Medical Policy

Utilization Management and Clinical Medical Policy

Policy Name:	Policy Number:	Scope:	Origination Date:	Effective Date:
Luspatercept (Reblozyl®)	**MP-RX-FP-76-23**	☒ **MMM MA** ☒ **MMM MultiHealth**	**11/30/2023**	**7/22/2026**
			Last Review Date: **7/22/2026**	**Frequently Revision:** **Annual**

Service Category:

- ☐ Anesthesia
- ☐ Surgery
- ☐ Radiology Procedures
- ☐ Pathology and Laboratory Procedures
- ☐ Medicine Services and Procedures
- ☐ Evaluation and Management Services
- ☐ DME/Prosthetics or Supplies
- ☒ Other: Part B Drugs

Service Description:

This document addresses the use of Luspatercept (Reblozyl®), an erythroid maturation agent, approved by the Food and Drug Administration (FDA) for the treatment of anemia in adults with beta thalassemia (β- thalassemia) and myelodysplastic syndrome (MDS) or myelodysplastic/myeloproliferative neoplasms (MDS/MPN) who require regular red blood cell transfusions.

Background Information:

Beta thalassemia is an inherited blood disorder caused by mutations in the beta-globin (HBB) gene. These mutations result in defective red blood cells (RBC) that have little or no hemoglobin, the iron-containing protein that is responsible for oxygen transport. People who inherit just one HBB gene mutation (thalassemia minor or thalassemia trait) are usually asymptomatic. People who inherit two defective genes develop beta thalassemia with moderate anemia that can be managed with intermittent RBC transfusions (beta thalassemia intermedia) or severe anemia that is transfusion-dependent (beta thalassemia major, also called Cooley's anemia). Hemoglobin E beta thalassemia (E/β-thalassemia) and hemoglobin S beta thalassemia (S/β-thalassemia, also known as sickle beta thalassemia) are related disorders that occur when beta thalassemia is combined with another gene mutation or abnormality.

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal myeloid neoplasms classified using current morphologic, cytogenetic, and molecular features. Some patients present with overlapping clinical features of myelodysplastic and myeloproliferative neoplasms (MDS/MPN overlap neoplasms), which are rarer and more difficult to define epidemiologically. Key clinical features of MDS/MPN-RS-T include anemia and thrombocytosis.

Reblozyl is a first in class drug and classified as an erythroid maturation agent. While Reblozyl may reduce the transfusion burden, it does not completely eliminate the need for RBC transfusions. The goal of treatment in these patients focuses on symptom control, quality of life improvement, reduction or elimination of RBC transfusions and toxicity minimization.

Per labeling, Reblozyl is to be administered by a healthcare professional as a subcutaneous injection. At this time, Reblozyl is not recommended for pediatric use due to findings from toxicity studies in juvenile animals.

According to NCCN, Reblozyl (luspatercept-aamt) is recommended for the management of anemia in several hematologic malignancies. In myelofibrosis, NCCN includes luspatercept as a Category 2A option for myelofibrosis-associated anemia in patients with ongoing symptomatic splenomegaly and/or constitutional symptoms, to be given in combination with ruxolitinib; in patients without splenomegaly or constitutional symptoms; and in patients with splenomegaly and constitutional symptoms well controlled on a current JAK inhibitor, to be given in combination with a JAK inhibitor. In lower-risk myelodysplastic syndromes (MDS)

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associated with symptomatic anemia and no del(5q), NCCN recommends luspatercept as a Category 2A option for disease with ring sideroblasts <15% (or <5% with an SF3B1 mutation) and serum erythropoietin ≤500 mU/mL, either as a single agent, particularly when serum erythropoietin is >200 mU/mL, or following no response to or relapse after an erythropoiesis-stimulating agent. NCCN also recommends luspatercept as a Category 1 option for lower-risk MDS with symptomatic anemia and no del(5q), with ring sideroblasts ≥15% (or ≥5% with an SF3B1 mutation), either as a preferred single agent or following no response to or relapse after imetelstat. In addition, NCCN considers luspatercept a Category 2A single-agent option for treatment of anemia in MDS/MPN overlap neoplasms with SF3B1 mutation and thrombocytosis.

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

Approved Indications

A. Anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions.
B. Anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions.
C. Anemia failing an erythropoiesis stimulating agent and requiring 2 or more RBC 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).

Other Uses

A. See Background Information above.

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Medical Necessity Guidelines:

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Luspatercept (Reblozyl®)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

β-thalassemia:

Initial requests for Reblozyl (luspatercept) for β-thalassemia may be approved if the following criteria are met:

i. Individual is 18 years of age or older; **AND**
ii. Individual has a diagnosis of beta thalassemia or hemoglobin E beta (E/β)-thalassemia; **AND**
iii. Documentation is provided that individual required regular red blood cell transfusions at initiation, defined as *both* of the following (NCT02604433):
    A. Individual received six to twenty (6-20) RBC units in the last 24 weeks; **AND**
    B. Individual had no transfusion-free period greater than 35 days in the last 24 weeks; **AND**
iv. Individual has a baseline hemoglobin (Hgb) level less than or equal to 11 g/dL.

Myelofibrosis-associated Anemia:

Initial requests for Relobzyl (luspatercept) for myelofibrosis-associated anemia may be approved if the following criteria are met:

i. Individual has a diagnosis of myelofibrosis-associated anemia (NCCN 2A); **AND**
ii. Individual meets one of the following:
    A. Individual has ongoing symptomatic splenomegaly and/or constitutional symptoms and is using in combination with ruxolitinib; **OR**
    B. Individual has no splenomegaly or constitutional symptoms; **OR**
    C. Individual has splenomegaly and constitutional symptoms well controlled on current JAK inhibitor, to be given in combination with a JAK inhibitor.

MDS-RS, MDS/MPN-RS-T, MDS or MDS/MPN-T-SF3B1:

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Initial requests for Reblozyl (luspatercept) for MDS-RS (myelodysplastic syndromes with ring sideroblasts), MDS/MPN-RS-T (myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis), MDS (myelodysplastic syndromes), or MDS/MPN-T-SF3B1 (myelodysplastic/myeloproliferative neoplasm with thrombocytosis and SF3B1 Mutation) may be approved if the following criteria are met:

i. Individual is 18 years of age or older; **AND**
ii. Individual has one of the following (A, B, C, D or E):
   A. Documentation is provided that individual has a diagnosis of very low to intermediate risk myelodysplastic syndromes (MDS) (Label); **AND**
      1. Individual is ESA-naïve; **AND**
      2. Documentation is provided that individual may require regular red blood cell (RBC) transfusions;

   OR

   B. Documentation is provided that individual has a diagnosis of 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) (Label); **AND**
      1. Individual has failed an erythropoiesis-stimulating agent (ESA); **AND**
      2. Documentation is provided that individual requires 2 or more RBC units over 8 weeks;

   OR

   C. Documentation is provided that individual has a diagnosis of lower-risk myelodysplastic syndromes (MDS) associated with symptomatic anemia and no del(5q), with or without other cytogenetic abnormalities, with ring sideroblasts less than 15% (or ring sideroblasts less than 5% with an SF3B1 mutation) (NCCN 2A); **AND**
      1. Serum erythropoietin (EPO) level is less than or equal to 500 mU/mL; **AND**
      2. Individual meets one of the following criteria:
         i. Serum EPO level is greater than 200 mU/mL; **OR**
         ii. Individual has had no response to or relapse after an erythropoiesis-stimulating agent (ESA) alone (despite adequate iron stores);

   OR

   D. Documentation is provided that individual has a diagnosis of lower-risk myelodysplastic syndromes (MDS) associated with symptomatic anemia and no del(5q), with or without other cytogenetic abnormalities, with ring sideroblasts greater than or equal to 15% (or ring sideroblasts greater than or equal to 5% with an SF3B1 mutation) (NCCN 1); **AND**
      1. Individual is using as a single agent; **OR**

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2. Individual has had no response to or relapse after imetelstat;

OR

E. Documentation is provided that individual has a diagnosis of MDS/MPN with SF3B1 mutation and thrombocytosis (NCCN 2A); **AND**
   1. Luspatercept is used as a single agent; **AND**
   2. Documentation is provided that disease is SF3B1 mutation positive; **AND**
   3. Thrombocytosis is present (defined as platelets greater than or equal to 450 x 10^9/L).

iii. Documentation is provided that individual has a baseline hemoglobin (Hgb) level 11 g/dL or less.

B. Criteria For Continuation of Therapy

β-thalassemia:

Continuation requests for Reblozyl (luspatercept) for β-thalassemia may be approved if the following criteria are met:

i. Documentation is provided that individual demonstrates continued need for treatment and has confirmation of response to treatment as evidenced by a decrease in transfusion burden from baseline; **AND**
ii. Hemoglobin level is not greater than 11 g/dL.

Myelofibrosis-associated Anemia:

Continuation requests for Reblozyl (luspatercept) for myelofibrosis-associated anemia may be approved if the following criteria are met:

i. Individual demonstrates continued need for treatment and has confirmation of response to treatment as evidenced by a decrease in transfusion burden from baseline.

MDS-RS, MDS/MPN-RS-T, MDS or MDS/MPN-T-SF3B1:

Continuation requests for Reblozyl (luspatercept) for MDS-RS, MDS/MPN-RS-T, MDS, or MDS/MPN-T- SF3B1 may be approved if the following criteria are met:

i. Documentation is provided that individual demonstrates continued need for treatment and has confirmation of response to treatment as evidenced by a decrease in transfusion burden from baseline; **AND**
ii. Hemoglobin level is not greater than 11.0 g/dL

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C. Authorization Duration

i. Initial Approval Duration: 6 months
ii. Reauthorization Approval Duration: 12 months

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

β-thalassemia

Reblozyl (luspatercept) for β-thalassemia may not be approved for the following:

i. Individual has a diagnosis of sickle beta thalassemia (S/β-thalassemia); **OR**
ii. Individual has a diagnosis of alpha (α)-thalassemia; **OR**
iii. Individual has a platelet count greater than 1000 x 109/L; **OR**
iv. History of deep vein thrombosis (DVT) or stroke within the last 24 weeks; **OR**
v. Use beyond 9 weeks of treatment (i.e., administration of consecutive 3 doses) in the absence of response (response defined as decrease in transfusion burden from baseline) at maximum dose level (i.e., 1.25 mg/kg every 3 weeks).

Myelofibrosis-associated Anemia

Requests for Reblozyl (luspatercept) may not be approved when the above criteria are not met and for all other indications.

MDS-RS, MDS/MPN-RS-T, MDS or MDS/MPN-T-SF3B1

Reblozyl (luspatercept) for MDS-RS, MDS/MPN-RS-T, MDS, or MDS/MPN-T-SF3B1 may not be approved for the following:

i. Individual has had an inadequate response to ESAs or has MDS/MPN-T-SF3B1 and one of the following:
   A. Individual has unresolved iron deficiency (defined as serum ferritin less than or equal to 15µg/L, or transferrin saturation less than or equal to 20%) (NCT02631070); **OR**
   B. Use beyond 9 weeks of treatment (i.e., administration of consecutive 3 doses) in the absence of response (response defined as decrease in transfusion burden from baseline) at maximum dose level (i.e., 1.75 mg/kg every 3 weeks);

OR

ii. Individual is ESA-naïve and one of the following (Platzbecker, et al.);

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A. Individual has unresolved iron deficiency (defined as serum ferritin less than 100 µg/L); **OR**

B. Individuals has uncontrolled hypertension.

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Limits or Restrictions:

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Drug	Recommended Dosage	Limit
Reblozyl (luspatercept) 25mg, 75mg vials	***β-thalassemia*** • Starting Dose: 1 mg/kg sc every 3 weeks. • Dose could be increased if patient has no reduction in RBC transfusion burden to a maximum of 1.25 mg/kg. ***Myelodysplastic Syndromes*** • Starting Dose: 1 mg/kg sc every 3 weeks. - For ESA-naïve MDS, increase dose to maintain patient's hemoglobin concentrations - within the target range of 10 g/dL to 12 g/dL to a maximum of 1.75 mg/kg. (2.2) - For ESA-refractory or intolerant MDS, increase dose if patient is not RBC transfusion- - free to a maximum of 1.75 mg/kg.	1.75 mg/kg per 3 weeks
Exceptions		
• Assess and review hemoglobin results prior to each administration of Reblozyl. - Dose should be titrated based on response. - See Prescribing Information for dose recommendations.		

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Codes Information:

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

ICD-10 Diagnostic Codes:

Codes	Description
C93.10	Chronic myelomonocytic leukemia, not having achieved remission
C94.4 – C94.42	Acute panmyelosis with myelofibrosis
C94.6	Myelodysplastic disease, not elsewhere classified
D46.0 – D46.9	Myelodysplastic syndromes
D47.1	Chronic myeloproliferative disease
D47.4	Osteomyelofibrosis
D56.1	Beta Thalassemia
D56.5	Hemoglobin E-Beta thalassemia
D75.81	Myelofibrosis

HCPCS Codes:

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

Reference Information:

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2. Beta Thalassemia. National Organization for Rare Disorders. Available at https://rarediseases.org/rare-diseases/thalassemiamajor/.
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4. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2022. URL: http://www.clinicalpharmacology.com. Updated periodically.
5. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm.
6. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
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8. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2026; Updated periodically.
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10. Myeloproliferative Neoplasms—Health Professional Version. National Cancer Institute. Available at https://www.cancer.gov/types/myeloproliferative.
11. NCCN Clinical Practice Guidelines in Oncology™. © 2025 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on May 20, 2026.
    a. Myelodysplastic Syndromes. Version 3.2026. Revised January 12, 2026.
    b. Myeloproliferative Neoplasms. Version 1.2026. Revised January 22, 2026.
12. NCT02604433. ClinicalTrials.gov. U.S. National Library of Medicine. Available at https://clinicaltrials.gov/ct2/show/NCT02604433?term=nct02604433&draw=2&rank=1.
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14. Orazi A, et al. Myelodysplastic Syndromes/Myeloproliferative Neoplasms, Chapter 5, in Swerdlow S. Campo E, Harris NL, et al (Eds). World Health Organization Classification and Tumours of Haematopoietic and Lymphoid Tissues, Revised 4th edition. Volume 2. IARC Press, Lyon, 2017, 82- 96.
15. Thalassemia. Cooley's Anemia Foundation. Available at https://www.thalassemia.org/learn-about-thalassemia/about-thalassemia/. Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

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Policy History:

Type of Review	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review	Updated Background Information to align with current NCCN recommendations for Reblozyl, including additional uses in myelofibrosis-associated anemia, lower-risk MDS, and MDS/MPN with SF3B1 mutation and thrombocytosis. Updated Initial Approval criteria to incorporate current FDA-labeled indications and NCCN-supported uses, clarify ESA-naïve and ESA-refractory pathways, and refine criteria for ring sideroblast and SF3B1 mutation subgroups. Coding Reviewed: Consolidated codes C46.0-C46.9 into one range and updated description. Consolidated codes C94.40-C94.42 into one range and updated description. Wording and formatting changes. Updated reference information and incorporated new policy template.	7/13/2026	7/22/2026
Annual Review	Wording and formatting changes. Updated clinical criteria for Myelofibrosis-associated Anemia and added: "Individual has splenomegaly and constitutional symptoms well controlled on current JAK inhibitor, to be given in combination with a JAK inhibitor" (Label, NCCN 2A). Added new clinical criteria for diagnosis of very low to intermediate risk MDS-RS lesser than 15% (or ring sideroblasts <5% with an SF3B1 mutation) (Label, NCCN 2A). Updated clinical criteria for diagnosis of very low to intermediate risk MDS-RS greater than or equal to 15% (or ring sideroblasts greater than or equal to 5% with an SF3B1 mutation) (Label, NCCN 1): deleted serum erythropoietin (EPO) level requirements and added "Use as a single agent; OR Following no response to or relapse after Imetelstat." Updated NCCN guidelines reference information. Coding Reviewed: No change.	8/25/2025	9/8/2025
Annual Review	Wording and formatting changes. Added new diagnosis for anemia for ESA-naiive patients. Updated MDS-RS criteria for del(5q), added MDS to continuation therapy, added myelofibrosis-associated anemia, added MDS/MPN-T-SF3B1. added criteria for MDS in ESA-naïve. Added dosage and exceptions to the quantity limits table. Coding Reviewed: Added ICD-10-CM D46.C. Coding Reviewed: Add ICD10-CM C93.10, C94.40, C94.41, C94.42, C94.6, D46.0, D46.1, D46.20, D46.21, D46.22, D46.A, D46.B, D46.4, D47.1, D47.4, D75.81. Changed wording for D46.9 Myelodysplasia NOS to Myelodysplastic syndrome, unspecified.	3/20/2025	4/2/2025
Policy Inception	Elevance Health's Medical Policy adoption.	N/A	11/30/2023