Clinical Policy: Luspatercept-aamt (Reblozyl)

Reference Number: PA.CP.PHAR.450
Effective Date: 07/2020
Last Review Date: 01/2024

Revision Log

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 (MDS) who may require regular red blood cell (RBC) transfusions without previous erythropoiesis stimulating agent use (ESA-naïve)
- 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
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 PA Health & Wellness® 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 at least 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 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).

Approval duration: 3 months (3 doses)

B. Myelodysplastic Syndromes (must meet all)**:**
1. Diagnosis of MDS, 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 is dependent on RBC transfusions;
5. If member has MDS with ring sideroblasts < 15% (or ring sideroblasts < 5% with SF3B1 mutation), failure of an erythropoiesis-stimulating agent (ESA) (*see Appendix B and D*), 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 does not have del(5q) cytogenetic abnormality;
7. 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).

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): PA.CP.PMN.53

II. Continued Therapy

A. Transfusion Dependent Beta Thalassemia (must meet all)**:**
1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01);
2. Member meets one of the following (a or b):
   a. For members who have received ≥ 9 weeks of treatment (≥ 3 doses): 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 and member has not yet received 9 weeks of treatment (3 doses) at the maximum dose of 1.25 mg/kg;
3. If request is for a dose increase, new dose does not exceed (a, b or c):
   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;
   c. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration: 6 months

B. Myelodysplastic Syndromes (must meet all)**:**
1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01);
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).

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 PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01);
   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): PA.CP.PMN.53

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 policies – PA.CP.PMN.53

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 not be a formulary agent for all relevant lines of business and 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

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/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).
- MDS COMMANDS trial subgroup analysis
  - The primary outcome of red blood cell transfusion independence for 12 weeks with a mean hemoglobin increase ≥ 1.5 g/dL was seen in 59% of the luspatercept group and 31% of the epoetin alfa group. The primary outcome was seen more often in MDS patients with positive ring sideroblasts treated with luspatercept compared to ESA (70% met in the luspatercept group compared to 31% met in the ESA group in SFB1 positive patients, and 42% met in the luspatercept group compared to 32% met in the ESA group with SFB1 negative patients). There was no difference seen (i.e., similar treatment benefit) between luspatercept and ESA use in patients with negative ring sideroblasts.
- NCCN guidelines for MDS
  - Current NCCN guidelines for Myelodysplastic Syndromes (version 2.2023) recommend luspatercept as first-line therapy for MDS with ring sideroblasts ≥ 15%

(or ring sideroblasts ≥ 5% with an SF3B1 mutation). ESA is recommended as the preferred treatment for MDS with ring sideroblasts < 15% (or ring sideroblasts < 5% with SF3B1 mutation).

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 (TDT)	1 mg/kg SC once every 3 weeks 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. If a patient does not achieve a reduction in RBC transfusion burden after 3 consecutive doses (9 weeks) at 1.25 mg/kg, discontinue treatment.	1.25 mg/kg
MDS	Initial: 1 mg/kg SC once every 3 weeks Dose increases for insufficient response after initiation of treatment:	1.75 mg/kg

Indication	Dosing Regimen	Maximum Dose
	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 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. August 2023. Available at: www.reblozyl.com. Accessed November 4, 2023.
2. Uwe Platzbecker, Della G, 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. *The Lancet*. 2023;402(10399):373-385. doi:https://doi.org/10.1016/s0140-6736(23)00874-7
3. 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.
4. Cappellini MD, Farmakis D, Porter J, et al. 2021 Guidelines for the management of transfusion dependent thalassemia (TDT) 4th Edition. Thalassemia International Federation (2021). Available at: https://thalassaemia.org.cy/wp-content/uploads/2021/06/GUIDELINE-4th-DIGITAL-BY-PAGE.pdf.
5. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Engl J Med*. 2020;382:140-151.
6. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed November 4, 2023.
7. National Comprehensive Cancer Network. Myelodysplastic Syndromes Version 2.2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf. Accessed November 4, 2023.
8. 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.

9. 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

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J0896	Injection, luspatercept-aamt, 0.25 mg

Reviews, Revisions, and Approvals	Date
Policy created.	07/2020
1Q 2021 annual review: no significant changes; references reviewed and updated.	01/2021
1Q 2022 annual review: coding information added; references reviewed and updated.	01/2022
1Q 2023 annual review: for TDT continued therapy, clarified criterion that positive response to therapy as evidenced by at least a 33% reduction in transfusion burden from baseline is required after 9 weeks of treatment (3 doses) at the maximum dose unless the request is for a dose increase prior to 9 weeks of treatment; per NCCN Compendium, removed requirement for combination w/G-CSF for MDS indication; references reviewed and updated.	01/2023
1Q 2024 annual review: RT4: added new indication for MDS treatment in ESA naïve patients; removed MDS transfusion requirement for ≥ 2 RBC units per 8 weeks; revised ESA redirection to apply only to MDS with ring sideroblasts < 15% (or ring sideroblasts < 5% with SF3B1 mutation) per NCCN; references reviewed and updated.	01/2024