Reblozyl® (luspatercept-aamt)
(Subcutaneous)

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I. Length of Authorization [1,12]

- Beta Thalassemia: Coverage will be provided initially for 15 weeks (5 initial doses) and may be renewed annually thereafter.
- Anemia Due to Myelodysplastic Syndromes: Coverage will be provided initially for 21 weeks (7 initial doses) and may be renewed every 6 months thereafter.
- Anemia Due to Myeloproliferative Neoplasms (MPN) – Myelofibrosis: Coverage will be provided initially for 24 weeks (8 initial doses) and may be renewed every 6 months thereafter.

Coverage and policy application may be contingent on federal or state laws or regulations. In the event of a conflict between this policy and applicable federal or state laws or regulations, state law should apply.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Reblozyl 25 mg single-dose vial: 2 vials every 21 days
- Reblozyl 75 mg single-dose vial: 2 vials every 21 days

B. Max Units (per dose and over time) [HCPCS Unit]:

- Beta Thalassemia: 600 billable units every 21 days
- Myelodysplastic Syndromes and Myeloproliferative Neoplasms: 800 billable units every 21 days

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age, unless otherwise specified**; **AND**

Universal Criteria [1]

- Females of reproductive potential have a negative pregnancy test prior to start of therapy and will use an effective method of contraception during treatment and for at least 3 months after treatment; **AND**

- Patient has not had a deep vein thrombosis or a thrombotic stroke which required medical intervention within 6 months prior to therapy; **AND**
- Other causes of anemia (e.g., hemolysis, bleeding, recent major surgery, vitamin deficiency, etc.) have been ruled out; **AND**
- Reblozyl is not being used as a substitute for RBC transfusions in patients requiring immediate correction of anemia; **AND**
- Patient has a pre-dose Hemoglobin (Hb) < 11.5 g/dL***** obtained within 7 days of the date of administration (unless otherwise specified); **AND**

Note: *If Hb is ≥ 11.5 g/dL, the dose must be delayed until the Hb is ≤ 11 g/dL. If an RBC transfusion occurred prior to dosing, the pretransfusion Hb must be considered for dosing purposes.*

Beta Thalassemia † Φ [1,4,8]

- Patient has a documented diagnosis of beta thalassemia (excludes isolated alpha-thalassemia and hemoglobin S/ß-thalassemia variants) as outlined by the following:
  - Patient diagnosis is confirmed by *HBB* sequence gene analysis showing biallelic pathogenic variants; **OR**
  - Patient has severe microcytic hypochromic anemia, absence of iron deficiency, anisopoikilocytosis with nucleated red blood cells on peripheral blood smear, and hemoglobin analysis that reveals decreased amounts or complete absence of hemoglobin A (HbA) and increased HbA_2 with or without increased amounts of hemoglobin F (HbF); **AND**
- Patient is red blood cell (RBC) transfusion dependent as defined by requiring 6-20 RBC units per 24 weeks; **AND**
- Patient does not have major end organ damage**§**, defined as any of the following:
  - Liver disease with an ALT > 3x the ULN or history of evidence of cirrhosis; **OR**
  - Heart disease, heart failure NYHA classification 3 or higher, or significant arrhythmia requiring treatment, or recent myocardial infarction within 6 months of treatment; **OR**
  - Lung disease, including pulmonary fibrosis or pulmonary hypertension which are clinically significant i.e., ≥ Grade 3; **OR**
  - Creatinine clearance < 60 mL/min

§*Requests for patients deemed to have any major end organ damage will be reviewed on a case-by-case basis.*

**********Requests for patients <18 years will be considered on a case-by-case basis for those with high transfusion burden and symptomatic iron overload, history of alloimmunization, or history of transfusion reactions*

Anemia Due to Myelodysplastic Syndromes (MDS) † ‡ Φ [1,5-7]

- Used as a single agent; **AND**
  - Used for the treatment of symptomatic anemia with Myelodysplastic Syndromes (MDS); **AND**
    - Patient has lower risk disease (IPSS-R very low, low, or intermediate-risk); **AND**

- Patient has ring sideroblasts <15% (or ring sideroblasts <5% with an SF3B1 mutation); **AND**
  - Patient has serum erythropoietin ≤ 500 mU/mL; **AND**
    - Used as first-line treatment (i.e. erythropoiesis stimulating agent-naïve); **OR**
    - Used following no response* to first-line treatment with a single agent erythropoiesis stimulating agent (ESA) (despite adequate iron stores); **OR**
- Patient has ring sideroblasts ≥15% (or ring sideroblasts ≥5% with an SF3B1 mutation); **OR**

o Used for the treatment of anemia with Myelodysplastic Syndromes/Myeloproliferative Neoplasm Overlap (MDS/MPN) and thrombocytosis with an SF3B1 mutation; **OR**

o Used for the treatment of anemia with MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T); **AND**

- Patient has ring sideroblasts ≥15% and a wild-type SF3B1 mutation; **OR**
- Patient has ring sideroblasts ≥ 5% (but < 15%) with a SF3B1 mutation; **AND**
  - Patient has required 2 or more red blood cell units over an 8-week timeframe
    - Patient is erythropoiesis stimulating agent (ESA) ineligible (i.e. serum erythropoietin > 200 mU/mL and not previously treated with ESA); **OR**
    - Patient has had an inadequate response to prior treatment with an ESA (i.e. epoetin alpha ≥ 40,000 units/week for at least 8 doses or darbepoetin alpha ≥ 500 mcg every 3 weeks for at least 4 doses or equivalent); **OR**
    - Patient has a documented contraindication or intolerance to the use of an ESA

***Note:** No response defined as a lack of ≥1.5 gm/dL rise in hemoglobin OR lack of a decrease in RBC transfusion requirement within 6-8 weeks when treated with ESAs.*

Anemia Due to Myeloproliferative Neoplasms (MPN) – Myelofibrosis ‡ [11]

- Patient has anemia with symptomatic splenomegaly and/or constitutional symptoms; **AND**
  - Used in combination with ruxolitinib; **OR**
- Patient has anemia with no symptomatic splenomegaly and/or constitutional symptoms; **AND**
  - Used as a single agent

† FDA Approved Indications; ‡ Compendia Recommended Indication(s); **Φ** Orphan Drug

IV. Renewal Criteria [1,5-8,12]

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Patient will not receive doses < 21 days apart; **AND**

- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: thromboembolic events, severe hypertension, extramedullary hematopoietic masses in patients with beta thalassemia, etc.; **AND**

Beta Thalassemia

- Patient is experiencing disease response as evidenced by a decrease in the number of RBC transfusions from baseline; **OR**
- For new starts: Patient has not achieved a reduction in RBC transfusion burden after at least 2 consecutive, initial (1 mg/kg) doses (6 weeks) and requires a dose increase to 1.25 mg/kg; **OR**
- Patient experienced a response followed by a lack/loss of response and requires a dose increase to 1.25 mg/kg (from 1 mg/kg)

Anemia Due to Myelodysplastic Syndromes (MDS)

- Patient is experiencing disease response as evidenced by a decrease in the number of RBC transfusions from baseline; **OR**
- For new starts: Patient has not achieved a reduction in RBC transfusion burden after at least 2 consecutive, initial (1 mg/kg) doses (6 weeks) and requires a dose increase to 1.33 mg/kg; **OR**
- Patient has not achieved a reduction in RBC transfusion burden after at least 2 consecutive, 1.33 mg/kg doses (6 weeks) and requires a dose increase to 1.75 mg/kg; **OR**
- Patient experienced a response followed by a lack/loss of response and requires a dose increase by one dose level from the level in which response was lost (not to exceed a dose of 1.75 mg/kg)

Anemia Due to Myeloproliferative Neoplasms (MPN) – Myelofibrosis

- Patient is experiencing disease response from baseline (e.g. decrease in the number of RBC transfusions from baseline, ≥ 1.5 g/dL hemoglobin increase without RBC transfusions from baseline, reduction in anemia-related fatigue symptoms, etc.); **OR**
- For new starts: Patient has not achieved disease response after at least 2 consecutive, initial (1 mg/kg or 1.33 mg/kg) doses (6 weeks) and requires a dose increase by one dose level from the initial level (1.33 mg/kg or 1.75mg/kg); **OR**
- Patient experienced a response followed by a lack/loss of response and requires a dose increase by one dose level from the level in which response was lost (not to exceed a dose of 1.75 mg/kg)

V. Dosage/Administration [1,12]

Indication	Dose
Beta Thalassemia	The recommended starting dose is 1 mg/kg once every 3 weeks by subcutaneous injection. – Dose increases for insufficient response: 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 the Reblozyl dose to 1.25 mg/kg. Do not increase the dose beyond the maximum dose of 1.25 mg/kg. Discontinue Reblozyl 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.
Anemia Due to Myelodysplastic Syndromes (MDS)	The recommended starting dose is 1 mg/kg once every 3 weeks by subcutaneous injection. – Dose increases for insufficient response: 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 Reblozyl dose to 1.33 mg/kg. 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 Reblozyl dose to 1.75 mg/kg. Do not increase the dose more frequently than every 6 weeks (2 doses) or beyond the maximum dose of 1.75 mg/kg. Discontinue Reblozyl 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. ***Note:*** *If, upon a dose modification (i.e., dose reduction), a patient loses response (i.e. requires a transfusion) or Hgb concentration drops by 1 g/dL or more in 3 weeks in the absence of transfusion, increase the dose by one dose level. Wait a minimum of 6 weeks between dose increases.*
Anemia Due to Myeloproliferative Neoplasms (MPN) – Myelofibrosis	The recommended starting dose is 1 mg/kg to 1.33 mg/kg once every 3 weeks by subcutaneous injection. – Dose increases for insufficient response: If a patient is not having beneficial response after at least 2 consecutive doses (6 weeks) at the current dose level, increase the Reblozyl dose to 1.33 mg/kg (in those on 1 mg/kg) or 1.75mg/kg (in those on 1.33 mg/kg). Do not increase the dose more frequently than every 6 weeks (2 doses) or beyond the maximum dose of 1.75 mg/kg.
– Dose decreases/interruptions: In the absence of transfusion, if Hb increase is >2 g/dL within 3 weeks or if the pre-dose Hb is ≥11.5 g/dL, reduce the dose or interrupt treatment until the Hgb is ≤11 g/dL. – Reblozyl should be reconstituted and administered by a healthcare professional.	

VI. Billing Code/Availability Information

HCPCS Code:

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

NDC(s):

- Reblozyl 25 mg single-dose vial: 59572-0711-xx
- Reblozyl 75 mg single-dose vial: 59572-0775-xx

VII. References

1. Reblozyl [package insert]. Summit, NJ; Celgene, Inc: August 2023. Accessed March 2024.

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10. Della Porta M, Platzbecker U, Santini V, et al; The Commands Trial: A Phase 3 Study of the Efficacy and Safety of Luspatercept Versus Epoetin Alfa for the Treatment of Anemia Due to IPSS-R Very Low-, Low-, or Intermediate-Risk MDS in Erythropoiesis Stimulating Agent-Naive Patients Who Require RBC Transfusions. Blood 2020; 136 (Supplement 1): 1–2. doi: https://doi.org/10.1182/blood-2020-140284.
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12. Gerds AT, Harrison C, Kiladjian JJ, et al. Safety and efficacy of luspatercept for the treatment of anemia in patients with myelofibrosis: Results from the ACE-536-MF-001 study [abstract]. J Clin Oncol 2023;41:7016-7016.
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Appendix 1 – Covered Diagnosis Codes

ICD-10	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
D46.4	Refractory anemia, unspecified
D46.9	Myelodysplastic syndrome, unspecified
D46.A	Refractory cytopenia with multilineage dysplasia
D46.B	Refractory cytopenia with multilineage dysplasia and ring sideroblasts
D46.Z	Other myelodysplastic syndromes
D47.1	Chronic myeloproliferative disease
D47.4	Osteomyelofibrosis
D56.1	Beta thalassemia
D75.81	Myelofibrosis

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used

to search for NCD, LCD, or LCA documents: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications, including any preceding information, may be applied at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC