Clinical Policy: Luspatercept-aamt (Reblozyl)
Reference Number: CP.PHAR.450
Effective Date: 03.01.20
Last Review Date: 08.20
Line of Business: Commercial, HIM, Medicaid

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Luspatercept-aamt (Reblozyl®) is an erythroid maturation agent.

FDA Approved Indication(s)
Reblozyl is indicated for the treatment of anemia in adult patients with:
- Beta thalassemia who require regular red blood cell (RBC) transfusions
- Very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) failing an erythropoiesis stimulating agent and requiring 2 or more RBC units over 8 weeks

Limitation(s) of use: Not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Reblozyl is medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Transfusion Dependent Beta Thalassemia (must meet all):
      1. Diagnosis of transfusion dependent thalassemia (TDT) with one of the following genotypes (a or b):
         a. Beta thalassemia;
         b. Hemoglobin E/beta thalassemia;
      2. Prescribed by or in consultation with a hematologist;
      3. Age ≥ 18 years;
      4. Total volume of transfusions exceeds 6 RBC units (see Appendix D) within the last 6 months;
      5. No transfusion-free period ≥ 35 days within the last 6 months;
      6. Documentation of baseline transfusion burden within the last 6 months;
      7. Dose does not exceed 1 mg/kg every 3 weeks.
   Approval duration: 2 months (2 doses)
B. Myelodysplastic Syndromes (must meet all):
   1. Diagnosis of MDS-RS or MDS/MPN-RS-T that meets one of the following classifications (a, b, or c) (see Appendix E):
      a. Very low, low, or intermediate risk as classified by IPSS-R;
      b. Low/intermediate-1 risk as classified by IPSS;
      c. Very low, low, or intermediate risk as classified by WPSS;
   2. Prescribed by or in consultation with a hematologist or oncologist;
   3. Age ≥ 18 years;
   4. Member requires ≥ 2 RBC units per 8 weeks documented for at least the last 16 weeks;
   5. Failure of an 8 week trial of an erythropoiesis-stimulating agent (ESA) used in combination with a granulocyte colony stimulating factor (G-CSF) (see Appendix B), unless one of the following applies (a or b):
      a. Clinically significant adverse effects are experienced or all are contraindicated;
      b. Documentation of current serum erythropoietin > 500 mU/mL;
   6. Member has one of the following (a or b):
      a. Ring sideroblast ≥ 15% of erythroid precursors in bone marrow;
      b. Ring sideroblast ≥ 5% if SF3B1 mutation is present;
   7. Member does not have del(5q) cytogenetic abnormality;
   8. Request meets one of the following (a or b):*
      a. Dose does not exceed 1 mg/kg every 3 weeks;
      b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
*Prescribed regimen must be FDA-approved or recommended by NCCN

Approval duration: 2 months (2 doses)

C. Other diagnoses/indications
   1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid

II. Continued Therapy
A. Transfusion Dependent Beta Thalassemia (must meet all):
   1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
   2. Member meets one of the following (a or b):
      a) Member is responding positively to therapy as evidenced by at least a 33% reduction in transfusion burden from baseline;
      b) Request is for a dose increase;
   3. If request is for a dose increase, new dose does not exceed (a or b):
      a) 1 mg/kg every 3 weeks;
      b) 1.25 mg/kg every 3 weeks, and documentation supports inadequate response to 1 mg/kg dosing.

Approval duration: 6 months
B. Myelodysplastic Syndromes (must meet all):
   1. Currently receiving medication via Centene benefit, or documentation supports that
      member is currently receiving Reblozyl for a covered indication and has received this
      medication for at least 30 days;
   2. Member meets one of the following (a or b):
      a. Member is responding positively to therapy as evidenced by a decreased
         transfusion burden;
      b. Request is for a dose increase;
   3. If request is for a dose increase, request meets one of the following (a, b, c, or d):*
      a. New dose does not exceed 1 mg/kg every 3 weeks;
      b. New dose does not exceed 1.33 mg/kg every 3 weeks, and documentation
         supports lack of transfusion independence after 2 consecutive doses at 1 mg/kg
         dosing;
      c. New dose does not exceed 1.75 mg/kg every 3 weeks and documentation supports
         lack of transfusion independence after 2 consecutive doses at 1.33 mg/kg dosing;
      d. New dose is supported by practice guidelines or peer-reviewed literature for the
         relevant off-label use (prescriber must submit supporting evidence).
*Prescribed regimen must be FDA-approved or recommended by NCCN
Approval duration: 6 months (2 months [2 doses] if request is for a dose increase)

C. Other diagnoses/indications (must meet 1 or 2):
   1. Currently receiving medication via Centene benefit and documentation supports
      positive response to therapy.
      
      Approval duration: Duration of request or 6 months (whichever is less); or
   2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT
      specifically listed under section III (Diagnoses/Indications for which coverage is
      NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance
      marketplace, and CP.PMN.53 for Medicaid

III. Diagnoses/Indications for which coverage is NOT authorized:
   A. Non-FDA approved indications, which are not addressed in this policy, unless there is
      sufficient documentation of efficacy and safety according to the off label use policies –
      CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and
      CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESA</td>
<td>erythropoiesis-stimulating agent</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>G-CSF</td>
<td>granulocyte colony stimulating factor</td>
</tr>
<tr>
<td>Hb</td>
<td>hemoglobin</td>
</tr>
<tr>
<td>IPSS</td>
<td>International Prognostic Scoring System</td>
</tr>
<tr>
<td>IPSS-R</td>
<td>International Prognostic Scoring System - Revised</td>
</tr>
<tr>
<td>MDS</td>
<td>myelodysplastic syndromes</td>
</tr>
<tr>
<td>MDS-RS</td>
<td>myelodysplastic syndromes with ring sideroblasts</td>
</tr>
<tr>
<td>MDS/MPN-RS-T</td>
<td>myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis</td>
</tr>
<tr>
<td>TDT</td>
<td>transfusion dependent thalassemia</td>
</tr>
<tr>
<td>WPSS</td>
<td>WHO Classification-based Scoring System</td>
</tr>
</tbody>
</table>
Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procrit®, Epogen®, Retacrit® (epoetin alfa)*</td>
<td>MDS: 40,000 to 60,000 SC units 1 to 2 times per week every week</td>
<td>Target hemoglobin up to 12 g/dL</td>
</tr>
<tr>
<td>Aranesp®, (darbepoetin alfa)*</td>
<td>MDS: 150 to 300 mcg SC every other week</td>
<td>Target hemoglobin up to 12 g/dL</td>
</tr>
<tr>
<td>Neupogen®, Nivestym™, Granix®, Zarxio® (filgrastim)</td>
<td>MDS: 1 to 2 mcg/kg SC 1 to 2 times per week</td>
<td>Varies</td>
</tr>
</tbody>
</table>

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

*Off-label

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: General Information

- Conversion of RBC units from mL: 1 RBC unit in this criteria refers to a quantity of packed RBCs approximately 200-350 mL.
  - Sites who use transfusion bags within this range, or ≥ 350 mL, the conversion in units should be done by dividing the volume transfused to the patient by 350 mL,
  - Sites who use transfusion bags < 200 mL, the conversion in units should be done by dividing the volume transfused to the patient by 200 mL.
- MDS and serum erythropoietin level
  - According to NCCN, for the treatment of symptomatic anemia in MDS with ring sideroblasts ≥ 15% (or ring sideroblasts ≥ 5% with an SF3B1 mutation), a trial of either recombinant human erythropoietin or darbepoetin in combination with a G-CSF is recommended when serum erythropoietin level is ≤ 500 mU/mL. If serum erythropoietin level is > 500 mU/mL for this indication, Reblozyl is recommended.
- MDS and combination treatment with ESA + G-CSF
  - This is the recommended combination per NCCN for the treatment of symptomatic anemia in MDS with ring sideroblasts ≥ 15% (or ring sideroblasts ≥ 5% with an SF3B1 mutation). Evidence suggests that G-CSF has synergistic erythropoietic activity when used in combination with an ESA and markedly enhances the erythroid response rates due to enhanced survival of red cell precursors. This is particularly evident for patients with greater than or equal to 15% ring sideroblasts in the marrow and serum erythropoietin level ≤ 500 mU/mL.
- MDS/MPN-RS-T indication
  - During regulatory review of the MEDALIST data by the FDA, a post-hoc re-classification of patients using the WHO 2016 criteria was conducted to assess the efficacy and safety of Reblozyl in patients with MDS/MPN-RS-T. Among the 229 patients enrolled in MEDALIST, 23 patients were found to have a diagnosis of
MDS/MPN-RS-T following this re-classification. In these patients with MDS/MPN-RS-T, a greater proportion of patients treated with Reblozyl (64.3%; n = 9/14) achieved the primary endpoint of transfusion independence for at least 8 weeks during weeks 1-24 compared to placebo (22.2%; n = 2/9).

Appendix E: MDS Risk Classification

- International Prognostic Scoring System - Revised (IPSS-R) classification:

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>≤ 1.5</td>
</tr>
<tr>
<td>Low</td>
<td>&lt; 1.5 – 3</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&lt; 3 – 4.5</td>
</tr>
<tr>
<td>High</td>
<td>&lt; 4.5 – 6</td>
</tr>
<tr>
<td>Very high</td>
<td>&gt; 6</td>
</tr>
</tbody>
</table>

- International Prognostic Scoring System (IPSS) classification:

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>0.5 – 1</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>1.5 – 2</td>
</tr>
<tr>
<td>High</td>
<td>2.5 – 3.5</td>
</tr>
</tbody>
</table>

- WHO Classification-based Prognostic Scoring System (WPSS) classification:

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>0</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
</tr>
<tr>
<td>High</td>
<td>3 – 4</td>
</tr>
<tr>
<td>Very high</td>
<td>5 – 6</td>
</tr>
</tbody>
</table>

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
</table>
| Transfusion-dependent beta thalasemia | 1 mg/kg SC once every 3 weeks  
Evaluation hemoglobin (Hgb) prior to next planned administration. If pre-dose Hgb ≥ 11.5 g/dL and Hgb level is not influenced by recent transfusion, delay dosing until the Hgb is ≤ 11 g/dL.  
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 to max dose of 1.25 mg/kg. | 1.25 mg/kg   |
| MDS                               | Initial: 1 mg/kg SC once every 3 weeks  
Dose increases for insufficient response after initiation of treatment: | 1.75 mg/kg   |
### Indication | Dosing Regimen | Maximum Dose
--- | --- | ---

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 dose to 1.33 mg/kg SC every 3 weeks.

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 dose to a maximum of 1.75 mg/kg SC every 3 weeks.

Discontinue 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.

### VI. Product Availability
Single dose vials for injection: 25 mg, 75 mg

### VII. References

### ICD-10-CM Diagnosis Codes that Support Coverage Criteria
The following is a list of diagnosis codes that support coverage for the applicable covered procedure code(s).

<table>
<thead>
<tr>
<th>ICD-10-CM Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>D56.1*</td>
<td>Beta thalassemia</td>
</tr>
</tbody>
</table>
Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.
Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

©2019 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene® and Centene Corporation® are registered trademarks exclusively owned by Centene Corporation.