Drug Coverage Policy

Effective Date 5/1/2025
Coverage Policy Number.....IP0115
Policy Title.....Reblozyl

Hematology – Reblozyl

- Reblozyl® (luspatercept-aamt subcutaneous injection – Celgene/Bristol Myers Squibb)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

OVERVIEW
Reblozyl, an erythroid maturation agent, is indicated for the following conditions:[1.]

- **Beta-thalassemia**, for the treatment of adults with anemia who require regular red blood cell (RBC) transfusions.
- **Myelodysplastic syndromes (MDS)**, very low to intermediate-risk, for the treatment of anemia in adults who may require regular RBC transfusions with anemia without previous erythropoiesis-stimulating agent (ESA) use (ESA-naïve).

- **MDS with ring sideroblasts**, very low- to intermediate-risk disease, or with **myelodysplastic/myeloproliferative neoplasm** (MDS/MPN) with ring sideroblasts and thrombocytosis for the treatment of anemic adults who have failed an ESA and require two or more RBC units over 8 weeks.

Clinical Efficacy

Beta-Thalassemia

In the BELIEVE trial, all patients required regular RBC transfusions at baseline, defined as at least six units of packed RBCs in the preceding 24 weeks, with no transfusion-free intervals > 35 days in that timeframe.[1,2] A response to Reblozyl was defined as a 33% reduction in transfusion requirement from pretreatment baseline and a reduction in transfusion requirements of at least two RBC units during Weeks 13 through 24 compared with pretreatment baseline. The percentage of patients who had a reduction in the transfusion burden of at least 33% from baseline during Weeks 13 through 24 plus a reduction of at least two RBC units over this 12-week interval was greater for patients given Reblozyl (21.4%) vs. patients given placebo (4.5%) [P < 0.001].

MDS or MDS/MPN

In the MEDALIST trial, patients were required to have ring sideroblasts according to World Health Organization criteria (i.e., ≥ 15% or ≥ 5% if *SF3B1* mutation was present).[1,3] Patients with deletion 5q [del(5q)] were excluded from enrollment. All patients were required to have disease refractory or unlikely to respond to ESAs (unless endogenous erythropoietin level was elevated), and the median pretransfusion hemoglobin level was 7.6 g/dL (range 5 to 10 g/dL). Patients had to require RBC transfusions (two or more RBC units over 8 weeks). During the initial 24 weeks of the trial, 58% of patients had transfusion independence for 8 weeks or longer compared with 13% of patients in the placebo group.[1] In the pivotal MEDALIST trial publication, which primarily involved patients with MDS, improvements in hemoglobin from baseline were sustained through at least Week 25. It is notable that the MDS disease course may evolve over time and potentially lead to loss of response of previously effective agents; thus, close follow-up is appropriate to verify that therapeutic response is maintained.

COMMANDS was an open-label trial that compared Reblozyl with epoetin alfa in patients with very low, low, or intermediate risk MDS or with MDS/MPN with ring sideroblasts and thrombocytosis.[1,4] Patients were required to have had two to six RBC units in 8 weeks and erythropoietin levels < 500 U/L at screening. The primary endpoint was RBC transfusion independence for at least 12 weeks with a concurrent mean hemoglobin increase of at least 1.5 g/dL during Weeks 1 to 24 which was met by 58.5% of patients in the Reblozyl group vs. 31.2% of patients in the epoetin alfa group.

Dosing Information

For all indications, the starting dose is 1 mg/kg given subcutaneously once every 3 weeks.[1] Assess and review hemoglobin levels and transfusion record prior to each dose. Discontinue if a patient does not experience a decrease in transfusion burden after 9 weeks of treatment (administration of three doses) at the maximum dose level. For beta-thalassemia, the maximum recommended dose is 1.25 mg/kg given once every 3 weeks. For MDS and MDS/MPN, the maximum dose is 1.75 mg/kg given once every 3 weeks.

Guidelines

The Thalassaemia International Federation published guidelines for the management of transfusion-dependent thalassemia (2021).[5]

- **Chelation therapy** was cited as an effective treatment modality in improving survival, decreasing the risk of heart failure, and decreasing morbidities from transfusional-induced iron overload. The optimal chelation regimen should be individualized and will vary among patients and their clinical status.

- **Allogeneic hematopoietic stem cell transplant (HSCT)** should be offered to patients with beta-thalassemia at an early age before complications due to iron overload have developed if a human leukocyte antigen (HLA) identical sibling is available. In some clinical circumstances, a matched unrelated donor can be adequate.
- **Reblozyl** can be considered for patients ≥ 18 years of age who require regular RBC transfusions.
- **Zynteglo™** (betibeglogene autotemcel intravenous infusion), a gene therapy, may be an option for selected patients when available. Examples include young patients (12 to 17 years of age) with a β^+ genotype who do not have an HLA-compatible sibling donor. Also, Zynteglo can be considered in patients 17 to 55 years of age with a β^+ genotype who do not have severe comorbidities and are at risk or ineligible to undergo allogeneic HSCT but can otherwise undergo an autologous gene therapy procedure with an acceptable risk.

The National Comprehensive Cancer Network guidelines for MDS (version 1.2025 – November 15, 2024) recommend Reblozyl in the following situations:[6]

- **MDS:** Reblozyl is recommended in various clinical scenarios, some of which are described. Treatment with Reblozyl is supported for lower-risk disease associated with symptomatic anemia with no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts ≥ 15% (or ring sideroblasts ≥ 5% with an *SF3B1* mutation) as a single agent (category 1). Treatment with Reblozyl is supported for lower-risk disease associated with symptomatic anemia with no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts < 15% (or ring sideroblasts < 5% with an *SF3B1* mutation) and serum erythropoietin levels ≤ 500 mU/L as a single agent or following no response to an ESA (despite adequate iron stores) [category 2A].
- **MDS/MPN:** Treatment with Reblozyl can be considered for MDS/MPN with an *SF3B1* mutation and thrombocytosis as a single agent (category 2A). Reblozyl can also be used for wild-type *SF3B1* if the patient has thrombocytosis and ring sideroblasts ≥ 15% [category 2A].

Medical Necessity Criteria

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Reblozyl. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Reblozyl as well as the monitoring required for adverse events and long-term efficacy, approval requires Reblozyl to be prescribed by a physician who has consulted with or who specializes in the condition.

Documentation: Documentation is required where noted in the criteria. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information.

FDA-Approved Indications

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1. **Transfusion Dependent Beta-Thalassemia.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   A) Initial Therapy. Approve for 4 months if the patient meets ALL of the following (i, ii, iii, and iv):
      i. Patient is ≥ 18 years of age; AND
      ii. Patient requires regular red blood cell transfusions as defined by meeting BOTH of the following (a and b):

a) Documentation provided that patient has received at least 6 units of packed red blood cells within the preceding 24 weeks; AND
b) According to the prescriber, patient has not had any transfusion-free period > 35 days within the preceding 24 weeks; AND

iii. Patient has not received a gene therapy for transfusion dependent beta-thalassemia in the past; AND
Note: Examples include Zynteglo (betibeglogene autotemcel intravenous infusion) and Casgevy (exagamglogene autotemcel intravenous infusion).

iv. The medication is being prescribed by or in consultation with a hematologist.

B) Patient is Currently Receiving Reblozyl. Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):

i. According to the prescriber, the patient has experienced a clinically meaningful decrease in transfusion burden as defined by a decrease of at least 2 units in red blood cell transfusion burden over the past 6 months compared with the pretreatment baseline (prior to the initiation of Reblozyl); AND

ii. Patient has not received a gene therapy for transfusion dependent beta-thalassemia in the past.
Note: Examples include Zynteglo (betibeglogene autotemcel intravenous infusion) and Casgevy (exagamglogene autotemcel intravenous infusion).

Dosing. Approve up to 1.25 mg/kg by subcutaneous injection administered not more frequently than once every 3 weeks.

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2. Myelodysplastic Syndrome. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, vii, and viii):

i. Patient is ≥ 18 years of age; AND

ii. Documentation provided that the patient has myelodysplastic syndromes and meets ONE of the following (a or b):
a) Ring sideroblast positivity; OR
Note: This is defined as ring sideroblasts ≥ 15% or ring sideroblasts ≥ 5% with an *SF3B1* mutation.
b) Serum erythropoietin level is ≤ 500 mU/mL; AND

iii. Patient has very low- to intermediate-risk myelodysplastic syndromes, as determined by the prescriber; AND
Note: This is determined using the International Prognostic Scoring System (IPSS).

iv. Documentation provided that the patient does not have a confirmed mutation with deletion 5q [del(5q)]; AND

v. Documentation provided that the patient currently requires blood transfusions, defined as at least two red blood cell units over the previous 8 weeks; AND

vi. Documentation provided that the patient's pretreatment hemoglobin level is < 10.0 g/dL; AND

vii. Reblozyl will not be used in combination with an erythropoiesis stimulating agent; AND

viii. The medication is being prescribed by or in consultation with an oncologist or hematologist.

B) Patient is Currently Receiving Reblozyl. Approve for 6 months if, according to the prescriber, the patient has experienced a clinically meaningful decrease in transfusion burden, or the hemoglobin level has increased by ≥ 1.5 g/dL compared with the pretreatment baseline.

Dosing. Approve up to 1.75 mg/kg by subcutaneous injection administered not more frequently than once every 3 weeks.

3. **Myelodysplastic/Myeloproliferative Neoplasm.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, vii, and viii):
     - i. Patient is ≥ 18 years of age; AND
     - ii. Documentation provided that the patient has myelodysplastic/myeloproliferative neoplasm and meets BOTH of the following (a and b):
       - **a)** Ring sideroblast positivity; AND
         Note: This is defined as ring sideroblasts ≥ 15% or ring sideroblasts ≥ 5% with an *SF3B1* mutation.
       - **b)** Thrombocytosis defined as platelet count ≥ 450 x 10^9/L; AND
     - iii. Patient has very low- to intermediate-risk disease, as determined by the prescriber; AND
       Note: This is determined using the International Prognostic Scoring System (IPSS).
     - iv. Documentation provided that the patient does not have a confirmed mutation with deletion 5q [del(5q)]; AND
     - v. Documentation provided that the patient currently requires blood transfusions, defined as at least two red blood cell units over the previous 8 weeks; AND
     - vi. Documentation provided that the patient's pretreatment hemoglobin level is < 10.0 g/dL; AND
     - vii. Reblozyl will not be used in combination with an erythropoiesis stimulating agent; AND
     - viii. The medication is being prescribed by or in consultation with an oncologist or hematologist.
   - **B)** Patient is Currently Receiving Reblozyl. Approve for 1 year if, according to the prescriber, the patient has experienced a clinically meaningful decrease in transfusion burden, or the hemoglobin level has increased by ≥ 1.5 g/dL compared with the pretreatment baseline.

   Dosing. Approve up to 1.75 mg/kg by subcutaneous injection administered not more frequently than once every 3 weeks.

Reblozyl for any other use is considered not medically necessary. Criteria will be updated as new published data are available.

Coding Information

Note:
1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J0896	Injection, luspatercept-aamt, 0.25 mg

References

1. Reblozyl® subcutaneous injection [prescribing information]. Summit; NJ: Celgene/Bristol-Myers Squibb; May 2024.

2. Cappellini MD, Viprakasit V, Taher AT, et al; BELIEVE Investigators. A Phase 3 Trial of luspatercept in patients with transfusion-dependent β-thalassemia. *N Engl J Med*. 2020;382(13):1219-1231.
3. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes. *N Engl J Med*. 2020;382(2):140-151.
4. Platzbecker U, Della Porta MG, Santini V, et al. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naïve, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomized controlled trial. *Lancet*. 2023; 402:373-385.
5. Farmakis D, Porter J, Taher A, et al, for the 2021 TIF Guidelines Taskforce. 2021 Thalassaemia International Federation guidelines for the management of transfusion-dependent thalassemia. *Hemasphere*. 2022; 6:8(e732).
6. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 1.2025 – November 15, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 3, 2025.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Review	**Beta Thalassemia. Removed** 'Treatment of anemia with a documented diagnosis of beta-thalassemia.' **Updated** 'Has not received Zynteglo (betibeglogene autotemcel intravenous infusion) in the past 12 months' TO 'Patient has not received a gene therapy for transfusion dependent beta-thalassemia in the past; Note: Examples include Zynteglo (betibeglogene autotemcel intravenous infusion) and Casgevy (exagamglogene autotemcel intravenous infusion).' **Added** criteria for 'Patient is Currently Receiving Reblozyl.' **Added** dosing.	7/1/2024
Annual Revision	**Retitled** coverage policy from "Hematology – Reblozyl for Non-Oncology Uses" to "Hematology – Reblozyl." **Added** criteria for coverage of Myelodysplastic Syndrome. **Added** criteria for coverage of Myelodysplastic/Myeloproliferative Neoplasm. **Added** dosing for Myelodysplastic Syndrome. **Added** dosing for Myelodysplastic/Myeloproliferative Neoplasm.	4/15/2025

	Added documentation requirements as noted for coverage of Transfusion Dependent Beta-Thalassemia. **Added** documentation requirements as noted for coverage of Myelodysplastic Syndrome. **Added** documentation requirements as noted for coverage of Myelodysplastic/Myeloproliferative Neoplasm.	

The policy effective date is in force until updated or retired.