Reblozyl® (luspatercept-aamt)
(Subcutaneous)

Document Number: IC-0503

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I. Length of Authorization[1,7]

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

- 600 billable units every 21 days

III. Initial Approval Criteria[1]

Coverage is provided in the following conditions:

Universal Criteria

- 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 at least for 3 months after treatment; **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; **AND**

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

- 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

Beta Thalassemia †, Φ [1,4,8]

- Patient must be 18 years or older*; **AND**
- 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 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**

***Note:** Request 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 † [1,5-7]

- Patient must be 18 years or older; **AND**
- 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 very low to intermediate risk disease defined as any one of the following:
    - IPSS-R: very low, low, or intermediate; **OR**
    - IPSS: low/intermediate-1; **OR**

- WPSS: very low, low, or intermediate; **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 erythropoiesis-stimulating agent (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 the following: thromboembolic events, severe hypertension, etc. ; **AND**
- Other causative factors *(e.g., a bleeding event)* have been ruled out; **AND**
- Reblozyl is not being used as a substitute for RBC transfusions in patients requiring immediate correction of anemia; **AND**
- 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

- 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 to 1.33 mg/kg (from 1 mg/kg)

***Note**: Discontinue therapy if the patient does not experience a decrease in transfusion burden after 15 weeks of treatment (administration of 6 doses) at the maximum dose level or if unacceptable toxicity occurs at any time.

V. Dosage/Administration[1,7,8]

Indication	Dose
Beta Thalassemia	The recommended starting dose is 1 mg/kg once every 3 weeks by subcutaneous injection.
– 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. – 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. – Dose increases: 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. – Continuation: If a patient experienced a response followed by a lack of or lost response, initiate a search for causative factors (e.g., a bleeding event). If typical causes for a lack or loss of hematologic response are excluded, follow dosing recommendations for management of patients with an insufficient response to therapy. – Discontinuation: Discontinue therapy 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. – Reblozyl should be reconstituted and administered by a healthcare professional.	
Myelodysplastic Syndrome	The recommended starting dose is 1 mg/kg once every 3 weeks by subcutaneous injection.
– 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 increases: 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. – Continuation: 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. If, upon 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. – Discontinuation: Discontinue therapy 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.	

–	Reblozyl should be reconstituted and administered by a healthcare professional.

VI. Billing Code/Availability Information

HCPCS Code:

- J3590 – Unclassified biologic
- C9399 – Unclassified drug or biologic
- J0896 – Injection, luspatercept-aamt, 0.25 mg: 1 billable unit= 0.25 mg (*effective 07/01/2020*)

NDC:

- Reblozyl 25 mg single-dose vial: 59572-0711-xx
- Reblozyl 75 mg single-dose vial: 59353-0775-xx

VII. References

1. Reblozyl [package insert]. Summit, NJ; Celgene, Inc: April 2020. Accessed June 2020.
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 2018 Jan 25]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1426/. Accessed November 2019.
5. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) luspatercept-aamt. National Comprehensive Cancer Network, 2020. 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 April 2020.
6. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Myelodysplastic Syndromes. Version 2.2020. National Comprehensive Cancer Network, 2020. 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 2020.

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 β-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: http://www.cms.gov/medicare-coverage-database/search/advanced-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.

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
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