Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Luspatercept (Reblozyl®)	MP-RX-FP-76-23	☒ MMM MA ☒ MMM Multihealth

Service Category

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

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

The FDA approved indications for Reblozyl include:

- Anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions.
- 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.
- 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).

The National Comprehensive Cancer Network (NCCN) gives a 2A category recommendation for the use of Reblozyl in MDS-RS with ring sideroblasts greater than or equal to 15% (or ring sideroblasts 5% to 14% with an SF3B1 mutation).

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 conditions that can occur when the body no longer makes enough

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healthy, normal blood cells in the bone marrow. This leads to a low number of one or more types of blood cells. A shortage of red blood cells (anemia) is the most common finding. MDS is also known as a form of blood cancer. Several types of MDS exist, based on how many types of blood cells are affected along with other factors. About one-third of MDS patients can progress to a rapidly growing cancer of bone marrow cells called acute myeloid leukemia (AML). The World Health Organization (WHO) provides classifications for myeloid neoplasms and acute leukemias. It classifies MDS into 6 main types, primarily based on how the cells in the bone marrow look under the microscope. MDSRS is not a common subtype of MDS and rarely turns into AML. Some patients present with clinical features that overlap between MDS and myeloproliferative neoplasms (MPN), which have their own WHO classifications. The mixed diagnosis indicates that the patient has abnormal blood cells combined with proliferation of cells. It is rarer than MDS and estimated incidence is more difficult to define. Key clinical features of MDS/MPN-RS-T include anemia and elevated platelet counts.

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.

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: N/A

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Applicable Codes

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.

HCPCS	Description
J0896	Injection, luspatercept-aamt, 0.25 mg (Reblozyl) (Effective 7/1/2020)

ICD-10	Description
C93.10	Chronic myelomonocytic leukemia, not having achieved remission
C94.40	Acute panmyelosis with myelofibrosis, not having achieved remission
C94.41	Acute panmyelosis with myelofibrosis, in remission
C94.42	Acute panmyelosis with myelofibrosis, in relapse
C94.6	Myelodysplastic disease, not elsewhere classified
D46.0	Refractory anemia without ring sideroblasts, so stated
D46.1	Refractory anemia with ring sideroblasts
D46.20	Refractory anemia with excess of blasts, unspecified
D46.21	Refractory anemia with excess of blasts 1
D46.22	Refractory anemia with excess of blasts 2
D46.A	Refractory cytopenia with multilineage dysplasia
D46.B	Refractory cytopenia with multilineage dysplasia and ring sideroblasts
D46.C	Myelodysplastic syndrome with isolated del(5q) chromosomal abnormality
D46.4	Refractory anemia, unspecified
D46.Z	Other myelodysplastic syndromes
D46.9	Myelodysplastic syndrome, unspecified
D47.1	Chronic myeloproliferative disease
D47.4	Osteomyelofibrosis
D56.1	Beta Thalassemia
D56.5	Hemoglobin E-Beta thalassemia
D75.81	Myelofibrosis

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.

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

Luspatercept (Reblozyl®)

A. Criteria For Initial Approval

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. II. Individual has symptomatic splenomegaly and is using in combination with ruxolitinib;
OR
iii. III. Individual has constitutional or no symptomatic splenomegaly.

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

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, or D):
   A. Documentation is provided that individual has a diagnosis very low to intermediate risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) greater than or equal to 15% (or ring sideroblasts 5% to 14% with an SF3B1 mutation) (Label, NCCN 2A); **AND**
      1. Individual meets *one* of the following criteria:

a. Serum erythropoietin (EPO) level of greater than 500 mU/mL; **OR**

b. Serum EPO level of less than or equal to 500 mU/mL following no response to combination treatment with erythropoiesis-stimulating agent (ESA), **OR**

c. Disease does not have del(5q) abnormalities;

OR

B. Individual has a diagnosis of myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) with *all* of the following:

1. Ring sideroblasts greater than or equal to 15% (WHO 2017), and documentation is provided; **AND**

2. Thrombocytosis (defined as platelets greater than or equal to 450 x109/L) (WHO 2017);

OR

C. Individual has a diagnosis MDS/MPN-T-SF3B1 with *all* of the following (NCCN 2A):

1. Thrombocytosis (defined as platelets greater than or equal to 450 x109/L) (WHO 2017); **AND**

2. Documentation is provided that disease is SF3B1 Mutation positive;

OR

D. Individual has a diagnosis of MDS; **AND**

1. Individual is ESA-naïve; **AND**

2. Documentation is provided that individual has serum EPO level less than 500 U/L;

AND

iii. Documentation is provided that individual has required regular red blood cell transfusions of two (2) or more RBC units over eight (8) weeks in the last 16 weeks; **AND**

iv. Individual has a baseline hemoglobin (Hgb) level less than or equal to 11 g/dL.

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.

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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.

C. 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 10^9/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

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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.);

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

B. Individuals has uncontrolled hypertension.

D. Authorization Duration

i. Initial Request: 6 months

ii. Continuation Requests: 12 months

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	Dosage	Limit
Reblozyl (luspatercept) 25mg, 75mg vials	Starting Dose: 1 mg/kg sc every 3 weeks	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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Reference Information

1. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016; 127-2391-2405.
2. Beta Thalassemia. National Organization for Rare Disorders. Available at https://rarediseases.org/rare-diseases/thalassemiamajor/.
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2022. URL: http://www.clinicalpharmacology.com. Updated periodically.
4. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm.
5. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
6. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes. N Engl J Med. 2020 Jan 9;382(2):140-151. doi: 10.1056/NEJMoa1908892.
7. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2022; Updated periodically.
8. Myelodysplastic Syndromes. American Cancer Society. Available at https://www.cancer.org/cancer/myelodysplastic-syndrome.html.
9. Myeloproliferative Neoplasms—Health Professional Version. National Cancer Institute. Available at https://www.cancer.gov/types/myeloproliferative.
10. NCCN Clinical Practice Guidelines in Oncology™. © 2022 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on June 25, 2022. a. Myelodysplastic Syndromes. Version 3.2022. Revised January 13, 2022.
11. NCT02604433. ClinicalTrials.gov. U.S. National Library of Medicine. Available at https://clinicaltrials.gov/ct2/show/NCT02604433?term=nct02604433&draw=2&rank=1.
12. NCT02631070. ClinicalTrials.gov. U.S. National Library of Medicine. Available at https://clinicaltrials.gov/ct2/show/NCT02631070?term=nct02631070&draw=2&rank=1.
13. 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.
14. 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

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review 8/16/2024	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 8/18/2023	Elevance Health's Medical Policy adoption.	N/A	11/30/2023