Utilization Review Policy 221

POLICY: Hematology – Reblozyl Utilization Management Medical Policy

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

EFFECTIVE DATE: 5/1/2020
LAST REVISION DATE: 01/08/2025

COVERAGE CRITERIA FOR: All UCare Plans

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].

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.

*Indications and/or approval conditions noted with **[EviCore]** are managed by EviCore healthcare for those clients who use EviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to EviCore at www.EviCore.com.*

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Reblozyl is recommended in those who meet one of the following criteria:

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.** 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 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.
  2. 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.

3. Myelodysplastic Syndrome. *[EviCore]* 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. According to the prescriber, 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. Patient does not have a confirmed mutation with deletion 5q [del(5q)]; AND

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

vi. 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.

4. Myelodysplastic/Myeloproliferative Neoplasm. *[EviCore]* 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. According to the prescriber, 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. Patient does not have a confirmed mutation with deletion 5q [del(5q)]; AND

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

vi. 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Reblozyl is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	01/04/2023
Selected Revision	**Beta Thalassemia:** In initial therapy criteria, regarding the requirement for regular red blood cell transfusions, this was further defined to mean that the patient has received at least 6 units of packed red blood cells within the preceding 24 weeks, and the patient has not had any transfusion-free period > 35 days within the preceding 24 weeks. The Note which previously stated that this includes patients who are transfusion-dependent was removed (no longer needed). In continuation criteria, a clinically meaningful decrease in transfusion burden was defined by as decreased in 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). **Myelodysplastic Syndrome:** In the initial therapy criteria, the requirement for myelodysplastic syndromes "with ring sideroblasts" was revised to state that the ring sideroblasts must be ≥ 15%, or ring sideroblasts must be ≥ 5% with an *SF3B1* mutation. In continuation criteria, the approval duration was decreased from 1 year to 6 months. Additionally, a clinically meaningful decrease in transfusion burden was defined by meeting one of the following: 1) if the patient had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of ≥ 4 units per 8 weeks, the red blood cell transfusion burden has decreased by ≥ 4 units per 8 weeks from pretreatment baseline; OR 2) if the patient had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of < 4 units per 8 weeks, hemoglobin has increased by at least 1.5 g/dL compared with the pretreatment baseline. **Myelodysplastic/Myeloproliferative Neoplasm:** In the initial therapy criteria, the requirement for myelodysplastic/myeloproliferative neoplasm "with ring sideroblasts" was revised to state that the ring sideroblasts must be ≥ 15%, or ring	01/11/2023

	sideroblasts must be ≥ 5% with an *SF3B1* mutation. Additionally, the requirement for "thrombocytosis-associated anemia" was reworded to "thrombocytosis defined as platelet count ≥ 450 x 10^9/L". In continuation criteria, a clinically meaningful decrease in transfusion burden was defined by meeting one of the following: 1) if the patient had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of ≥ 4 units per 8 weeks, the red blood cell transfusion burden has decreased by ≥ 4 units per 8 weeks from pretreatment baseline; OR 2) if the patient had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of < 4 units per 8 weeks, hemoglobin has increased by at least 1.5 g/dL compared with the pretreatment baseline.	
Annual Revision	**Myelodysplastic Syndrome:** In the initial therapy criteria, the requirement that a patient has ring sideroblasts ≥ 15% or ring sideroblasts ≥ 5% with an *SF3B1* mutation was changed to either the patient has ring sideroblast positivity (with the definition in a Note) or has serum erythropoietin levels ≤ 500 mU/mL. The requirement was removed that the patient has tried an erythropoiesis-stimulating agent for at least 6 weeks (unless intolerant) or that the serum erythropoietin level is greater than 500 mU/mL. In the criteria in which the patient is currently receiving Reblozyl, the following requirements that defined that the patient has experienced a clinically meaningful decrease in transfusion burden were removed: 1) for a patient that had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of ≥ 4 units per 8 weeks, that red blood cell transfusion burden has decreased by ≥ 4 units per 8 weeks from the pretreatment baseline; OR 2) for a patient that had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of < 4 units per 8 weeks, that the hemoglobin levels has increased by ≥ 1.5 g/dL compared with the pretreatment baseline. A patient is still required to have experienced a clinically meaningful decrease in transfusion burden per the prescriber (without the definitions above) and the phrase "or hemoglobin has increased by 1.5 g/dL compared with the pretreatment baseline" was added. **Myelodysplastic/Myeloproliferative Neoplasm:** In the initial therapy criteria, the requirement that a patient has ring sideroblasts ≥ 15% or ring sideroblasts ≥ 5% with an *SF3B1* mutation was changed to just state that the patient has ring sideroblast positivity (with the definition in a Note). The requirement was removed that the patient has tried an erythropoiesis-stimulating agent for at least 6 weeks (unless intolerant) or that the serum erythropoietin level is greater than 500 mU/mL. In the criteria in which the patient is currently receiving Reblozyl, the following requirements that defined that the patient has experienced a clinically meaningful decrease in transfusion burden were removed: 1) for a patient that had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of ≥ 4 units per 8 weeks, that red blood cell transfusion burden has decreased by ≥ 4 units per 8 weeks from the pretreatment baseline; OR 2) for a patient that had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of < 4 units per 8 weeks, that the hemoglobin has increased by ≥ 1.5 g/dL compared with the pretreatment baseline. A patient is still required to have experienced a clinically meaningful decrease in transfusion burden per the prescriber (without the definitions above) and the phrase "or hemoglobin has increased by 1.5 g/dL compared with the pretreatment baseline" was added.	12/20/2023
Selected Revision	**Transfusion Dependent Beta-Thalassemia:** The name of the indication of use was changed to as listed (previously it was cited as beta-thalassemia). The criterion that the patient has not received Zynteglo in the past was changed to state that the patient has not received a gene therapy for transfusion-dependent beta-thalassemia in the past. A Note was added that examples are Zynteglo and Casgevy.	04/24/2024
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/16/2024
Annual Revision	No criteria changes.	01/08/2025
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/15/2025