Clinical Policy: Luspatercept-aamt (Reblozyl)

Reference Number: LA.PHAR.450
Effective Date:
Last Review Date: 03.21
Line of Business: Medicaid **Revision Log**

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Luspatercept-aamt (Reblozyl®) is an erythroid maturation agent.

FDA Approved Indication(s)

Reblozyl is indicated for the treatment of anemia in adult patients with:

- **Beta thalassemia who require regular red blood cell (RBC) transfusions**
- **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) failing an erythropoiesis stimulating agent and requiring 2 or more RBC units over 8 weeks**

Limitation(s) of use: Not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

Policy/Criteria

Prior authorization is required. Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of Louisiana Healthcare Connections that Reblozyl is medically necessary when the following criteria are met:

I. Initial Approval Criteria

A. Transfusion Dependent Beta Thalassemia (must meet all):

1. **Diagnosis of transfusion dependent thalassemia (TDT) with one of the following genotypes (a or b):**
   a. **Beta thalassemia;**
   b. **Hemoglobin E/beta thalassemia;**
2. **Prescribed by or in consultation with a hematologist;**
3. **Age ≥ 18 years;**
4. **Total volume of transfusions exceeds 6 RBC units (*see Appendix D*) within the last 6 months;**
5. **No transfusion-free period ≥ 35 days within the last 6 months;**
6. **Documentation of baseline transfusion burden within the last 6 months;**
7. **Dose does not exceed 1 mg/kg every 3 weeks.**

Approval duration: 2 months (2 doses)

B. Myelodysplastic Syndromes (must meet all):
1. **Diagnosis of MDS-RS or MDS/MPN-RS-T that meets one of the following classifications (a, b, or c) (*see Appendix E*):**
   a. **Very low, low, or intermediate risk as classified by IPSS-R;**
   b. **Low/intermediate-1 risk as classified by IPSS;**
   c. **Very low, low, or intermediate risk as classified by WPSS;**
2. **Prescribed by or in consultation with a hematologist or oncologist;**
3. **Age ≥ 18 years;**
4. **Member requires ≥ 2 RBC units per 8 weeks documented for at least the last 16 weeks;**
5. **Failure of an 8 week trial of an erythropoiesis-stimulating agent (ESA) used in combination with a granulocyte colony stimulating factor (G-CSF) (*see Appendix B*), unless one of the following applies (a or b):**
   a. **Clinically significant adverse effects are experienced or all are contraindicated;**
   b. **Documentation of current serum erythropoietin > 500 mU/mL;**
6. **Member has one of the following (a or b):**
   a. **Ring sideroblast ≥ 15% of erythroid precursors in bone marrow;**
   b. **Ring sideroblast ≥ 5% if SF3B1 mutation is present;**
7. **Member does not have del(5q) cytogenetic abnormality;**
8. **Request meets one of the following (a or b):***
   a. **Dose does not exceed 1 mg/kg every 3 weeks;**
   b. **Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).**

Prescribed regimen must be FDA-approved or recommended by NCCN

Approval duration: 2 months (2 doses)

C. Other diagnoses/indications
1. **Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): LA.PMN.53 for Medicaid**

II. Continued Therapy

A. Transfusion Dependent Beta Thalassemia (must meet all):
1. **Currently receiving medication via Louisiana Healthcare Connections benefit or member has previously met all initial approval criteria;**
2. **Member meets one of the following (a or b):**
   a) **Member is responding positively to therapy as evidenced by at least a 33% reduction in transfusion burden from baseline;**
   b) **Request is for a dose increase;**
3. **If request is for a dose increase, new dose does not exceed (a or b):**
   a) **1 mg/kg every 3 weeks;**
   b) **1.25 mg/kg every 3 weeks, and documentation supports inadequate response to 1 mg/kg dosing.**

Approval duration: 6 months

B. Myelodysplastic Syndromes (must meet all):
1. **Currently receiving medication via Louisiana Healthcare Connections benefit, or documentation supports that member is currently receiving Reblozyl for a covered indication and has received this medication for at least 30 days;**
2. **Member meets one of the following (a or b):**
   a. **Member is responding positively to therapy as evidenced by a decreased transfusion burden;**
   b. **Request is for a dose increase;**
3. **If request is for a dose increase, request meets one of the following (a, b, c, or d):***
   a. **New dose does not exceed 1 mg/kg every 3 weeks;**
   b. **New dose does not exceed 1.33 mg/kg every 3 weeks, and documentation supports lack of transfusion independence after 2 consecutive doses at 1 mg/kg dosing;**
   c. **New dose does not exceed 1.75 mg/kg every 3 weeks, and documentation supports lack of transfusion independence after 2 consecutive doses at 1.33 mg/kg dosing;**
   d. **New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).**

Prescribed regimen must be FDA-approved or recommended by NCCN

Approval duration: 6 months (*2 months [2 doses] if request is for a dose increase*)

C. Other diagnoses/indications (must meet 1 or 2):
1. **Currently receiving medication via Louisiana Healthcare Connections benefit and documentation supports positive response to therapy.**
   Approval duration: Duration of request or 6 months (whichever is less); or
2. **Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): LA.PMN.53 for Medicaid**

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy –LA.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ESA: erythropoiesis-stimulating agent
FDA: Food and Drug Administration
G-CSF: granulocyte colony stimulating factor
Hb: hemoglobin
IPSS: International Prognostic Scoring System
IPSS-R: International Prognostic Scoring System - Revised
MDS: myelodysplastic syndromes
MDS-RS: myelodysplastic syndromes with ring sideroblasts
MDS/MPN-RS-T: myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis
TDT: transfusion dependent thalassemia

WPSS: WHO Classification-based Scoring System

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Procrit®, Epogen®, Retacrit® (epoetin alfa)*	MDS: 40,000 to 60,000 SC units 1 to 2 times per week every week	Target hemoglobin up to 12 g/dL
Aranesp® (darbepoetin alfa)*	MDS: 150 to 300 mcg SC every other week	Target hemoglobin up to 12 g/dL
Neupogen®, Nivestym™, Granix®, Zarxio® (filgrastim)	MDS: 1 to 2 mcg/kg SC 1 to 2 times per week	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
Off-label

Appendix C: Contraindications/Boxed Warnings

None reported

Appendix D: General Information

- **Conversion of RBC units from mL: 1 RBC unit in this criteria refers to a quantity of packed RBCs approximately 200-350 mL.**
  - **Sites who use transfusion bags within this range, or ≥ 350 mL, the conversion in units should be done by dividing the volume transfused to the patient by 350 mL,**
  - **Sites who use transfusion bags < 200 mL, the conversion in units should be done by dividing the volume transfused to the patient by 200 mL.**
- **MDS and serum erythropoietin level**
  - **According to NCCN, for the treatment of symptomatic anemia in MDS with ring sideroblasts ≥ 15% (or ring sideroblasts ≥ 5% with an SF3B1 mutation), a trial of either recombinant human erythropoetin or darbepoetin in combination with a G-CSF is recommended when serum erythropoietin level is ≤ 500 mU/mL. If serum erythropoietin level is > 500 mU/mL for this indication, Reblozyl is recommended.**
- **MDS and combination treatment with ESA + G-CSF**
  - **This is the recommended combination per NCCN for the treatment of symptomatic anemia in MDS with ring sideroblasts ≥ 15% (or ring sideroblasts ≥ 5% with an SF3B1 mutation). Evidence suggests that G-CSF has synergistic erythropoietic activity when used in combination with an ESA and markedly enhances the erythroid response rates due to enhanced survival of red cell precursors. This is particularly evident for patients with greater than or equal to**

15% ring sideroblasts in the marrow and serum erythropoetin level ≤ 500 mU/mL.

- **MDS/MPN-RS-T indication**
  - **During regulatory review of the MEDALIST data by the FDA, a post-hoc re-classification of patients using the WHO 2016 criteria was conducted to assess the efficacy and safety of Reblozyl in patients with MDS/MPN-RS-T. Among the 229 patients enrolled in MEDALIST, 23 patients were found to have a diagnosis of MDS/MPN-RS-T following this re-classification. In these patients with MDS/MPN-RS-T, a greater proportion of patients treated with Reblozyl (64.3%; n = 9/14) achieved the primary endpoint of transfusion independence for at least 8 weeks during weeks 1-24 compared to placebo (22.2%; n = 2/9).**

Appendix E: MDS Risk Classification

- **International Prognostic Scoring System - Revised (IPSS-R) classification:**

Risk Category	Risk Score
Very low	≤ 1.5
Low	< 1.5 – 3
Intermediate	< 3 – 4.5
High	< 4.5 – 6
Very high	> 6

- **International Prognostic Scoring System (IPSS) classification:**

Risk Category	Risk Score
Low	0
Intermediate-1	0.5 – 1
Intermediate-2	1.5 – 2
High	2.5 – 3.5

- **WHO Classification-based Prognostic Scoring System (WPSS) classification:**

Risk Category	Risk Score
Very low	0
Low	1
Intermediate	2
High	3 – 4
Very high	5 – 6

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Transfusion-dependent beta thalassemia	1 mg/kg SC once every 3 weeks Evaluation hemoglobin (Hgb) prior to next planned administration. If pre-dose Hgb ≥ 11.5 g/dL and Hgb level is not influenced by recent transfusion, delay dosing until the Hgb is ≤ 11 g/dL.	1.25 mg/kg

Indication	Dosing Regimen	Maximum Dose
	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 to max dose of 1.25 mg/kg.	
MDS	Initial: 1 mg/kg SC once every 3 weeks Dose increases for insufficient response after initiation of treatment: 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 SC every 3 weeks. If a patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1.33 mg /kg dose level, increase the dose to a maximum of 1.75 mg/kg SC every 3 weeks. 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	1.75 mg/kg

VI. Product Availability

Single dose vials for injection: 25 mg, 75 mg

VII. References

1. Reblozyl Prescribing Information. Cambridge, MA: Acceleron Pharma, Inc. April 2020. Available at: www.reblozyl.com. Accessed October 27, 2020.
2. Cappellini MD, Vipralasit 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 [Oral]. Oral presented at: 60th American Society of Hematology Annual Meeting and Exposition (ASH); December 1-4, 2018; San Diego, CA.
3. Cappellini MD, Cohen A, Porter J, et al. Guidelines for the management of transfusion dependent thalassemia (TDT) 3rd Edition. Thalassemia International Federation (2014):20.
4. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Engl J Med*. 2020;382:140-151.
5. National Comprehensive Cancer Network. Myelodysplastic Syndromes Version 1.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf. Accessed October 27, 2020.

6. **Patnaik MM, Tefferi A. Refractory anemia with ring sideroblasts (RARS) and RARS with thrombocytosis (RARS-T) – "2019 Update on Diagnosis, Risk-stratification, and Management." *Am J Hematol.* 2019;94(4): 475–488.**
7. **Reblozyl Data on File. Use of Reblozyl (luspatercept-aamt) in patients with myelodysplastic/myeloproliferative neoplasm with ring siderblasts and thrombocytosis. Bristol Meyers Squibb. 2020 May.**

ICD-10-CM Diagnosis Codes that Support Coverage Criteria
The following is a list of diagnosis codes that support coverage for the applicable covered procedure code(s).

ICD-10-CM Code	Description
D56.1*	Beta thalassemia

Reviews, Revisions, and Approvals	Date
Converted corporate to local policy	03.2021

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable LHCC administrative policies and procedures.

This clinical policy is effective as of the date determined by LHCC. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. LHCC retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom LHCC has no control or right of control. Providers are not agents or employees of LHCC.