Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

Effective Date: 10/03/2024

Reblozyl® (luspatercept-aamt)

HCPCS: J0896

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. Genetic testing confirming diagnosis of β-thalassemia
      ii. Must not have hemoglobin S/β-thalassemia or α-thalassemia
      iii. 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
   c. Diagnosis of myelodysplastic syndrome (MDS)
      i. Must have anemia requiring at least 2 units of red blood cells over 8 weeks (about 2 months)
      ii. World Health Organization (WHO)/French American British (FAB) classification that meets IPSS-R classification of very low, low, or intermediate risk disease
      iii. Less than 5% blasts in the bone marrow
      iv. Must be refractory, intolerant, or ineligible to receive an erythropoietin stimulating agents (ESA) unless serum epopoietin is greater than 500 mU/mL or for those with IPSS-R very low, low, or intermediate disease without a del(5q) mutation with ring sideroblasts (RS) greater than or equal to 15% or RS greater than or equal to 5% with an SF3B1 mutation 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 Documentation of non-response or response that is no longer maintained to prior ESA-containing regimen of either recombinant human erythropoietin 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
         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
      v. Must not have MDS associated with del 5q cytogenetic abnormality

vi. 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

d. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing
   b. Authorization Period: Aligns with FDA recommended or guideline supported treatment duration and provided for at least 60 days and up to 6 months at a time
   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

***Note: Coverage and approval duration 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.

Background Information:

- Beta-thalassemia

  - 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 call α-, β-, γ-, δ-, δβ-, or εγδβ-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.

  - The 2021 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 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.

  - 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.

- 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.

- Guidelines recommend the use of Reblozyl in patients who are regularly transfused and have a hemoglobin of less than 11 g/dL when not influenced by a recent red blood cell transfusion. They also state that if improvement is not seen following the first 3 doses, or after 9 weeks of therapy, Reblozyl should be discontinued.

- Myelodysplastic Syndrome

  - 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. In ESA treatment experienced patients, 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. This subtype was also not included in the clinical trial assessing efficacy of Reblozyl in ESA treatment naïve patients.

  - 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 cytogenic 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 IPSS-R in all clinical trials.

  - Reblozyl for use in ESA treatment experienced patients 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-value < 0.001).

- Reblozyl for use in ESA treatment naïve patients was approved based on the results of the COMMANDS trial, a phase III, open-label, randomized controlled study of 356 patients with myelodysplastic syndromes of very low risk, low risk, or intermediate risk. Subjects had not experienced prior treatment with ESAs and required regular red blood cell transfusions of at least 2 – 6 packed red blood cell units per 8 weeks for greater than or equal to 8 weeks immediately before randomization. Patients must not have MDS associated with del 5q cytogenetic abnormality or secondary MDS known to have arisen as the result of chemical injury or treatment with chemotherapy and/or radiation for other diseases. The primary endpoint was red blood cell transfusion independence for at least 12 weeks with a concurrent mean hemoglobin increase of at least 1.5 g/dL during weeks 1 – 24. Results showed 58.5% of patients treated with Reblozyl vs. 31.2% of patients treated with epoetin alfa achieved the primary endpoint (p-value < 0.0001).

- The current NCCN guidelines recommend ESA treatment in all patients unless their serum epopoietin is greater than 500 mU/mL or those with IPSS-R very low, low, or intermediate disease without a del(5q) mutation with RS greater than or equal to 15% or RS greater than or equal to 5% with an SF3B1 mutation. In instances where a patient presents with an eoppoietin greater than 500 mU/mL or IPSS-R very low, low, or intermediate disease without a del(5q) mutation with RS greater than or equal to 15% or RS greater than or equal to 5% with an SF3B1 mutation, guidelines recommend Reblozyl as first-line therapy.

References:

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5. Piga A, Perrotta S, Gamberini MR, et al. Luspatercept improves hemoglobin levels and blood transfusion requirements in a study of patients with β-thalassemia. Blood. 2019 Mar 21; 133 (12): 1279-1289. doi: .10.1182/blood-2018-10-879247.
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11. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. NEJM. 2020 Jan 9; 382: 140 – 51.
12. National Comprehensive Cancer Network. Myelodysplastic syndromes (Version 2.2024). 2024 May 22. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf. Accessed on: July 25, 2024.

13. Platzbecker U, Della Porta MG, Santini V, et al. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusiondependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial. Lancet. 2023 July 29; 402 (10399): 373 – 85.

<table>
<tr><th colspan="3">Policy History</th></tr>
<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>2.2</td><td>Effective Date: 10/03/2024</td><td>Updated authorization period to state “aligns with FDA recommended or guideline supported treatment duration and provided for at least 60 days and up to 6 months at a time” and added an exception to ESA use in those with IPSS-R very low, low, or intermediate disease without a del(5q) mutation with ring sideroblasts (RS) greater than or equal to 15% or RS greater than or equal to 5% with an SF3B1 mutation</td></tr>
<tr><td>2.1</td><td>Effective Date: 10/12/2023</td><td>Updated to remove prescriber requirements, the sideroblast requirements in myelodysplastic syndrome, and require ESA’s as first-line therapy unless a patient has serum epopoietin greater than 500 mU/mL.</td></tr>
<tr><td>2.0</td><td>Effective Date: 06/08/2023</td><td>Updated to remove the statement not allowing use with other disease modifying therapies</td></tr>
<tr><td>1.9</td><td>Effective Date: 12/01/2022</td><td>Updated to include the trial and failure of preferred products statement</td></tr>
<tr><td>1.8</td><td>Effective Date: 10/06/2022</td><td>Update to remove statement not allowing use with gene therapy</td></tr>
<tr><td>1.7</td><td>Effective Date: 08/04/2022</td><td>Annual review of medical policy. No changes to the criteria were made at this time</td></tr>
<tr><td>1.6</td><td>Effective Date: 08/12/2021</td><td>Updated to remove the upper limit on ring sideroblast when the SF3B1 mutation is present</td></tr>
<tr><td>1.5</td><td>Effective Date: 08/13/2020</td><td>Updated to not allow use following gene therapy</td></tr>
<tr><td>1.4</td><td>Effective Date: 06/11/2020</td><td>Updated to include new indication of myelodysplastic syndrome</td></tr>
<tr><td>1.3</td><td>Effective Date: 04/02/2020</td><td>UM medical management system update for BCBS
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<tr><td>BCN</td><td>Yes</td></tr>
<tr><td>MAPPO</td><td>Yes</td></tr>
<tr><td>BCNA</td><td>Yes</td></tr>
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<tr><td>1.2</td><td>Effective Date: 03/16/2020</td><td>UM medical management system update for MAPPO and BCNA
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<tr><td>1.1</td><td>Effective Date: 02/01/2020</td><td>UM medical management system update for BCN
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><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></table></td></tr>
<tr><td>1.0</td><td>Effective Date: 12/05/2019</td><td>New drug review</td></tr>
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** 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.*

Blue Cross Blue Shield/Blue Care Network of Michigan
Medication Authorization Request Form
Reblozyl® (luspatercept–aamt) HCPCS CODE: J0896

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

This form is to be used by participating physicians to obtain coverage for Reblozyl. For commercial members only, please complete this form and submit via fax to 1-877-325-5979. If you have any questions regarding this process, please contact BCBSM Provider Relations and the Medical Drug Helpdesk at 1-800-437-3803 for assistance.

PATIENT INFORMATION	PHYSICIAN INFORMATION
Name	**Name**
ID Number	**Specialty**
D.O.B. ☐Male ☐Female	**Address**
Diagnosis	**City /State/Zip**
Drug Name	**Phone/Fax: P**: ( ) - **F**: ( ) -
Dose and Quantity	**NPI**
Directions	**Contact Person**
Date of Service(s)	**Contact Person Phone / Ext.**

STEP 1: DISEASE STATE INFORMATION

1. Is this request for: ☐ Initiation ☐ Continuation ***Date patient started therapy***: _____
2. Site of administration? ☐ Provider office/Home infusion ☐ Other: _____
   ☐ Hospital outpatient facility (go to #3) *Reason for Hospital Outpatient administration:* _____
3. Please specify location of administration if hospital outpatient infusion: _____
4. Please provide the NPI number for the place of administration: _____
5. **Initiation AND Continuation of therapy:**
   a. Please check the patient's diagnosis**:** ☐ Beta thalassemia ☐ Myelodysplastic syndrome (MDS) ☐ Other: _____
   b. **Beta thalassemia:**
      i. How was the patient diagnosed with beta thalassemia? ***(Please attach any tests confirming diagnosis)***
         ☐ Genetic testing: _____ ☐ Other: _____
      ii. Does the patient have Hemoglobin S/β-thalassemia or α-thalassemia?
         ☐ Yes ☐ No Comment _____
      iii. Is the patient considered transfusion dependent with a history of at least 100 mL/kg/year of pRBCs in the previous two years?
         ☐ Yes ☐ No Comment _____
      iv. Is the patient managed under standard thalassemia guidelines with ≥ 8 transfusions of pRBCs per year in the previous two years?
         ☐ Yes ☐ no Comment: _____
   c. **Myelodysplastic syndrome (MDS):**
      i. Does the patient have anemia requiring at least 2 units of red blood cells over 8 weeks? ☐ Yes ☐ No
      ii. Please select the patient's World Health Organization (WHO)/French American British (FAB) with IPSS-R classification for MDS:
         ☐ Very low risk ☐ Low risk ☐ Intermediate risk ☐ High risk
      iii. Does the patient have ring sideroblast ≥ 15% of erythroid precursors in bone marrow OR ≥ 5% if the SF3B1 mutation is present? ☐ Yes ☐ No
      iv. Does the patient have less than 5% blasts in the bone marrow? ☐ Yes ☐ No
      v. Has the patient used erythropoietin or darbepoetin alpha? ☐ Yes ☐ No
         1. Provide the product name, dose, frequency, and length of therapy: _____
            a. What was the response to the treatment?
               ☐ Never responded ☐ Lost response ☐ Intolerance to treatment ☐ Adverse event ☐ Other: _____
         2. What is the patient's endogenous serum erythropoietin level in U/L? _____
      vi. Has the patient used any prior therapy with disease-modifying agents for underlying MDS disease (examples: immune-modulatory drug, hypomethylating agents, or immunosuppressive therapy)? ☐ Yes, Please provide the name of the drug: _____ ☐ No
      vii. Does the patient have MDS associated with del 5q cytogenetic abnormality? ☐ Yes ☐ No
      viii. Does the patient have secondary MDS known to have arisen as the result of chemical injury or treatment with chemotherapy and/or radiation for other diseases?
         ☐ Yes ☐ No
6. **Continuation request: Reblozyl start date**: _____
   ☐ Reduction in transfusions for transfusion dependent patients
   ☐ Increase in hemoglobin with non- transfusions patients
   ☐ Other: _____
   ☐ None
7. *Please add any other supporting medical information necessary for our review*

Coverage will not be provided if the prescribing physician's signature and date are not reflected on this document.

☐ Request for expedited review: I certify that applying the standard review time frame may seriously jeopardize the life or health of the member or the member's ability to regain maximum function

Physician's Name **Physician Signature** **Date**

Step 2: Checklist	☐ Form Completely Filled Out ☐ Attach Chart Notes	☐ Attach Diagnostic Tests and Labs
Step 3: Submit	**By Fax: BCBSM Specialty Pharmacy Mailbox 1-877-325-5979**	**By Mail: BCBSM Specialty Pharmacy Program P.O. Box 312320, Detroit, MI 48231-2320**

1/31/2020; 7/1/2020; 10/1/2020; 8/12/202; 10/7/2022