Medical Drug Clinical Criteria

Subject:	Reblozyl (luspatercept)		
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Table of Contents

Overview

This document addresses the use of Reblozyl (luspatercept). Reblozyl is an erythroid maturation agent used to treat anemia in adults with beta thalassemia (β-thalassemia) and myelodysplastic syndrome (MDS) or myelodysplastic/myeloproliferative neoplasms (MDS/MPN) require regular red blood cell transfusions.

The FDA approved indications for Reblozyl include:

- 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).

The National Comprehensive Cancer Network (NCCN) gives a 2A category recommendation for the use of Reblozyl in MDS-RS with ring sideroblasts greater than or equal to 15% (or ring sideroblasts 5% to 14% with an SF3B1 mutation).

Beta thalassemia is an inherited blood disorder caused by mutations in the beta-globin (*HBB*) gene. These mutations result in defective red blood cells (RBC) that have little or no hemoglobin, the iron-containing protein that is responsible for oxygen transport. People who inherit just one *HBB* gene mutation (thalassemia minor or thalassemia trait) are usually asymptomatic. People who inherit two defective genes develop beta thalassemia with moderate anemia that can be managed with intermittent RBC transfusions (beta thalassemia intermedia) or severe anemia that is transfusion-dependent (beta thalassemia major, also called Cooley's anemia). Hemoglobin E beta thalassemia (E/β-thalassemia) and hemoglobin S beta thalassemia (S/β-thalassemia, also known as sickle beta thalassemia) are related disorders that occur when beta thalassemia is combined with another gene mutation or abnormality.

Myelodysplastic syndromes (MDS) are conditions that can occur when the body no longer makes enough healthy, normal blood cells in the bone marrow. This leads to a low number of one or more types of blood cells. A shortage of red blood cells (anemia) is the most common finding. MDS is also known as a form of blood cancer. Several types of MDS exist, based on how many types of blood cells are affected along with other factors. About one-third of MDS patients can progress to a rapidly growing cancer of bone marrow cells called acute myeloid leukemia (AML). The World Health Organization (WHO) provides classifications for myeloid neoplasms and acute leukemias. It classifies MDS into 6 main types, primarily based on how the cells in the bone marrow look under the microscope. MDS-RS is not a common subtype of MDS and rarely turns into AML. Some patients present with clinical features that overlap between MDS and myeloproliferative neoplasms (MPN), which have their own WHO classifications. The mixed diagnosis indicates that the patient has abnormal blood cells combined with proliferation of cells. It is rarer than MDS and estimated incidence is more difficult to define. Key clinical features of MDS/MPN-RS-T include anemia and elevated platelet counts.

Reblozyl is a first in class drug and classified as an erythroid maturation agent. While Reblozyl may reduce the transfusion burden, it does not completely eliminate the need for RBC transfusions. The goal of treatment in these

patients focuses on symptom control, quality of life improvement, reduction or elimination of RBC transfusions and toxicity minimization.

Per labeling, Reblozyl is to be administered by a healthcare professional as a subcutaneous injection. At this time, Reblozyl is not recommended for pediatric use due to findings from toxicity studies in juvenile animals.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Reblozyl (luspatercept)

Initial requests for Reblozyl (luspatercept) for β-thalassemia may be approved if the following criteria are met:

I. Individual is 18 years of age or older; **AND**
II. Individual has a diagnosis of beta thalassemia or hemoglobin E beta (E/β)-thalassemia; **AND**
III. Documentation is provided that individual required regular red blood cell transfusions at initiation, defined as *both* of the following (NCT02604433):
    A. Individual received six to twenty (6-20) RBC units in the last 24 weeks; **AND**
    B. Individual had no transfusion-free period greater than 35 days in the last 24 weeks; **AND**
IV. Individual has a baseline hemoglobin (Hgb) level 11 g/dL or less.

Continuation requests for Reblozyl (luspatercept) for β-thalassemia may be approved if the following criteria are met:

I. Documentation is provided that individual demonstrates continued need for treatment and has confirmation of response to treatment as evidenced by a decrease in transfusion burden from baseline; **AND**
II. Hemoglobin level 11 g/dL or less.

Reblozyl (luspatercept) for β-thalassemia may not be approved for the following:

I. Individual has a diagnosis of sickle beta thalassemia (S/β-thalassemia); **OR**
II. Individual has a diagnosis of alpha (α)-thalassemia; **OR**
III. Individual has a platelet count greater than 1000 x 10^9/L; **OR**
IV. History of deep vein thrombosis (DVT) or stroke within the last 24 weeks; **OR**
V. Use beyond 9 weeks of treatment (i.e., administration of consecutive 3 doses) in the absence of response (response defined as decrease in transfusion burden from baseline) at maximum dose level (i.e., 1.25 mg/kg every 3 weeks).

Initial requests for Relobzyl (luspatercept) for myelofibrosis-associated anemia

I. Individual has a diagnosis of myelofibrosis-associated anemia (NCCN 2A); **AND**
II. Individual has symptomatic splenomegaly and is using in combination with ruxolitinib; **OR**
III. Individual has constitutional or no symptomatic splenomegaly.

Continuation requests for Reblozyl (luspatercept) for myelofibrosis-associated anemia may be approved if the following criteria are met:

I. Individual demonstrates continued need for treatment and has confirmation of response to treatment as evidenced by a decrease in transfusion burden from baseline.

Initial requests for Reblozyl (luspatercept) for MDS-RS (myelodysplastic syndromes with ring sideroblasts), MDS/MPN-RS-T (myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis), MDS (myelodysplastic syndromes), or MDS/MPN-T-SF3B1 (myelodysplastic/myeloproliferative neoplasm with thrombocytosis and SF3B1 Mutation) may be approved if the following criteria are met:

I. Individual is 18 years of age or older; **AND**
II. Individual has one of the following (A, B, C, or D):
    A. Documentation is provided that individual has a diagnosis very low to intermediate risk MDS-RS greater than or equal to 15% (or ring sideroblasts 5% to 14% with an SF3B1 mutation) (Label, NCCN 1, 2A); **AND**

1. Individual meets *one* of the following criteria:
    a. Serum erythropoietin (EPO) level of greater than 500 mU/mL; **OR**
    b. Serum EPO level of less than or equal to 500 mU/mL following no response to treatment with erythropoiesis-stimulating agent (ESA); **OR**
    c. Disease does not have del(5q) abnormalities; **OR**

B. Individual has a diagnosis of MDS/MPN-RS-T with *all* of the following:
    1. Ring sideroblasts greater than or equal to 15% (WHO 2017), and documentation is provided; **AND**
    2. Thrombocytosis (defined as platelets greater than or equal to 450 x10^9/L) (WHO 2017); **OR**

C. Individual has a diagnosis MDS/MPN-T-SF3B1 with *all* of the following (NCCN 2A):
    1. Thrombocytosis (defined as platelets greater than or equal to 450 x10^9/L) (WHO 2017); **AND**
    2. Documentation is provided that disease is SF3B1 Mutation positive; **OR**

D. Individual has a diagnosis of MDS; **AND**
    1. Individual is ESA-naïve; **AND**
    2. Documentation is provided that individual has serum EPO level less than 500 U/L;

AND

III. Documentation is provided that individual has required regular red blood cell transfusions of two (2) or more RBC units over eight (8) weeks in the last 16 weeks; **AND**

IV. Individual has a baseline hemoglobin (Hgb) level 11 g/dL or less.

Continuation requests for Reblozyl (luspatercept) for MDS-RS, MDS/MPN-RS-T, MDS, or MDS/MPN-T-SF3B1 may be approved if the following criteria are met:

I. Documentation is provided that individual demonstrates continued need for treatment and has confirmation of response to treatment as evidenced by a decrease in transfusion burden from baseline; **AND**

II. Hemoglobin level is 11.0 g/dL or less.

Reblozyl (luspatercept) for MDS-RS, MDS/MPN-RS-T, MDS, or MDS/MPN-T-SF3B1 may not be approved for the following:

I. Individual has had an inadequate response to ESAs or has MDS/MPN-T-SF3B1 and one of the following:
    A. Individual has unresolved iron deficiency (defined as serum ferritin less than or equal to 15µg/L, or transferrin saturation less than or equal to 20%) (NCT02631070); **OR**
    B. Use beyond 9 weeks of treatment (i.e., administration of consecutive 3 doses) in the absence of response (response defined as decrease in transfusion burden from baseline) at maximum dose level (i.e., 1.75 mg/kg every 3 weeks); **OR**

II. Individual is ESA-naïve and one of the following (Platzbecker, et al.);
    A. Individual has unresolved iron deficiency (defined as serum ferritin less than 100 µg/L); **OR**
    B. Individuals has uncontrolled hypertension.

Requests for Reblozyl (luspatercept) may not be approved when the above criteria are not met and for all other indications.

Approval Duration for β-thalassemia, MDS-RS, MDS/MPN-RS-T, MDS, Myelofibrosis-associated anemia, MDS/MPN-T-SF3B1:

Initial Requests: 6 months
Continuation Requests: 12 months

Quantity Limits

Reblozyl (luspatercept) Quantity Limits

Drug	Limit
Reblozyl 25 mg, 75 mg vial	1.75 mg/kg per 3 weeks

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member

coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS	
J0896	Injection, luspatercept-aamt, 0.25 mg (Reblozyl)

ICD-10 Diagnosis	
C93.10	Chronic myelomonocytic leukemia, not having achieved remission
C94.40	Acute panmyelosis with myelofibrosis, not having achieved remission
C94.41	Acute panmyelosis with myelofibrosis, in remission
C94.42	Acute panmyelosis with myelofibrosis, in relapse
C94.6	Myelodysplastic disease, not elsewhere classified
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
D46.22	Refractory anemia with excess of blasts 2
D46.A	Refractory cytopenia with multilineage dysplasia
D46.B	Refractory cytopenia with multilineage dysplasia and ring sideroblasts
D46.C	Myelodysplastic syndrome with isolated del(5q) chromosomal abnormality
D46.4	Refractory anemia, unspecified
D46.Z	Other myelodysplastic syndromes
D46.9	Myelodysplastic syndrome, unspecified
D47.1	Chronic myeloproliferative disease
D47.4	Osteomyelofibrosis
D56.1	Beta Thalassemia
D56.5	Hemoglobin E-Beta thalassemia
D75.81	Myelofibrosis

Document History

Revised: 08/16/2024
Document History:

- 08/16/2024 – Annual Review: wording, update MDS-RS criteria for del(5q), add MDS to continuation therapy, add myelofibrosis-associated anemia, add MDS/MPN-T-SF3B1. Coding Reviewed: Add ICD-10-CM C93.10, C94.40, C94.41, C94.42, C94.6, D46.0, D46.1, D46.20, D46.21, D46.22, D46.A, D46.B, D46.4, D47.1, D47.4, D75.81. Changed wording for D46.9 Myelodysplasia NOS to Myelodysplastic syndrome, unspecified.
- 09/11/2023 – Select Review: add criteria for MDS in ESA-naïve, wording and formatting. Coding Reviewed: Added ICD-10-CM D46.C.
- 08/18/2023 – Annual Review: No changes. Coding Reviewed: No changes.
- 08/19/2022 – Annual Review: wording and formatting changes. Coding Reviewed: Formatting changes to ICD-10-CM D46.Z, D46.9.
- 08/20/2021 – Annual Review: Update criteria to add continuation criteria. Wording and formatting changes. Coding reviewed: No changes.
- 08/01/2021 – Administrative update to add documentation.
- 02/19/2021 – Annual Review: Updated references. Coding reviewed: No changes.
- 05/15/2020 – Select Review: Update criteria and quantity limits to add new indications for Reblozyl for MDS and MDS/MPN. Clarify non-approvable criteria for beta thalassemia to continuation of use. Add initiation and continuation approval durations. Coding Reviewed: Added HCPCS J0896 (Effective 7/1/2020), Delete J3490, J3590, C9399 (Effective 6/30/2020) ICD-10 Dx-D46.Z-D46.9

- 02/21/2020 – Annual Review: Add new clinical criteria document for Reblozyl (luspatercept). Coding Reviewed: Added: C9399, J3490, J3590, HCPCS, AND D56.1, D56.5 ICD-10-CM

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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.