POLICY: Hematology – Reblozyl® (luspatercept-aamt for subcutaneous injection)

DATE REVIEWED: 11/13/2019; selected revision 04/15/2020

OVERVIEW

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

1. Beta-thalassemia, for treatment of adults with anemia who require regular red blood cell (RBC) transfusions; AND
2. Myelodysplastic syndromes with ring sideroblasts (MDS-RS) or myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) associated anemia, for those failing an erythropoiesis stimulating agent and requiring two or more red blood cell units over 8 weeks in adult patients with very low- to intermediate-risk disease.

Reblozyl is not indicated for use as a substitute for red blood cell transfusions in patients who require immediate correction of anemia. In the pivotal study evaluating Roblozyl for MDS/MPN, 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), and deletion. Safety and efficacy have not been established in patients < 18 years of age.

Disease Overview

Beta-thalassemia, an inherited blood disorder, is characterized by reduced levels of functional hemoglobin (Hb).[2] Patients with a severe form (beta-thalassemia major) become symptomatic due to low Hb level (e.g., increased cardiac effort, tachycardia, poor growth) or ineffective erythropoiesis (e.g., bone changes, massive splenomegaly). Even with treatment, severe complications may arise due to iron overload secondary to increased intestinal absorption and frequent blood transfusions. The frequency of symptomatic patients with beta-thalassemia is estimated at approximately 1 in 100,000 individuals in the general population but is less common in the US.

Myelodysplastic syndromes are cancers in which cells in the bone marrow do not mature and become healthy blood cells.[5] Patients with MDS with refractory anemia and ring sideroblasts have too few red blood cells in the blood with too much iron inside the cell. However, the number of white blood cells and platelets is normal. Supportive therapy may include transfusions and use of erythropoiesis-stimulating agents (ESAs). A red blood cell transfusion is given when the red blood cell count is low and signs or symptoms of anemia, such as shortness of breath or fatigue, occur. ESAs may be given to increase the number of mature red blood cells made by the body and to lessen the effects of anemia. Myelodysplastic/myeloproliferative neoplasms are diseases of the blood and bone marrow with features of myelodysplastic syndromes as well as myeloproliferative neoplasms (e.g., a greater than normal number of blood stem cells become one or more types of blood cells and the total number of blood cells slowly increases).

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

Guidelines do not address Reblozyl for treatment of beta-thalassemia. Standards of Care Guidelines for Thalassemia (2012) are published by the Children's Hospital and Research Center of Oakland.[3] Life-long blood transfusions and iron chelation are the main treatments for beta-thalassemia. Transfusions are usually needed every 3 to 4 weeks and are recommended to maintain the pre-transfusion Hb level above 9 to 10 g/dL and post-transfusion Hb level should not exceed 14 g/dL. Blood transfusions are given to improve anemia as well as suppress ineffective erythropoiesis. Most serious growth, bone, and neurologic complications are prevented with regular transfusions. Once transfusions are started, transfusion-related complications become a major source of morbidity. Hydroxyurea is described as an experimental agent for beta-thalassemia. The Thalassaemia International Federation (2014) also recommends transfusions and iron chelation for treatment of beta-thalassemia.[4] These guidelines state that transfusions are usually administered every 2 to 5 weeks and are recommended to maintain the pre-transfusion Hb level above 9 to 10.5 g/dL and post-transfusion Hb level below 14 to 15 g/dL. The primary goal of chelation therapy is to maintain safe levels of body iron by balancing iron from blood transfusion with iron excretion by chelation. Despite literature suggesting hydroxyurea may be beneficial in certain patients with beta-thalassemia, use is not recommended outside of a clinical trial.

The National Comprehensive Cancer Network (NCCN) guidelines for MDS (version 2.2020 – February 28, 2020) recommend Roblozyl in patients symptomatic anemia due to MDS, in patients who have no response to ESAs (defined by rise in hemoglobin level or decrease in transfusion burden) following 3 to 4 months of treatment.[6] Reblozyl is also a treatment option for patients who have serum erythropoietin levels > 500 mU/mL.

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 indication(s). 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.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

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 criteria (i, ii, and iii):
     - **i.** The patient is ≥ 18 years of age; AND

ii. According to the prescriber, the patient requires regular red blood cell transfusions.
Note: This includes patients who are transfusion-dependent; AND
iii. The medication is being prescribed by or in consultation with a hematologist.

B) Continuation of Therapy. Approve for 1 year if according to the prescriber, the patient has experienced a clinically meaningful decrease in transfusion burden.

Dosing. Approve up to 1.25 mg/kg by subcutaneous injection, 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 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. The patient is ≥ 18 years of age; AND
ii. According to the prescriber, the patient has myelodysplastic syndromes with ring sideroblasts; AND
iii. The patient has very low- to intermediate-risk myelodysplastic syndromes, as determined by the prescriber.
Note: This is determined using the International Prognostic Scoring System (IPSS); AND
iv. The patient does not have a confirmed mutation with deletion 5q (del 5q); AND
v. The patient currently requires blood transfusions, defined as at least two red blood cell units over the previous 8 weeks; AND
vi. The patient meets ONE of the following (a or b):
a) The patient tried an erythropoiesis stimulating agent for at least 3 months, unless intolerant; OR
b) Serum erythropoietin level is greater than m500 U/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) Continuation of Therapy. Approve for 1 year if, according to the prescriber, the patient has experienced a clinically meaningful decrease in transfusion burden.

Dosing. Approve up to 1.75 mg/kg by subcutaneous injection, 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. The patient is ≥ 18 years of age; AND
ii. According to the prescriber, the patient has myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis-associated anemia; AND
iii. The patient has very low- to intermediate-risk disease, as determined by the prescriber.
Note: This is determined using the International Prognostic Scoring System (IPSS); AND
iv. The patient does not have a confirmed mutation with deletion 5q (del 5q); AND
v. The patient currently requires blood transfusions, defined as at least two red blood cell units over the previous 8 weeks; AND
vi. The patient meets ONE of the following (a or b):

a) The patient tried an erythropoiesis stimulating agent for at least 3 months, 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) Continuation of Therapy. Approve for 1 year if, according to the prescriber, the patient has experienced a clinically meaningful decrease in transfusion burden.

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

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Reblozyl has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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® for subcutaneous injection [prescribing information]. Summit; NJ and Cambridge, MA: Celgene and Acceleron; April 2020.
2. National Organization for Rare Disorders (NORD). Beta thalassemia. Available at: https://rarediseases.org/rare-diseases/thalassemia-major//. Accessed on November 8, 2019.
3. Standards of Care Guidelines for Thalassemia – 2012. Children's Hospital and Research Center Oakland. Available at: https://thalassemia.com/documents/SOCGuidelines2012.pdf. Accessed October 25, 2019.
4. Cappellini MD, Cohen A, Porter J, et al. Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT) [Internet]. 3rd edition. Nicosia (CY): Thalassaemia International Federation; 2014. Available at: https://www.ncbi.nlm.nih.gov/books/NBK269382/. Accessed on October 28, 2019.
5. National Cancer Institute, National Institutes of Health. Myelodysplastic syndromes treatment. Updated October 30, 2019. Accessed on April 7, 2020. Available at: https://www.cancer.gov/types/myeloproliferative/patient/myelodysplastic-treatment-pdq.
6. The NCCN® Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (Version 2.2020 – February 28, 2020). 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org/clinical.asp. Accessed on April 7, 2020.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	11/13/2019
Update	11/18/2019: No criteria changes. Note added to clarify that the requirement for regular blood cell transfusions includes patients who are transfusion-dependent.	--
Update	12/17/2019: No criteria changes. Dosing added to the overview to support initial approval duration of 4 months. Labeling supports discontinuation of Reblozyl if benefit not observed after 6 weeks at starting dose followed by 9 weeks at the maximum dose.	--
Selected revision	**Myelodysplastic Syndromes and Myelodysplastic/Myeloproliferative Neoplasm:** These new FDA-approved indications were added to the policy.	04/15/2020