Drug Coverage Policy

Effective Date 4/1/2026
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 where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. 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.

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 disease, 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 requirements 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 who received 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.[I] In the pivotal MEDALIST trial publication, which primarily involved patients with MDS, improvements in hemoglobin from baseline were sustained through at least Week 25.

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 (SC) 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 SC given once every 3 weeks. For MDS and MDS/MPN, the maximum dose is 1.75 mg/kg SC given once every 3 weeks.

Guidelines

The Thalassaemia International Federation published guidelines for the management of transfusion-dependent beta-thalassemia (2025).[5] The guidelines are extensive.

- Reblozyl is recommended for patients ≥ 18 years of age with transfusion-dependent beta-thalassemia who require regular RBC transfusions (Grade B, Class I).

Various National Comprehensive Cancer Network (NCCN) guidelines address Reblozyl.

- **MDS:** The NCCN guidelines for MDS (version 3.2026 – January 12, 2026)[6] recommends Reblozyl 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) [both category 2A].
- **MDS/MPN:** The NCCN guidelines for MDS (version 3.2026 – January 12, 2026) suggest that treatment with Reblozyl can be considered for MDS/MPN with an *SF3B1* mutation and thrombocytosis as a single agent for the treatment of anemia (category 2A).[6,7]
- **Myelofibrosis-Associated Anemia:** The NCCN guidelines for Myeloproliferative Neoplasms (version 2.2025 – July 8, 2025) recommend Reblozyl for the management of myelofibrosis-associated anemia in patients without splenomegaly or constitutional symptoms as an other recommended regimen (category 2A).[8] Reblozyl is also recommended for patients with splenomegaly and/or constitutional symptoms when given in combination with a Janus Associated Kinases (JAK) inhibitor (category 2A).

Medical Necessity Criteria

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Reblozyl. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 or in consultation with a physician who specializes in the condition being treated.

Certain indications and/or approval conditions that are delegated to EviCore by Evernorth will follow Oncology Medications (1403) coverage policy for prior authorization medical necessity criteria. Note: Any listed preferred product requirements in this coverage policy, inclusive of oncology and/or oncology-related uses, are applicable as noted.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, prescription receipts and/or other information. All documentation must include patient-specific identifying information.

Reblozyl is considered medically necessary when ONE of the following is met

FDA-Approved Indications

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 6 months if the patient meets ALL of the following (i, ii, iii, iv and v):
      i. Patient is ≥ 18 years of age; AND

ii. According to the prescriber, the patient requires regular red blood cell transfusions as defined by meeting BOTH of the following (a and b):
   a) Patient has received at least 6 units of packed red blood cells within the preceding 24 weeks; AND
   b) Patient has not had any transfusion-free period > 35 days within the preceding 24 weeks; AND
iii. Patient is not currently receiving Aqvesme (mitapivat tablets); AND
iv. 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).
v. 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 ALL of the following criteria (i, ii, and iii):
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 is not currently receiving Aqvesme (mitapivat tablets); AND
iii. 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, and vi):
i. Patient is ≥ 18 years of age; AND
ii. 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).
iii. Patient does not have a confirmed mutation with deletion 5q [del(5q)] **[documentation required]**; AND
iv. According to the prescriber, the patient has symptomatic anemia; AND
v. Reblozyl will not be used in combination with an erythropoiesis stimulating agent; AND
vi. 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.

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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, and iv):
i. Patient is ≥ 18 years of age; AND

ii. 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).
iii. According to the prescriber, the patient has anemia; AND
iv. 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.

Other Uses with Supportive Evidence

4. Myelofibrosis. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D)
A) Patient is ≥ 18 years of age; AND
B) Patient has myelofibrosis-related anemia; AND
C) Patient meets ONE of the following (i or ii):
i. Patient has no splenomegaly or constitutional symptoms; OR
ii. Patient meets BOTH of the following (a and b):
a) Patient has splenomegaly or constitutional symptoms; AND
b) Reblozyl will be used in combination with a Janus Associated Kinases (JAK) inhibitor. Note: Example of JAK inhibitors are Jakafi (ruxolitinib tablets) and Inrebic (fedratinib capsules).
D) The medication is being prescribed by or in consultation with an oncologist or hematologist.

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. Guidelines for the Management of Transfusion-Dependent β-Thalassemia (TDT) [Internet]. 5th ed. Nicosia, Cyprus: Thalassemia International Federation; 2025. PMID: 40367250.
6. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 3.2026 – January 12, 2026. © 2026 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 16, 2026.
7. Komrokji RS, Platzbecker U, Fenaux P, et al. Luspatercept for myelodysplastic syndromes/myeloproliferative neoplasma with ring sideroblasts and thrombocytosis. *Leukemia*. 2022;36:1432-1435.
8. The NCCN Myeloproliferative Neoplasms Clinical Practice Guidelines in Oncology (version 2.2025 – July 8, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 16, 2026.

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.	4/15/2025

	Added dosing for Myelodysplastic/Myeloproliferative Neoplasm. **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.	
Selected Revision	**Documentation Instructions.** **Updated from** "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 **to** "Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, prescription receipts and/or other information. All documentation must include patient-specific identifying information" **Transfusion Dependent Beta-Thalassemia:** For Initial Therapy, the duration of approval was changed to 6 months; previously, it was 4 months. For Initial Therapy and for a Patient Currently Receiving Reblozyl, a requirement was added that the patient is not currently receiving Aqvesme (mitapivat tablets). **Myelodysplastic Syndrome:** For initial therapy, the requirement was removed that the patient has ring sideroblast positivity or the patient has a serum erythropoietin level ≤ 500 mU/mL. The requirement was removed that the patient currently requires blood transfusions, defined as at least two red blood cell units over the previous 8 weeks. The requirement that the pretreatment hemoglobin level is < 10.0 g/dL was changed to according to the prescriber, the patient has symptomatic anemia. Updated authorization duration for continuing therapy with Rebozyl from 6 months to 1 year. **Myelodysplastic/Myeloproliferative Neoplasm:** The requirements were removed that the patient has ring sideroblast positivity and thrombocytosis defined as a platelet count ≥ 450 x 10^9/L. Also, the following requirements were removed: patient does not have a confirmed mutation with deletion 5q[del(5q)]; patient currently requires blood	4/1/2026

	transfusions transfusions, defined as at least two red blood cell units over the previous 8 weeks; and Reblozyl will not be used in combination with an erythropoiesis stimulating agent. The requirement that the pretreatment hemoglobin level is < 10.0 g/dL was changed to according to the prescriber, the patient has anemia. **Myelofibrosis:** This was added as a new condition of approval. Dosing for this indication was also added.	

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