UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Reblozyl Utilization Management Medical Policy
- Reblozyl® (luspatercept-aamt subcutaneous injection – Celgene/Acceleron)

REVIEW DATE: 01/04/2023; selected revision 01/11/2023

OVERVIEW

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

- **Beta thalassemia**, for treatment of adults with anemia who require regular red blood cell (RBC) transfusions.
- **Myelodysplastic syndromes** with ring sideroblasts (MDS-RS) or **myelodysplastic/myeloproliferative neoplasm** with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) associated anemia, for adults with very low- to intermediate-risk disease who have failed an erythropoiesis-stimulating agent (ESA) and require two or more RBC units over 8 weeks.

Clinical Efficacy

Beta Thalassemia

In the BELIEVE trial (published), 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.[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 2 units RBC during Weeks 13 through 24 compared with pretreatment baseline.

MDS and MDS/MPN-RS-T

In the MEDALIST trial (published), patients were required to have ring sideroblasts according to World Health Organization (WHO) criteria (i.e., ≥ 15% or ≥ 5% if *SF3B1* mutation was present).[3] Patients with deletion 5q were excluded from enrollment. All patients were required to have disease refractory 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). Regarding response criteria, an erythroid response was defined as a reduction in RBC transfusion of ≥ 4 units per 8 weeks in patients with pretreatment baseline transfusion burden of ≥ 4 units per 8 weeks. For patients with a pretreatment baseline transfusion burden of < 4 units per 8 weeks, a response was defined as an increase in hemoglobin of ≥ 1.5 g/dL over a period of 8 weeks compared with pretreatment baseline. 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.

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).[4]

- **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 (NCCN) guidelines for MDS (version 1.2023 – September 12, 2022) recommend Reblozyl in the following situations:[5]

- **MDS:** 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), in one of the following situations: 1) serum erythropoietin > 500 mU/mL; OR 2) serum erythropoietin ≤ 500 mU/mL following no response to an ESA ± granulocyte colony-stimulating factor (G-CSF) [category 2A].
- **MDS/MPN:** Treatment with Reblozyl can be considered for MDS/MPN with *SF3B1* mutation and thrombocytosis as a single agent. Reblozyl can also be used for wild-type *SF3B1* if the patient has thrombocytosis and ring sideroblasts ≥ 15% [category 2B].

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.

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. Beta Thalassemia. Approve for the duration noted if the patient meets one of the following criteria (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 Zynteglo (betibeglogene autotemcel intravenous infusion) in the past; AND
- **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 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); AND
- **ii.** Patient has not received Zynteglo (betibeglogene autotemcel intravenous infusion) in the past.

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, viii, and ix):
- **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 sideroblasts ≥ 15%; OR
  - **b)** Ring sideroblasts ≥ 5% with an *SF3B1* mutation; 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.** Patient meets ONE of the following (a or b):
  - **a)** Patient tried an erythropoiesis stimulating agent for at least 6 weeks, unless intolerant; OR
  - **b)** Serum erythropoietin level is greater than 500 mU/L; AND
- **vii.** Pretreatment hemoglobin level is < 10.0 g/dL; AND
- **viii.** Reblozyl will not be used in combination with an erythropoiesis stimulating agent; AND

ix. 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 as defined by meeting one of the following (i or ii):

i. Patient had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of ≥ 4 units per 8 weeks: Red blood cell transfusion burden has decreased by ≥ 4 units per 8 weeks from the pretreatment baseline; OR

ii. Patient had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of < 4 units per 8 weeks: Hemoglobin 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 criteria (A or B):

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

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) Presence of ring sideroblasts as defined by one of the following [(1) or (2)]:

(1) Ring sideroblasts ≥ 15%; OR

(2) Ring sideroblasts ≥ 5% with an *SF3B1* mutation; AND

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. Patient meets ONE of the following (a or b):

a) Patient tried an erythropoiesis stimulating agent for at least 6 weeks, unless intolerant; OR

b) Serum erythropoietin level is greater than 500 mU/L; AND

vii. Pretreatment hemoglobin level is < 10.0 g/dL; AND

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

ix. 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 as defined by meeting one of the following (i or ii):

i. Patient had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of ≥ 4 units per 8 weeks: Red blood cell transfusion burden has decreased by ≥ 4 units per 8 weeks from the pretreatment baseline; OR

ii. Patient had a pretreatment (prior to the initiation of Reblozyl) transfusion burden of < 4 units per 8 weeks: Hemoglobin 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 and Cambridge, MA: Celgene/Acceleron; July 2022.
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 Mar 26;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 Jan 9;382(2):140-151.
4. 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).
5. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 1.2023 – September 12, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 9, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Myelodysplastic Syndrome:** The duration of a trial of an erythropoiesis stimulating agent was changed to be at least 6 weeks in duration, unless intolerant (previously was at least 3 months). **Myelodysplastic/Myeloproliferative Neoplasm:** The duration of a trial of an erythropoiesis stimulating agent was changed to be at least 6 weeks in duration, unless intolerant (previously was at least 3 months).	12/08/2021
Selected Revision	**Beta Thalassemia:** In both initial and continuation criteria, a requirement was added that the patient has not received Zynteglo (betibeglogene autotemcel intravenous infusion) in the past.	10/05/2022
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 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.	01/11/2023