Reblozyl (luspatercept-aamt) Medical Drug Program Summary

Retired 9/1/2022

For patients with late stage metastatic disease (Stage IV), please refer to MP 2.373 Step Therapy Treatment in Cancer, Including Treatments for Stage Four, Advanced Metastatic Cancer and Severe Related Health Conditions for additional guidance

FDA APPROVED INDICATIONS AND DOSAGE[1]

Agent(s)	Indication(s)	Dosage
Reblozyl® (luspatercept-aamt) Subcutaneous injection	• Treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions • Treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more RBC units over 8 weeks in adult patients with very low – to – intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) Limitation of Use: Reblozyl is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia	**Anemia in beta thalassemia:** The recommended starting dose is 1 mg/kg once every 3 weeks by subcutaneous injection If the pre-dose Hgb is greater than or equal to 11.5 g/dL and the Hgb level is not influenced by recent transfusion, delay dosing until the Hgb is less than or equal to 11 g/dL Do not increase the dose beyond the maximum dose of 1.25 mg/kg Discontinue Reblozyl if a patient does not experience a decrease in transfusion burden after 9 weeks of treatment (administration of 3 doses) at the maximum dose level or if unacceptable toxicity occurs at any time **Anemia in MDS-RS or MDS/MPN-RS-T:** 1 mg/kg once every 3 weeks by subcutaneous injection Do not increase the dose beyond the maximum dose of 1.75 mg/kg

		Discontinue Reblozyl if a patient does not experience a decrease in transfusion burden after 9 weeks of treatment (administration of 3 doses) at the maximum dose level or if unacceptable toxicity occurs at any time

CLINICAL RATIONALE
Beta Thalassemia[2]
Thalassemia is a complex group of diseases that are relatively rare in the United States but common in Mediterranean regions and South and Southeast Asia. As a consequence of immigration patterns, the occurrence of thalassemia disorders in the United States is increasing.

Beta thalassemia disorders result from decreased production of Beta globin chains, resulting in relative excess of Alpha globin chains. The degree of excess nonfunctional Alpha chains is the major predictor of disease severity. $Beta^0$ thalassemia refers to the absence of production of Beta globin. When patients are homozygous for the $Beta^0$ thalassemia gene, they cannot make any normal Beta chains (hemoglobin A). $Beta^+$ thalassemia indicates a mutation that presents as decreased but not absent production of Beta globin. Thalassemia patients in which one or both of their beta thalassemia mutations are $beta^+$ mutations make some hemoglobin A, and the disorder may be less severe. Beta thalassemia major is a clinical diagnosis referring to a patient who has a severe form of the disease and requires chronic transfusions early in life. Beta thalassemia intermedia is a clinical diagnosis of a patient characterized by a less severe chronic anemia and a more variable clinical phenotype.

Prior to consideration of transfusion therapy, it is critical to confirm the patient's diagnosis. In addition to complete blood count (CBC), hemoglobin electrophoresis is the first diagnostic test. Fractions of hemoglobin A, A_2, F, H, E, and other variants are measured. Hemoglobin electrophoresis or high-performance liquid chromatography is used. Mutations may overlap on the screening test, resulting in incorrect diagnosis or a false negative. Therefore, genetic analysis for both Beta thalassemia and Alpha thalassemia mutations are necessary.

Patients with thalassemia intermedia may have exaggerated anemia due to temporary nutritional deficiencies or infectious complications. It is important to complete a detailed medical history concerning factors that may temporarily lower hemoglobin, including viral illness, marrow-suppressing medication, nutritional deficiencies in folic acid or iron, or exposure to environmental factors such as lead. Correcting these deficiencies may raise the hemoglobin level enough to obviate the need for transfusion. Therefore, laboratory screening of patients is necessary to rule out other causes of anemia.

Blood transfusion is the mainstay of care for individuals with thalassemia major and many with intermedia. The purpose of transfusion is twofold: to improve the anemia and to suppress the ineffective erythropoiesis. Chronic transfusions prevent most of the serious growth, skeletal, and neurological complications of thalassemia major.

The decision to start transfusions is based on inability to compensate for the low hemoglobin (signs of increased cardiac effort, tachycardia, sweating, poor feeding, and poor growth), or less commonly, on increasing symptoms of ineffective erythropoiesis (bone changes, massive splenomegaly). The decision to institute chronic transfusion should not be based exclusively on the presence of anemia. Anemia should be linked with a significant impairment in quality of life, or associated morbidities. Factors to consider include poor growth; inability to maintain daily routines and activities such as going to school or work.

The decision to start regular transfusions is clear when the initial hemoglobin level is well below 6 g/dL. Patients with a hemoglobin level less than 7 g/dL may sometimes require regular transfusions in the presence of growth impairment, marked skeletal change, or extramedullary hematopoiesis.

The goal of transfusion is to shut off erythropoiesis as much as possible. Transfusions should generally be given at an interval of three to four weeks (with aging patients every 2 weeks may be necessary). The amount of blood received on transfusion day is determined by pre-transfusion hemoglobin levels. The target is to maintain the pre-transfusion hemoglobin level between 9 and 10 g/dL. The post transfusion hemoglobin should not exceed 14 g/dL.

Myelodysplastic Syndrome[3]
The myelodysplastic syndromes (MDS) represent myeloid clonal hemopathies with a relatively heterogeneous spectrum of presentation. The initial evaluation of patients with suspected MDS requires careful assessment of the peripheral blood smear and blood counts, marrow morphology, cytogenetics, duration of abnormal blood counts, other potential causes of cytopenias, and concomitant illnesses.

The current WHO guidelines identify six entities of MDS:
- MDS with single lineage dysplasia (MDS-SLD)
- MDS with ring sideroblasts (MDS-RS)
- MDS with multilineage dysplasia (MDS-MLD)
- MDS with excess blasts (MDS-EB)
- MDS with isolated del(5q) ± one other abnormality except -7/del(7q)
- MDS unclassifiable (MDS-U)

MDS-RS patients have anemia and no blasts as well as greater than or equal to 15% of erythroid precursors with ring sideroblasts or greater than or equal to 5% ring sideroblasts if SF3B1 mutation is present. MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) includes cases that present with clinical and morphologic features consistent with MDS-RS along with thrombocytosis (platelets greater than or equal to 450 X 10^9/L). NCCN recommends that anemia in these diagnoses should first be treated by:
- Treating coexisting causes
- Replacing iron, folate, B_{12}, if needed
- RBC transfusions
- Supportive care

Serum erythropoietin stimulating agents (EPO) should be used after these measures unless there is del(5q) ± one other cytogenetic abnormality (except those involving chromosome 7) in which lenalidomide should be used before starting an EPO. NCCN does list luspatercept as recommended therapy following incomplete response to EPO.

The Revised International Prognostic Scoring System (IOSS-R) is a scale that defines five risk groups (very low, low, intermediate, high, and very high) for MDS. This scale adds a numerical value to the patient's hemoglobin, absolute neutrophil count, platelets, bone

marrow blasts, cytogenetic category (very good, good, intermediate, poor, or very poor). NCCN gives further information relating to IPSS-R score and median survival and progression in the absence of therapy.

IPSS-R Risk Category (% IPSS-R population)	Overall Score	Median survival (y) in the Absence of Therapy	25% AML Progression (y) in the absence of therapy
Very Low (19)	less than or equal to 1.5	8.8	Not Reached
Low (38)	greater than 1.5 and less than or equal to 3.0	5.3	10.8
Intermediate (20)	greater than 3.0 and less than or equal to 4.5	3	3.2
High (13)	greater than 4.5 and less than or equal to 6.0	1.6	1.4
Very high (10)	greater than 6.0	0.8	0.7

Efficacy[1]
Reblozyl (luspatercept-aamt) is a recombinant fusion protein that binds several endogenous TGF-Beta superfamily ligands thereby diminishing Smad2/3 signaling. Reblozyl promotes erythroid maturation through differentiation of late-stage erythroid precursors (normoblasts) in mice.

The efficacy of Reblozyl was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 336 patients with beta thalassemia requiring regular red blood cell (RBC) transfusions (BELIEVE trial). Regular RBC transfusions in this study were defined as 6-20 RBC units in the 24 weeks prior to randomization and no transfusion-free period for greater than or equal to 35 days during that period. All patients were eligible to receive best supportive care, which included RBC transfusions; iron-chelating agents; use of antibiotic, antiviral, and antifungal therapy; and/or nutritional support, as needed.

The BELIEVE trial excluded patients with hemoglobin S/Beta thalassemia or Alpha-thalassemia (26 patients in the study had Beta thalassemia combined with Alpha thalassemia) or who had major organ damage (liver disease, heart disease, lung disease, renal insufficiency). Patients with deep vein thrombosis or stroke or recent use of ESA, immunosuppressant, or hydroxyurea therapy were also excluded.

The efficacy of Reblozyl was established based upon the proportion of patients achieving RBC transfusion burden reduction (greater than or equal to 33% reduction from baseline) with a reduction of at least 2 units from week 13 to week 24. Of those patients treated with Reblozyl, 21.4% of patients had greater than or equal to 33% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks in weeks 13 to week 24 compared to 4.5% of patients in the placebo arm (95% CI, less than 0.0001 p-value). In week 37 to week 48 of those patients treated with Reblozyl, 19.6% had greater than or equal to 33% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks compared to 3.6% in the placebo arm (95% CI, less than0.0001 p-value).

The efficacy of Reblozyl was evaluated in the MEDALIST trial, a multicenter, randomized, double-blind, placebo-controlled trial in patients with IPSS-R (revised international prognostic scoring system) very low, low, or intermediate-risk myelodysplastic syndromes (MDS) who have ring sideroblasts and require red blood cell transfusions (2 or more RBC units over 8 weeks). For eligibility, patients were required to have had an inadequate response to prior treatment with an erythropoiesis-stimulating agent (ESA), be intolerant of ESAs, or have a serum erythropoietin greater than 200 U/L. The MEDALIST trial excluded patients with deletion 5q (del 5q), white blood cell count greater than 13 Gi/L, neutrophils less than 0.5 Gi/L, platelets less than 50 Gi/L, or with prior use of a disease modifying agent for treatment of MDS.

All patients received best supportive care, which included RBC transfusions as needed. The primary efficacy assessment was conducted after completion of 24 weeks on study drug. Patients with a decrease in transfusion requirement or increase in hemoglobin could continue on blinded study drug thereafter until unacceptable toxicity, loss of efficacy, or disease progression.

The efficacy of Reblozyl was established based upon the proportion of patients who were red blood cell transfusion independent (RBC-TI)., defined as the absence of any RBC transfusion during any consecutive 8-week period occurring entirely within Weeks 1 through 24. The efficacy results are shown in the chart below.

Endpoint	**Reblozyl (N=153) n, % (95% CI)**	**Placebo (N=76) n, % (95% CI)**	**Common Risk Difference (95% CI)**	**p-value**
RBC-TI greater than or equal to 8 weeks during Weeks 1-24	58 (37.9) (30.2, 46.1)	10 (13.2) (6.5, 22.9)	24.6 (14.5, 34.6)	less than 0.0001
RBC-TI greater than or equal to 12 weeks during Weeks 1-24	43 (28.1) 21.1, 35.9)	6 (7.9) 3.0, 16.4)	20.0 (10.9, 29.1)	0.0002
RBC-TI greater than or equal to 12 weeks during Weeks 1-48	51 (33.3) 25.9, 41.4)	9 (11.8) (5.6, 21.3)	21.4 (11.2, 31.5)	0.0003

Safety[1]

Hemoglobin (Hgb) results should be assessed and reviewed prior to each administration of Reblozyl. If an RBC transfusion occurred prior to dosing, the pretransfusion Hgb must be considered for dosing purposes. If the pre-dose Hgb is greater than or equal to 11.5 g/dL and the Hgb level is not influenced by recent transfusion, delay dosing until the Hgb is less than or equal to 11 g/dL.

For a diagnosis of beta thalassemia, if a patient does not achieve a reduction in RBC transfusion burden after at least 2 consecutive doses (6 weeks) at the 1 mg//kg starting dose, increase the Reblozyl dose to 1.25 mg/kg. Do not increase the dose beyond the maximum dose of 1.25 m/kg.

For a diagnosis of MDS-RS or MDS/MPN_RS-T, if a patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose, increase the Reblozyl dose to 1.33 mg/kg. If a patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1.33 mg/kg dose level, increase the Reblozyl dose to 1.75 mg/kg. Do not increase the dose more frequently than every 6 weeks (2 doses) or beyond the maximum dose of 1.75 mg/kg.

If a patient experienced a response followed by a lack of or lost response to Reblozyl, initiate a search for causative factors (e.g., a bleeding event). If typical causes for a lack or loss of hematologic response are excluded, follow dosing recommendations for management of patients with an insufficient response to Reblozyl therapy.

Discontinue Reblozyl if a patient does not experience a decrease in transfusion burden after 9 weeks of treatment (administration of 3 doses) at the maximum dose level or if unacceptable toxicity occurs at any time.

Reblozyl (luspatercept-aamt) has no FDA labeled contraindications.

Reblozyl (luspatercept-aamt) Medical Drug Criteria

Coverage and policy application may be contingent on federal or state regulations. In the event of conflict between this policy and applicable federal or state regulations, regulatory requirements should apply per policyholder

TARGET AGENT(S)
Reblozyl® luspatercept-aamt

Brand (generic)	GPI	Multisource Code	HCPCS/ J Code
Reblozyl (luspatercept-aamt)			
25 mg subcutaneous injection	82400540102120	M, N, O, or Y	J0896
75 mg subcutaneous injection	82400540102140	M, N, O, or Y	J0896

CRITERIA FOR APPROVAL
Initial Evaluation
Target Agent(s) will be approved when ALL of the following are met:
1. ONE of the following:
    A. The requested agent is eligible for continuation of therapy AND ONE of the following:
        i. Information has been provided that indicates the patient has been treated with the requested agent within the past 90 days
        OR
        ii. The prescriber states the patient has been treated with the requested agent within the past 90 days AND is at risk if therapy is changed

Agents Eligible for Continuation of Therapy
Reblozyl (luspatercept-aamt)

OR

B. The patient has a diagnosis of Beta thalassemia requiring regular red blood cell (RBC) transfusions AND ALL of the following:
   i. The diagnosis was confirmed by BOTH of the following: (medical records including lab tests and/or chart notes required)
      1. Hemoglobin analysis by hemoglobin electrophoresis or high-performance liquid chromatography
      AND
      2. Genetic analysis for both Beta thalassemia and Alpha thalassemia mutations

   AND

   ii. The patient does not have hemoglobin S/Beta thalassemia

   AND

   iii. The patient requires RBC transfusions at least every 5 weeks with no transfusion-free period greater than 35 days

   AND

   iv. The patient does not require immediate correction of anemia

   AND

   v. All other causes of anemia (e.g., nutritional deficiencies, viral infection, environmental factors, marrow suppressing medications) have been evaluated and treated if applicable

   AND

   vi. ONE of the following: (medical records including lab tests and/or chart notes required)
      1. The patient's pre-dose hemoglobin level is less than or equal to 11.5 g/dL
      OR
      2. The patient's pre-dose hemoglobin level is greater than 11.5 g/dL AND the level is due to a recent transfusion

OR

C. The patient has a diagnosis of anemia associated with myelodysplastic syndrome with ring sideroblasts (MDS-RS) AND ALL of the following:
   i. The patient has very low – to - intermediate risk disease

   AND

   ii. ONE of the following:
      1. BOTH of the following:
         A. The patient has tried and had an inadequate response to an erythropoiesis stimulating agent (ESA) [e.g., Aranesp (darbepoetin alfa), Epogen/Procrit (epoetin alfa), Mircera (methoxy polyethylene glycol – epoetin beta), Retacrit (epoetin alfa-epbx)]
         AND
         B. The patient has required 2 or more red blood cell (RBC) units over 8 weeks

      OR

      2. The requested indication is supported by ALL requirements in either FDA labeling or NCCN 1 or 2A recommended use for the

requested agent [i.e., this indication must be supported by ALL requirements in the FDA label or NCCN "Recommended Use" box

OR

3. The patient has Stage four, advanced metastatic cancer or a severe adverse health condition experienced as a result of stage four, advanced metastatic cancer

AND

iii. The patient does not require immediate correction of anemia

AND

iv. ONE of the following: (medical records including lab tests and/or chart notes required)

1. The patient's pre-dose hemoglobin level is less than or equal to 11.5 g/dL

OR

2. The patient's pre-dose hemoglobin level is greater than 11.5 g/dL AND the level is due to a recent transfusion

OR

D. The patient has a diagnosis of anemia associated with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) AND ALL of the following:

i. The patient has very low – to - intermediate risk disease

AND

ii. ONE of the following:

1. BOTH of the following:

a. The patient has tried and had an inadequate response to an erythropoiesis stimulating agent (ESA) [e.g., Aranesp (darbepoetin alfa), Epogen/Procrit (epoetin alfa), Mircera (methoxy polyethylene glycol – epoetin beta), Retacrit (epoetin alfa-epbx)]

AND

b. The patient has required 2 or more red blood cell (RBC) units over 8 weeks

OR

2. The requested indication is supported by ALL requirements in either FDA labeling or NCCN 1 or 2A recommended use for the requested agent [i.e., this indication must be supported by ALL requirements in the FDA label or NCCN "Recommended Use" box

OR

3. The patient has Stage four, advanced metastatic cancer or a severe adverse health condition experienced as a result of stage four, advanced metastatic cancer

AND

iii. The patient does not require immediate correction of anemia

AND

iv. ONE of the following: (medical records including lab tests and/or chart notes required)

1. The patient's pre-dose hemoglobin level is less than or equal to 11.5 g/dL
   OR
2. The patient's pre-dose hemoglobin level is greater than 11.5 g/dL AND the level is due to a recent transfusion

OR

E. The patient has another FDA labeled indication for the requested agent

AND

2. ONE of the following:
   A. The patient's age is within FDA labeling for the requested indication for the requested agent
   OR
   B. The prescriber has provided information in support of using the requested agent for the patient's age

AND

3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist, oncologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis

AND

4. The patient does NOT have any FDA labeled contraindications to the requested agent

AND

5. The requested quantity (dose) is within FDA labeled dosing for the requested indication

Renewal Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan's Medical Drug Review process

AND

2. ONE of the following:
   A. The patient has a diagnosis of Beta thalassemia requiring regular red blood cell transfusions AND the patient had a decrease in transfusion burden from baseline with the requested agent
   OR
   B. The patient has another FDA labeled diagnosis for the requested agent AND has had clinical benefit with the requested agent

AND

3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist, oncologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis

AND

4. The patient does NOT have any FDA labeled contraindications to the requested agent

AND

5. The requested quantity (dose) is within FDA labeled dosing for the requested indication