Drug Coverage Policy

Effective Date 7/1/2024
Coverage Policy Number.....IP0115
Policy Title.....Reblozyl for Non-Oncology Uses

Hematology – Reblozyl for Non-Oncology Uses

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

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Cigna Healthcare Coverage Policy

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 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.[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. 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 3.2023 – November 10, 2023) recommend Reblozyl in the following situations:[6]

- **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) 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 2B). Reblozyl can also be used for wild-type *SF3B1* if the patient has thrombocytosis and ring sideroblasts ≥ 15% [category 2B].

Medical Necessity Criteria

The use of luspatercept for oncology indications are addressed in a separate coverage policy.

Reblozyl is considered medically necessary when the following criteria are 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 4 months if the patient meets all 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 all the following (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 beta-thalassema 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.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven (criteria will be updated as new published data are available).

Coding / Billing 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.

Covered when medically necessary when used to report Luspatercept (Reblozyl):

HCPCS Codes	Description
J0896	Injection, luspatercept-aamt, 0.25 mg

References

1. Reblozyl® subcutaneous injection [prescribing information]. Summit; NJ: Celgene/Bristol-Myers Squibb; August 2023.
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 3.2023 – November 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 13, 2023.

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

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