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Last P&T Approval/Version: 01/29/2025
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Policy Number: C18002-A

Reblozyl (luspatercept-aamt)

PRODUCTS AFFECTED

Reblozyl (luspatercept-aamt)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Anemia in beta thalassemia, Anemia in myelodysplastic syndromes

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. BETA THALASSEMIA:
1. Documentation of diagnosis of β-thalassemia or Hemoglobin E/β-thalassemia NOTE: Not to be used in patients with sickle beta thalassemia (Hemoglobin S/β-thalassemia) or alpha

thalassemia
AND
2. Documentation member requires regular blood transfusions (6-20 RBC units per 24 weeks)
AND
3. Documentation of pre-treatment transfusion burden required [DOCUMENTATION REQUIRED]
AND
4. Prescriber attests that member will continue to receive best supportive care (RBC transfusions, iron-chelating agents, use of antibiotic, antiviral, and antifungal therapy, and/or nutritional support, as needed)
AND
5. Documentation that member's (pre-transfusion if done) hemoglobin is ≤11g/dL
AND
6. Prescriber attests 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

B. ANEMIA:
1. Documented diagnosis of myelodysplastic syndrome OR documented diagnosis of myelodysplastic/myeloproliferative neoplasm
AND
2. Member has documented lower risk disease defined as one of the following: (i) Revised International Prognostic Scoring System (IPSS-R): Very Low, Low, Intermediate (Score 0 to ≤ 4.5); (ii) IPSS: Low/Intermediate-1 (Score 0 to 1), OR (iii) WHO-Based Prognostic Scoring System (WPSS): Very Low, Low, Intermediate (Score 0 to 2)
AND
3. (a) i. Documentation of ONE of the following: Ring sideroblasts ≥ 15% OR Ring sideroblasts ≥5% with an SF3B1 mutation
AND
ii. Documentation of one of the following: (1) Serum erythropoietin >500 mU/mL OR (2) Both of the following: Serum erythropoietin ≤500 mU/mL AND member has had an inadequate response to prior treatment with an erythropoiesis stimulating (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 member has a documented contraindication or intolerance to the use of an erythropoiesis-stimulating agent
OR
(b) Documentation of ring sideroblasts <5% and Serum erythropoietin <500 mU/mL
AND
4. Documentation of member's pretreatment hemoglobin ≤11g/dL
AND
5. Documentation member is requiring 2 or more red blood cell (RBC) units over 8 weeks
AND
6. Prescriber attests 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

CONTINUATION OF THERAPY:

A. BETA THALASSEMIA:
1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
AND
2. Documentation that member has had a decrease in RBC transfusion burden from pre-treatment
AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

B. ANEMIA:
1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
2. Documentation the member is being treated for symptomatic anemia associated with myelodysplastic syndromes
   AND
3. Documentation the member no longer requires pRBC transfusions (transfusion independence)
   AND
4. Prescriber attests to or clinical reviewer has found no evidence of adverse effects or drug toxicity

DURATION OF APPROVAL:
Initial authorization: 9 weeks, Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a board-certified hematologist, or other specialist with expertise in the diagnosis and management of myelodysplastic syndromes [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
Beta Thalassemia: Maximum dose of 1.25 mg/kg subcutaneous every 21 days
Anemia: Maximum dose of 1.75 mg/kg subcutaneous every 21 days

PLACE OF ADMINISTRATION:
The recommendation is that injectable medications in this policy will be for pharmacy or medical benefit coverage and the subcutaneous injectable products administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.

Note: Site of Care Utilization Management Policy applies for Reblozyl (luspatercept-aamt). For information on site of care, see: Specialty Medication Administration Site of Care Coverage Criteria (molinamarketplace.com)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Subcutaneous

DRUG CLASS:
Erythroid Maturation Agents

FDA-APPROVED USES:
Indicated for the treatment of:
- Anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions
- Anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions
- Anemia failing an erythropoiesis stimulating agent and requiring 2 or more RBC units over 8 weeks in adult patients with 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)

Limitations of Use: Reblozyl is not indicated for use as a substitute for RBC transfusion in patients who require immediate correction of anemia.

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
D46.22 Refractory anemia with excess of blasts 2
D46.B Refractory cytopenia with multilineage dysplasia and ring sideroblasts
D56.1 Beta thalassemia
D56.5 Hemoglobin E-beta thalassemia

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Beta thalassemia is part of a group of rare, inherited blood disorders caused by a genetic defect in hemoglobin, characterized by reduced levels of functional hemoglobin.
Hemoglobin is an iron-containing protein in red blood cells that carries oxygen to cells throughout the body. Low levels of hemoglobin lead to a lack of oxygen in many parts of the body and anemia, which can cause pale skin, weakness, fatigue, and more serious complications. Organ damage (e.g., renal disease, cardiomyopathy, diabetes) can result. There are three main forms of beta thalassemia – minor, intermedia, and major, terms which indicate the severity of the disease.
Individuals with the minor form, also known as beta thalassemia trait, may experience minor anemia, but they usually do not have symptoms and often are unaware that they have the condition. Individuals with the intermedia form experience a wide range of symptoms, and the severity falls in the broad range between the major and minor forms. Beta thalassemia major, also known as Cooley's anemia, is the severest form of the disorder. Individuals with beta thalassemia major often require regular blood transfusions (about every 2–4 weeks) and lifelong, ongoing medical care. These Individuals are at risk for iron overload, or too much iron in the body, due to the chronic blood transfusions and require medicines to remove extra iron from their bodies (called chelation). People with beta thalassemia are also at an increased risk of developing blood clots. Hematologists treat patients with beta thalassemia. There are CDC funded Thalassemia Treatment Centers throughout the country.

Reblozyl Efficacy and Safety
The approval of Reblozyl for beta thalassemia, which received a Priority Review designation from the FDA, is based on the results of the clinical trial BELIEVE evaluating patients with beta thalassemia who required RBC transfusions. BELIEVE is a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial in which (n=336) patients with beta thalassemia requiring regular red blood cell transfusions (defined as 6-20 RBC units per 24 weeks) with no transfusion-free period greater than 35 days during that period were randomized 2:1 to Reblozyl (n=224) or placebo (n=112). All patients were eligible to receive best supportive care, which included RBC transfusions; iron-chelating agents; use of antibiotic, antiviral, and antifungal therapy; and/or nutritional support, as needed.
Reblozyl was administered subcutaneously once every 3 weeks as long as a reduction in transfusion requirement was observed or until unacceptable toxicity. Key eligibility criteria included adult patients with beta thalassemia (with the exception of sickle beta thalassemia) without major organ damage or recent DVT stroke, platelet counts less than or equal to 1000 x 109 /L or recent use of ESA. In addition, patients

on immunosuppressants or hydroxyurea therapy were also excluded. Patients received a starting dose of Reblozyl 1 mg/kg subcutaneous injection every 3 weeks. The median duration of treatment was similar between the Reblozyl and placebo arms (63.3 weeks vs. 62.1 weeks, respectively). Per protocol, patients in the Reblozyl and placebo arms were to remain on therapy for at least 48 weeks in the double-blind phase of the trial. Among patients receiving Reblozyl, 94% were exposed for 6 months or longer and 72% were exposed for greater than one year. The median age of patients who received Reblozyl was 30 years (range: 18, 66); 59% female; 54% White, and 36% Asian.

Results

The trial achieved a clinically meaningful and statistically significant improvement in the primary endpoint. Twenty-one percent of the patients who received Reblozyl achieved at least a 33% reduction in transfusion burden (with a reduction of at least 2 units) during weeks 13–24 after randomization compared to 4.5% of the patients who received a placebo. The transfusion reduction meant that the member needed fewer transfusions over 12 consecutive weeks while taking Reblozyl. While the study also met key secondary endpoints, including transfusion burden reduction of at least 33% (with a reduction of at least 2 units), during weeks 37 to 48, which was achieved in 19.6% (n=44) of patients in the Reblozyl arm and 3.6% (n=4) in the placebo arm, it still indicates that 80.4% of patients did not meet the secondary endpoint. Other efficacy endpoints included transfusion burden reduction of greater-than or equal to 50% (with a reduction of at least 2units) during weeks 13-24 and weeks 37-48. A greater-than or equal to 50% reduction in transfusion burden was observed in 7.6% of patients (n=17) receiving Reblozyl vs. 1.8% of patients(n=2) in the placebo arm at weeks 13- 24.

Reblozyl approval for use in ESA naïve adults was based on results from the COMMANDS trial (NCT03682536). COMMANDS was a multi-center, open-label, randomized active-controlled trial comparing Reblozyl versus epoetin alfa in patients with anemia due to IPSS-R very low, low, or intermediate-risk myelodysplastic syndromes or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) in ESA-naïve patients (with endogenous sEPO levels of <500U/L) who require regular red blood cell transfusions. For eligibility, patients were required to have had 2 to 6 RBC units/8 weeks confirmed for a minimum of 8 weeks immediately preceding randomization. Additional inclusion criteria were < 5% blasts in bone marrow and endogenous serum erythropoietin (sEPO) level of <500 U/L. The trial included 356 patients randomized 1:1 to Reblozyl (N=178) or epoetin alfa (N=178). All patients received best supportive care, which included RBC transfusions as needed. Patients were treated for 24 weeks and were assessed for efficacy at that time point. Treatment beyond 24 weeks was optional based upon response to treatment and absence of disease progression.

The efficacy of Reblozyl in the treatment of anemia in ESA-naïve adult patients with MDS was established at the time of the interim efficacy analysis based upon the proportion of patients who experienced both red blood cell transfusion independence (RBC-TI) [defined as the absence of any RBC transfusion during any consecutive 12-week period] and an associated concurrent mean improvement in hemoglobin by at least 1.5 g/dL for any consecutive 12 week period during Weeks 1-24. At the time of this publication, no guidelines have been updated that reflect this expanded label.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Reblozyl (luspatercept-aamt) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications to Reblozyl (luspatercept-aamt) include: No labeled contraindications.

Discontinue REBLOZYL if a member does not experience a decrease in transfusion burden after 9 weeks of treatment (administration of 3 doses) at the maximum dose level.

OTHER SPECIAL CONSIDERATIONS:

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

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
J0896	Injection, luspatercept-aamt, 0.25 mg

AVAILABLE DOSAGE FORMS:
REBLOZYL SOLR 25MG single-dose vial
REBLOZYL SOLR 75MG single-dose vial

REFERENCES

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5. Langhi, D., Ubiali, E., Marques, J., Verissimo, M., Loggetto, S., Silvinato, A., & Bernardo, W. (2016). Guidelines on Beta-thalassemia major – regular blood transfusion therapy: Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular: project guidelines: Associação Médica Brasileira – 2016. Revista Brasileira De Hematologia E Hemoterapia, 38(4), 341-345 doi: 10.1016/j.bjhh.2016.09.003
6. Uwe Platzbecker, Della, G., Santini, V., Zeidan, A. M., Komrokji, R. S., Shortt, J., … Sheida Hayati. (2023). Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial. The Lancet, 402(10399), 373–385. https://doi.org/10.1016/s0140-6736(23)00874-7
7. National Comprehensive Cancer Network. 2025. Myelodysplastic Syndromes (Version 1.2025). [online] Available at: < mds.pdf) > [Accessed 7 January 2025].

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Continuation of Therapy References	Q1 2025
REVISION- Notable revisions: Required Medical Information FDA-Approved Uses References	Q1 2024
REVISION- Notable revisions: Required Medical Information Continuation of Therapy FDA-Approved Uses Background References	Q4 2023
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements Quantity Contraindications/Exclusions/Discontinuation Other Special Considerations Available Dosage Forms	Q1 2023
Q2 2022 Established tracking in new format	Historical changes on file