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Effective Date: 8/12/2021

Reblozyl® (luspatercept-aamt)

FDA approval: November 8, 2019

HCPCS: J0896

Benefit: Medical

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

- A. Coverage of the requested drug is provided when all the following are met:
 - a. FDA approved age
 - b. Diagnosis of anemia in adult patients with beta-thalassemia who require regular red blood cell (RBC) transfusions
 - i. Prescribed by a hematologist
 - ii. Genetic testing confirming diagnosis of β -thalassemia
 - iii. Must not have hemoglobin S/ β -thalassemia or α -thalassemia
 - iv. Must be considered transfusion dependent with a history of at least 100 mL/kg/year of packed red blood cells (pRBC) in the previous two years OR be managed under standard thalassemia guidelines with ≥ 8 transfusions of pRBCs per year in the previous two years
 - v. Have not received prior treatment with any gene therapy (such as Lentiglobin) or are being considered for treatment with any other gene therapy for beta-thalassemia
 - c. Diagnosis of myelodysplastic syndrome (MDS)
 - i. Prescribed by or in consultation with a hematologist or oncologist
 - ii. Must have anemia requiring at least 2 units of red blood cells over 8 weeks
 - iii. World Health Organization (WHO)/French American British (FAB) classification that meets IPSS-R classification of very low, low, or intermediate risk disease
 - iv. Ring sideroblast $\geq 15\%$ of erythroid precursors in bone marrow OR $\geq 5\%$ if the SF3B1 mutation is present
 - v. Less than 5% blasts in the bone marrow
 - vi. Must be refractory, intolerant, or ineligible to receive erythropoietin stimulating agents (ESA) defined as at least one of the following:
 - 1. Documentation of non-response or response that is no longer maintained to prior ESA-containing regimen of either recombinant human erythropoietin $> 40,000$ IU/week for at least 8 doses or equivalent OR darbepoetin alpha > 500 μg every 3 weeks for at least 4 doses or equivalent

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2. Documentation of discontinuation of prior ESA-containing regimen at any time after introduction due to intolerance or an adverse event
 3. A low chance of response to an ESA based on endogenous serum erythropoietin level > 200 U/L for subjects not previously treated with ESA's
- vii. Must not have used any prior therapy with disease-modifying agents for underlying MDS disease (examples: immune-modulatory drug, hypomethylating agents, or immunosuppressive therapy)
 - viii. Must not have MDS associated with del 5q cytogenetic abnormality
 - ix. Must not have secondary MDS known to have arisen as the result of chemical injury or treatment with chemotherapy and/or radiation for other diseases

B. Quantity Limitations, Authorization Period and Renewal Criteria

- a. Quantity Limits: Align with FDA recommended dosing
- b. Initial Authorization Period: 6 months
- c. Renewal Criteria: Continuation of therapy is provided based on documentation of clinical response demonstrated through a reduction in transfusions for transfusion dependent (TD) patients or increase in hemoglobin in non-transfusion dependent (NTD) patients
- d. Renewal Authorization Criteria: 1 year

***Note: Coverage may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at <http://www.cms.hhs.gov/>. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Therapeutic considerations:

A. FDA approved indication / Diagnosis

**Please refer to most recent prescribing information.*

B. Background Information

a. Beta-thalassemia

- i. The term "thalassemia" refers to a group of blood disorders characterized by a decrease or absence of synthesis of normal hemoglobin globulin chains. According to the chain whose synthesis is impaired, the thalassemias are called α -, β -, γ -, δ -, $\delta\beta$ -, or $\epsilon\gamma\delta\beta$ -thalassemias. Beta-thalassemias result from a genetic defect in the HBB gene leading to a reduction in production of β -globulin chains, an excess of α -globulin chains, and a decrease in functioning hemoglobin. Low levels of hemoglobin cause a lack of oxygen in many parts of the body and anemia. People with anemia in beta-thalassemia often require lifelong blood transfusions for survival and subsequent treatment for iron overload due to these transfusions.
- ii. The 2014 International Thalassemia Federation guidelines for transfusion dependent thalassemias recommend diagnosis should begin with genetic testing because of the extreme diversity in clinical severity of thalassemia subtypes. The degree of excess nonfunctional α -chains is the major predictor of disease severity. The less β -globulin production, the more non-functional α -chains in the bloodstream. β_0 -thalassemia refers to the complete absence of production of β -globulin. When patients are homozygous for a β_0 -thalassemia gene, they cannot make any normal β -chains. β_{-} -thalassemia indicates a mutation that presents decreased but not absent production of β -globulin. In thalassemia patients in which one or both of their β -thalassemia mutations are β_{-} -mutations, the

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disorder may be less severe. Beta-thalassemia major is a clinical diagnosis referring to a patient who has a severe form of the disease and requires chronic transfusions early in life. Beta-thalassemia intermedia is a clinical diagnosis of a patient characterized by a less severe chronic anemia and a more variable clinical phenotype. Reblozyl was not studied in patients with S/ β -thalassemia or α -thalassemia. Patients with other β -thalassemia subtypes that were transfusion dependent were included in the clinical trial.

- iii. Treatment guidelines also recommend all patients undergo at least an annual comprehensive assessment at a thalassemia center. During such an assessment, recommendations are summarized after consultation with multiple specialists including a hematologist, a nurse specialist, a hepatologist, a cardiologist, an endocrinologist, a psychologist, a genetics counselor, a social worker, and a dietitian.
 - iv. Blood transfusion is the mainstay of care for individuals with thalassemia major and many with intermedia. The purpose of transfusion is twofold: to improve the anemia and to suppress the ineffective erythropoiesis. Chronic transfusions prevent most of the serious growth, skeletal, and neurological complications of thalassemia major. The decision to start regular transfusions is clear when the initial hemoglobin level is well below 6 g/dL. Continuation of infusions can be assessed by withholding transfusions and monitoring weekly hemoglobin levels. If the hemoglobin drops under 7 g/dL on two occasions two weeks apart, then regular transfusions should be commenced. Guidelines define a patient as transfusion dependent when they are getting infusions of packed red blood cells every 2 – 5 weeks to maintain the pre-transfusion hemoglobin of 9 g/dL - 10.5 g/dL and the post-transfusion hemoglobin less than 14 - 15 g/dL. This translates to approximately 100 mL/kg/year of packed red blood cells.
- b. Myelodysplastic Syndrome
- i. Myelodysplastic syndromes are a group of blood cancers that occur as a result of disordered development of blood cells within the bone marrow. The World Health Organization has classified six types of MDS based on how many early cell types show dysplasia, the type of cytopenias a patient is experiencing, the portion of ring sideroblasts, the portion of blasts in the blood or bone marrow, and the type of genetic mutations in the bone marrow cells. Reblozyl was only studied in patients with the MDS with ring sideroblasts (MDS-RS) subtype. In this subtype, patients have ring sideroblasts greater than or equal to 15% of erythroid precursors in bone marrow or greater than or equal to 5% if the SF3B1 mutation is present. They also present with less than 5% blasts in the bone marrow. Patients with the MDS-RS subtype do not have MDS associated with a del 5q cytogenetic abnormality. The classification system for MDS automatically classifies patients with the del 5q mutation as a separate unique subtype.
 - ii. One in three patients with MDS will progress to acute myeloid leukemia (AML). Risk of disease progression to AML and risk of mortality are assessed using the Revised International Prognostic Scoring System (IPSS-R). The IPSS-R categorizes patients into 1 of 5 groups, from very low risk to very high risk using the patient's disease presentation including cytogenetic groups, percentage of medullary blasts, hemoglobin, platelets, and absolute neutrophil count. The IPSS-R can help determine whether to treat or observe patients at the time of diagnosis. Reblozyl was only studied in patients classified as very low, low, or intermediate risk using the IPPS-R.
 - iii. Reblozyl was approved based on the results of the MEDALIST trial, a phase III, placebo-controlled study in 229 patients with very low, low, or intermediate risk non-del(5q) MDS with ring sideroblasts. All patients were red blood cell transfusion-dependent defined as anemia requiring at least 2 units of red blood cells over 8 weeks. Patients had disease that was refractory to or unlikely

to respond to erythropoiesis-stimulating agents (ESAs) or were intolerant to ESA therapy. Refractory was defined as non-response or response that is no longer maintained to prior ESA therapy of either recombinant human erythropoietin at a dose of 40,000 IU/week for at least 8 weeks or darbepoetin alpha greater than 500 µg every 3 weeks for at least 4 doses. Patients were considered unlikely to respond when they had an endogenous serum erythropoietin level greater than 200 U/L. Patients must not have used any prior therapy with disease-modifying agents for underlying MDS disease and must not have secondary MDS known to have arisen as the result of chemical injury or treatment with chemotherapy or radiation for other diseases. The primary endpoint was transfusion independence for 8 weeks or longer during weeks 1 through 24. The primary endpoint was observed in 38% of the patients in the Reblozyl group compared with 13% of those in the placebo group (p < 0.001).

C. Efficacy

**Please refer to most recent prescribing information.*

D. Medication Safety Considerations

**Please refer to most recent prescribing information.*

E. Dosing and administration

**Please refer to most recent prescribing information.*

F. How supplied

**Please refer to most recent prescribing information.*

References:

1. Reblozyl [prescribing information]. Summit, NJ: Celgene Corporation; April 2020.
2. Manufacturer press release. Available at: <https://www.businesswire.com/news/home/20191108005496/en/FDA-Approves-REBLOZYL%C2%AE-luspatercept-aamt-Treatment-Anemia-Adults>. Accessed on: November 10, 2019.
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4. Cappelini 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. *Blood*. 2018; 132: 163. doi: 10.1182/blood-2018-163.
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12. National Comprehensive Cancer Network. Myelodysplastic syndromes (Version 3.2021). 2021 Jan 15. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf. Accessed on July 8, 2021.

Policy History												
#	Date	Change Description										
1.6	Effective Date: 08/12/2021	Updated to remove the upper limit on ring sideroblast when the SF3B1 mutation is present										
1.5	Effective Date: 08/13/2020	Updated to not allow use following gene therapy										
1.4	Effective Date: 06/11/2020	Updated to include new indication of myelodysplastic syndrome										
1.3	Effective Date: 04/02/2020	UM medical management system update for BCBS <table border="1" style="margin-left: 20px;"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>Yes</td> </tr> <tr> <td>BCN</td> <td>Yes</td> </tr> <tr> <td>MAPPO</td> <td>Yes</td> </tr> <tr> <td>BCNA</td> <td>Yes</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	Yes	BCNA	Yes
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1.2	Effective Date: 03/16/2020	UM medical management system update for MAPPO and BCNA <table border="1" style="margin-left: 20px;"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>No</td> </tr> <tr> <td>BCN</td> <td>No</td> </tr> <tr> <td>MAPPO</td> <td>Yes</td> </tr> <tr> <td>BCNA</td> <td>Yes</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	No	BCN	No	MAPPO	Yes	BCNA	Yes
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1.1	Effective Date: 02/01/2020	UM medical management system update for BCN <table border="1" style="margin-left: 20px;"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>No</td> </tr> <tr> <td>BCN</td> <td>Yes</td> </tr> <tr> <td>MAPPO</td> <td>No</td> </tr> <tr> <td>BCNA</td> <td>No</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	No	BCN	Yes	MAPPO	No	BCNA	No
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1.0	Effective Date: 12/05/2019	New drug review										

* The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or <http://dailymed.nlm.nih.gov/dailymed/index.cfm>.