Reblozyl® (luspatercept-aamt)
(Subcutaneous)

Document Number: IC-0503

Last Review Date: 04/04/2022
Date of Origin: 12/03/2019
Dates Reviewed: 12/2019, 04/2020, 07/2020, 10/2020, 04/2021, 04/2022

I. Length of Authorization [1]

- Beta Thalassemia: Coverage will be provided initially for 15 weeks (5 initial doses) and may be renewed annually thereafter.
- Myelodysplastic Syndrome: Coverage will be provided initially for 21 weeks (7 initial doses) and may be renewed every 6 months thereafter.

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 Syndrome: 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 baseline Hemoglobin (Hb) < 11.5 g/dL (if Hb is 11.5 g/dL or higher, the dose must be delayed until the Hb is 11 g/dL or less) ***(Note:** If an RBC transfusion occurred prior to dosing, the pretransfusion Hgb must be considered for dosing purposes. Lab values are obtained within 7 days of the date of administration);* **AND**

Beta Thalassemia † Φ [1,4,8]

- Patient has a documented diagnosis of beta thalassemia (excludes 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, anisopoikilocytosis with nucleated red blood cells on peripheral blood smear, and hemoglobin analysis that reveals decreased amounts or complete absence of hemoglobin A and increased amounts of hemoglobin F; **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*

Myelodysplastic Syndrome † ‡ Φ [1,5-7]

- Patient has required 2 or more red blood cell units over an 8 week timeframe; **AND**
- Patient has a diagnosis of one of the following:
  - Myelodysplastic syndrome with ring sideroblasts (MDS-RS); **OR**
  - Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T); **AND**
- Patient has lower risk disease (IPSS-R very low, low, or intermediate-risk); **AND**

- Patient has symptomatic anemia with ring sideroblasts ≥15% (or ring sideroblasts ≥5% with an SF3B1 mutation); **AND**
    - Serum erythropoietin >200 mU/mL; **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**
    - Patient has a documented contraindication or intolerance to the use of an erythropoiesis-stimulating agent

† FDA approved indications; ‡ Compendia Recommended Indication(s); Φ Orphan Drug

IV. Renewal Criteria [1,5-8]

- 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, etc.; **AND**

Beta Thalassemia

- Patient is experiencing disease response as evidenced by a decrease in the number of RBC transfusions; **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)

Myelodysplastic Syndrome

- Patient is experiencing disease response as evidenced by a decrease in the number of RBC transfusions; **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)

*Note: 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.

V. Dosage/Administration [1]

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.
Myelodysplastic Syndrome	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 starting dose, increase the Reblozyl dose to 1.75 mg/kg. Do not increase the dose beyond the maximum dose of 1.75 mg/kg. *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.*
– If a planned administration of Reblozyl is delayed or missed, administer Reblozyl as soon as possible and continue dosing as prescribed, with at least 3 weeks between doses. – Assess and review hemoglobin (Hgb) results prior to each administration. If an RBC transfusion occurred prior to dosing, the pretransfusion Hgb must be considered for dosing purposes. – Dose decreases/interruptions: If Hgb increase is >2 g/dL or the pre-dose Hgb is ≥11.5 g/dL and the Hgb level is not influenced by recent transfusion, 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:

- 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: October 2021. Accessed March 2022.
2. Cappellini MD, Viprakasit 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. Abstract #163. Presented at the 2018 ASH Annual Meeting, December 1, 2018; San Diego, CA.

3. Galanello R and Origa R. Beta-thalassemia. *Orphanet J Rare Dis.* 2010 May 21;5:11. Available at: https://ojrd.biomedcentral.com/articles/10.1186/1750-1172-5-11. Accessed November 2019.
4. Origa R. Beta-Thalassemia. 2000 Sep 28 [Updated 2021 Feb 4]. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1426/. Accessed March 2022.
5. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) luspatercept-aamt. National Comprehensive Cancer Network, 2022. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2022.
6. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Myelodysplastic Syndromes. Version 3.2022. National Comprehensive Cancer Network, 2022. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2022.
7. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes. January 9, 2020. N Engl J Med 2020; 382:140-151 DOI: 10.1056/NEJMoa1908892.
8. Cappellini MD, Viprakasit V, Taher AT, et al. A Phase 3 Trial of Luspatercept in Patients With Transfusion-Dependent ß-Thalassemia. N Engl J Med, 382 (13), 1219-1231; 2020 Mar 26. PMID: 32212518. DOI: 10.1056/NEJMoa1910182

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C93.10	Chronic myelomonocytic leukemia not having achieved remission
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

D56.1	Beta thalassemia

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

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 Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications may be covered 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, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
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