hepatitis B core antibody, total Ig or IgG, and antibody to hepatitis B surface antigen prior to beginning (or at the beginning of) systemic anticancer therapy; do not delay treatment for screening/results. Detection of chronic or past HBV infection requires a risk assessment to determine antiviral prophylaxis requirements, monitoring, and follow-up.

CLINICAL SUMMARY / APPENDIX

Luspatercept-aamt, an erythroid maturation agent, is a recombinant fusion protein that binds several endogenous TGF-β superfamily ligands, thereby diminishing Smad2/3 signaling. In models of β-thalassemia and MDS, luspatercept-aamt decreased abnormally elevated Smad2/3 signaling, and improved hematology parameters associated with ineffective erythropoiesis in mice. Luspatercept-aamt promoted erythroid maturation through differentiation and increasing the percentage of late-stage erythroid

precursors (normoblasts) in the bone marrow of mice and increased erythroid precursors in humans, thereby increasing erythropoiesis (BMS, 2023).

The prescribing information includes the following warnings and precautions for Reblozyl: thrombosis/thromboembolism in patients with beta thalassemia, hypertension, and embryo-fetal toxicity. The most common adverse reactions (10% or more) include fatigue, headache, musculoskeletal pain, arthralgia, dizziness/vertigo, nausea, diarrhea, cough, abdominal pain, dyspnea, COVID-19, edema peripheral, hypertension, and hypersensitivity.

FDA approval of Reblozyl (luspatercept-aamt) for treatment of anemia in adults with beta thalassemia who require regular blood transfusions (RBC) was based on the BELIEVE trial (NCT02604433). BELIEVE is a multicenter, randomized, double-blind, placebo-controlled trial in which (n = 336) patients with beta thalassemia (including beta^{+} thalassemia, beta^{0} thalassemia, and hemoglobin E/beta thalassemia; beta thalassemia with mutation and/or multiplication of alpha globin was also allowed) requiring regular red blood cell transfusions (6-20 RBC units per 24 weeks) with no transfusion-free period greater than 35 days during that period were randomized 2:1 to Reblozyl (n = 224) or placebo (n = 112). The BELIEVE trial excluded patients with hemoglobin S/beta-thalassemia or alpha-thalassemia or who had major organ damage (liver disease, heart disease, lung disease, renal insufficiency). Patients with recent deep vein thrombosis or stroke or recent use of ESA, immunosuppressant, or hydroxyurea therapy were also excluded.

The primary endpoint of the proportion of patients achieving RBC transfusion burden reduction from baseline of at least 33%, with a reduction of at least 2 units from week 13 to week 24, was achieved in 21.4% of Reblozyl-treated patients compared to 4.5% of placebo-treated patients. Furthermore, the proportion of patients achieving at least a 50% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks was higher with Reblozyl (7.6% vs 18%). Patients were included in the BELIEVE trial if they required regular RBC transfusions defined as 6 to 20 RBC units per 24 weeks, with no transfusion-free period greater than 35 days during that period.

Reblozyl for the treatment of anemia in myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis was FDA approved based on a double-blind, placebo-controlled, phase 3 trial (MEDALIST).The MEDALIST trial evaluated the safety and efficacy of Reblozyl compared to placebo in patients with Revised International Prognostic Scoring System very low-, low-, or intermediate-risk disease with chronic anemia and who are refractory to, intolerant of, or ineligible for treatment with an erythropoiesis-stimulating agent, ring sideroblast–positive and require frequent RBC transfusions. The primary endpoint was red blood cell transfusion independence (RBC-TI) for at least 8 weeks between Week 1 and Week 24. Secondary endpoints included RBC-TI for at least 12 weeks between Week 1 and Week 24, and between Week 1 and Week 48 and achievement of modified hematologic improvement- erythroid response for any consecutive 56-day period (assessed using International Working Group 2006 criteria). Results demonstrated that 37.9% of Reblozyl-treated patients met the primary endpoint compared to 13.2% of placebo-treated patients. Results also favored Reblozyl for the secondary endpoints as well (RBC-TI for at least 12 weeks; 28.1% vs 7.9%, mHIE response; 52.9% vs 11.8%).

Reblozyl for use in ESA treatment naïve patients was approved based on the results of the COMMANDS trial, a phase III, open-label, randomized controlled study of 356 patients with myelodysplastic syndromes of very low risk, low risk, or intermediate risk. Subjects had not experienced prior treatment with ESAs and required regular RBC transfusions of at least 2 – 6 packed RBC units per 8 weeks for greater than or equal to 8 weeks immediately before randomization. Patients must not have MDS associated with del 5q cytogenetic abnormality or secondary MDS known to have arisen as the result of chemical injury or treatment with chemotherapy and/or radiation for other diseases. The primary endpoint was RBC transfusion independence for at least 12 weeks with a concurrent mean hgb increase of at least 1.5 g/dL during weeks 1 – 24. Results showed 58.5% of patients treated with Reblozyl vs. 31.2% of patients treated with epoetin alfa achieved the primary endpoint (p-value < 0.0001).

National Comprehensive Cancer Network (NCCN)

Luspatercept-aamt (is recommended by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) as a first-line treatment option for symptomatic anemia in lower-risk MDS.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines©) response criteria for myelodysplastic syndromes (V1.2023) defined as a lack of ≥ 1.5 g/dL rise in Hb and/or lack of a decrease in RBC transfusion requirement by 6-8 weeks of treatment.

REFERENCES

Government Agency

Centers for Medicare and Medicaid Services (CMS). Medicare coverage database: National coverage determination (NCD) (search: no NCD identified; no applicable LCD for MAC identified; search terms: Reblozyl; luspatercept-aamt). Available from CMS.

Prescribing Information

Reblozyl [prescribing information]. Summit, NJ: Celgene Corporation; May 2024.

Peer-reviewed Literature, Guidelines, and Consensus

1. Cappellini MD, Viprakasit V, Taher AT, et al; BELIEVE Investigators. A phase 3 trial of luspatercept in patients with transfusion-dependent β-thalassemia. N Engl J Med. 2020;382(13):1219-1231. doi:10.1056/NEJMoa1910182 [PubMed 32212518]
2. Farmakis D, et al. 2021 Thalassaemia International Federation Guidelines for the Management of Transfusion-dependent Thalassemia. Hemasphere. 2022 Aug;6(8):e732.
3. Hwang JP, Feld JJ, Hammond SP, et al. Hepatitis B virus screening and management for patients with cancer prior to therapy: ASCO provisional clinical opinion update. J Clin Oncol. 2020;38(31):3698-3715. doi:10.1200/JCO.20.01757 [PubMed 32716741]
4. Platzbecker U, Della Porta MG, Santini V, et al. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial. Lancet. 2023;402(10399):373-385. doi:10.1016/S0140-6736(23)00874-7 [PubMed 37311468]
5. NCCN Drugs and Biologics Compendium (NCCN Compendium®). Accessed August 2024.
6. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Accessed August 2024.

IMPORTANT REMINDER

This Medicare Part B Step Therapy Medical Necessity Guideline is provided for informational purposes only and neither constitutes nor replaces professional medical advice. Physicians, hospitals, and other providers are expected to administer or use drugs/biologicals in the most effective and clinically appropriate manner. Treating physicians and other health care providers is solely responsible for all medical care decisions. In accordance with the member's Evidence of Coverage (EOC), every benefit plan has its own coverage provisions, limitations, and exclusions. In the event of a conflict between this policy and the member's EOC, the member's EOC provisions will take precedence.

Aspire Health Plan (AHP) adheres to Medicare guidelines, including National Coverage Determination (NCD), Local Coverage Determinations (LCDs), Local Coverage Articles (LCAs), and other relevant Medicare manuals established by CMS. Compliance with these guidelines is required when applicable. Refer to the CMS website at http://www.cms.hhs.gov. For the most up-to-date Medicare policies and coverage, please search the Medicare Coverage Database. All LCDS are the same for each state within a Jurisdiction. Medicare Part B Administrative Contractor (MAC) for CA [Jurisdiction E (1)]: Active LCDs - JE Part B – Noridian (noridianmedicare.com). In the event of a discrepancy between this policy and the Medicare NCD or LCD, the Medicare NCD/LCD will govern.

This policy is utilized by AHP to determine coverage in the absence of applicable CMS Medicare guidelines. Please refer to the links provided in the References section below to access the Medicare source materials that were used for developing this resource document. This document does not serve as a substitute for the official Medicare source materials that provide detailed information on Medicare coverage requirements. In the event of a conflict between this document and Medicare source materials, the Medicare source materials will take precedence.

The inclusion of a code in this policy does not imply that the health service it describes is covered or not covered. Benefit coverage for health services is determined by the member-specific plan document and applicable laws that may mandate coverage for a particular service. Inclusion of a code does not imply or guarantee reimbursement or payment of a claim. Other Policies and Standards may also apply. Providers are expected to retain or have access to the necessary documentation when requested to support coverage.

The use of physician samples or manufacturer discounts does not guarantee later coverage under the provisions of the medical certificate and/or pharmacy benefit. All criteria must be met to obtain coverage of the listed drug product.

POLICY HISTORY

Committee Date	Summary of Changes
08/27/2024	New Policy (effective 12/15/2024)