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Medication Policy Manual | **Policy No:** dru631

Topic: Reblozyl, luspatercept-aamt | **Date of Origin:** May 15, 2020

Committee Approval Date: June 4, 2026 | **Next Review Date:** 2027

Effective Date: August 1, 2026

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Reblozyl (luspatercept-aamt) is an injected medication used to treat certain types of anemias in patients who require regular red blood cell transfusions (RBCTs).

Policy/Criteria

Most contracts require pre-authorization approval of Reblozyl (luspatercept-aamt) prior to coverage.

I. Continuation of therapy (COT): Reblozyl (luspatercept-aamt) may be considered medically necessary for COT when criteria A and B below are met.

A. One of the following (1, 2, or 3) is met:

1. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

2. For diagnoses listed in the coverage criteria below, criteria a and b must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

B. Site of care administration requirements are met [refer to Medication Policy Manual, *Site of Care Review*, dru408].

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Reblozyl (luspatercept-aamt) may be considered medically necessary when there is clinical documentation (such as chart notes) that criteria A, B, and C below are met:

A. Site of care administration requirements are met [refer to Medication Policy Manual, *Site of Care Review*, dru408].

AND

B. Reblozyl (luspatercept-aamt) is prescribed by, or in consultation with a hematologist.

AND

C. Luspatercept will be used in one of the following settings when 1 or 2 below are met:

1. A diagnosis of **beta thalassemia** when criteria (a and b) below are met.

a. Documented transfusion dependence, defined as transfusion of at least six units of packed red blood cells (PRBCs) in the previous 24 weeks.

AND

b. No transfusion-free period greater than 35 days (5 weeks) in the previous 24 weeks.

OR

2. A diagnosis of **myelodysplastic syndrome (MDS) with ring sideroblasts** when criteria (a, b, and c) below are met.

a. The MDS is classified as very low, low, or intermediate risk MDS according to the IPSS-R (see *Appendix 1*).

AND

b. Documented transfusion dependence, defined as transfusion of at least six units of packed PRBCs in the previous 24 weeks.

AND

c. Erythropoiesis-stimulating agents (ESA) treatment was ineffective, not tolerated, or is contraindicated (see *Appendix 2*).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Reblozyl (luspatercept-aamt) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Reblozyl (luspatercept-aamt) may be approved in the following quantities:

1. Beta-thalassemia: Up to 1.25 mg/kg every 3 weeks.

2. MDS: Up to 1.75 mg/kg every 3 weeks.

C. Authorization **shall** be reviewed every 12 months. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit evidenced by a reduction or sustained reduction in the need for PRBC transfusions (PRBCTs).

IV. Reblozyl (luspatercept-aamt) is considered investigational when used for all other conditions.

Position Statement

Summary

- The intent of this policy is to allow for coverage of Reblozyl (luspatercept-aamt) in transfusion dependent patients with beta-thalassemia or lower-risk MDS, up to the doses shown to be safe and effective in clinical trials.
- *Beta-thalassemia:*
  - Evidence to support the use of Reblozyl (luspatercept-aamt) in beta-thalassemia was based on a phase 3, randomized, double-blind, placebo-controlled study in patients with beta thalassemia who required regular RBCTs. Reblozyl (luspatercept-aamt) reduced transfusion burden more than placebo. [1,2]
  - Current standard of care for patients with beta-thalassemia addresses the symptoms of the disease, primarily using life-long, ongoing RBCTs with additional iron chelation therapy to manage iron overload. Reblozyl (luspatercept-aamt), hematopoietic stem cell transplant (HSCT), and one-time gene therapies may be considered in select patients. [3]
- *MDS*:
  - The safety and efficacy of Reblozyl (luspatercept-aamt) was also evaluated in a phase 3, randomized, double-blind, placebo-controlled study in patients with very low, low, or intermediate risk MDS with ring sideroblasts who were dependent on RBCTs and unable to have treatment with ESAs. Patients treated with Reblozyl (luspatercept-aamt) needed less transfusions compared to patients treated with placebo. [4]
  - Subsequently, the FDA indication was expanded based on an open-label, comparative trial in ESA-naive transfusion-dependent anemia due to lower-risk MDS. [5] Despite an improvement in transfusion-independence with luspatercept as compared to epoetin, the clinical meaningfulness of the difference is uncertain. The trial included a higher percentage of patients with characteristics associated with better response to ESAs [lower baseline serum erythropoietin (sEPO), lower percentage of blasts, and low RBCT requirement]. Given the lack of clinical meaningful difference and the significantly higher cost of luspatercept relative to ESA therapy, the use of luspatercept is reserved for patients who are refractory, intolerant, or ineligible for ESAs as outlined in the coverage criteria.

    * Guidelines by the NCCN recommend luspatercept or ESAs as first-line treatment for lower-risk MDS with or without ring sideroblasts, unless not a treatment option [such as in patients with a baseline serum erythropoietin (EPO) level over 500]. Other treatment options include chemotherapy (azacitidine, decitabine), targeted therapy (imetelstat), immunosuppressive therapy (anti-thymocyte globulin, cyclosporine), and immunomodulators (lenalidomide). [6]

- In clinical trials, Reblozyl (luspatercept-aamt) doses were increased after six weeks (two doses) is there was suboptimal response, defined as no decrease in transfusion burden versus baseline. For the third dose (at week 9), the patient increased to the maximum dose of 1.25 mg/kg (beta-thalassemia) or 1.75 mg/kg (MDS). The majority of patients in clinical trials achieved a response within approximately four to five treatment cycles. After nine weeks of treatment at the maximum dose (after 15 weeks of treatment total), Reblozyl (luspatercept-aamt) is discontinued if there is no decrease in transfusion burden. Therefore, if a patient does not have a reduction in transfusion burden after 15 weeks of therapy, additional Reblozyl (luspatercept-aamt) may not be covered. [1,4,5,8]
- Reblozyl (luspatercept-aamt) may be covered for up to the doses shown to be safe and effective in the pivotal trials. The safety and effectiveness of higher doses have not been established.
- There is insufficient evidence to support the use of Reblozyl (luspatercept-aamt) in any other conditions.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medical necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing equally efficacious potentially higher-value treatment options, considering effectiveness, safety, and cost. NCCN is a CMS recognized compendium that is considered a reference standard, rather than a gold standard, of care. NCCN compendia are not strictly evidence-based and therefore may not be supported by the best available evidence or meet benefit contract definitions of medical necessity. Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

Beta-thalassemia

- Safety and efficacy of luspatercept were evaluated in a phase 3, multicenter, randomized, double-blind, placebo-controlled trial in adult patients with beta-thalassemia who required regular RBCTs ("transfusion-dependent"). [2]
    * Patients were required to have received 6 to 20 RBC units within 24 weeks prior to the study and no transfusion-free periods of greater than 35 days.
    * Patients were randomized to receive 48 weeks of treatment with either luspatercept or placebo every 3 weeks. Treatments were administered in addition to best supportive care (BSC) which included RBCT and iron chelation therapy to maintain a patient's baseline hemoglobin level.
    * The primary endpoint was erythroid response defined as a ≥33% reduction from baseline in RBCT burden (with a reduction of ≥2 units).
    * Study results demonstrated a greater reduction in transfusion burden in patients treated with Reblozyl (luspatercept-aamt) compared to placebo.

MDS

- In patients with lower-risk MDS with ring sideroblasts, safety and efficacy of luspatercept were evaluated in a phase 3, multicenter, randomized, double-blind, placebo-controlled trial in patients who were refractory, intolerant, or ineligible for ESA treatment. [4]
    * Patients were required to have ≥2 RBC units in the previous 8 weeks and very low, low, or intermediate risk disease by the IPSS-R classification system.
    * Patients received treatment with Reblozyl (luspatercept-aamt) or placebo every 3 weeks.
    * The primary endpoint was RBC-transfusion independence (RBC-TI) ≥8 weeks between week 1 and 24, which was demonstrated in more patients in the luspatercept treatment group than in the placebo group.
- Subsequently, the FDA indication was expanded based on a published, phase 3, multicenter, randomized, open-label, comparative trial in patients with transfusion-dependent anemia due to lower-risk MDS and not previously treated with ESAs. [5]
    * The primary endpoint was RBC-transfusion independence (RBC-TI) ≥ 12 weeks AND a concurrent mean Hgb increase of at least 1.5 g/dL (between week 1 and 24), assessed in the intention-to-treat population.
    * All patients had:
        - Anemia due to very-low, low, or intermediate risk MDS [excluding MDS with del(5q)] [9% very low, 72% low]
        - Required 2–6 PRBC units per 8 weeks for ≥8 weeks immediately before randomization [median 3 RBCTs in prior 8 weeks* [63% with <4 RBCTs in 8 weeks)]
        - sEPO < 500 U/L [79% had sEPO <200].
        - No prior use of ESA.
    * Patients were randomized to receive 24 weeks of open-label treatment: luspatercept or epoetin alfa, stratified by baseline transfusion burden (<4 units

per 8 weeks vs ≥4 units per 8 weeks), endogenous serum EPO (≤200 U/L vs >200 to <500 U/L), and ring sideroblast status (positive vs negative). Of randomized patients, 73% with ring sideroblasts. Baseline Hgb 7.8 (7-8).

* Treatment was continued in patients with clinical benefit (defined as a transfusion reduction of ≥2 units RBCs per 8 weeks vs baseline) until evidence of disease progression, death, unacceptable toxicity, or withdrawal of consent.
* There was a statistically higher rate of transfusion-independence at 12 weeks with luspatercept (67%) as compared to epoetin (46%). However, the clinical meaningfulness of the difference in the reductions in RBCT burden or in RBC-TI between luspatercept and epoetin is unknown. Of note, the trial included a higher percentage of patients with characteristics associated with better response to ESA [sEPO <500, lower percentage of blasts, and pretreatment RBCTs <2/month ("low RBCT requirement")]. In addition, data at up to 1.5 years follow-up showed sustained benefit in luspatercept treated patients (30.2%) compared to epoetin (13.8%), however the long-term durability of response is unknown.[9] Given the lack of clinical meaningful difference and the significantly higher cost of luspatercept relative to ESA therapy, the use of luspatercept is reserved for those who are refractory, intolerant, or ineligible for ESAs as outlined in the coverage criteria.
* Although there is interest in the effect of biomarkers (ring sideroblasts or mutations such as SF3B1) on response to treatment of MDS-related anemia, the data from the exploratory analyses of these markers remain inconclusive as this study was not powered to establish cause and effect. Therefore, any associate of baseline mutations and response to either therapy remains unproven.
* Of note, the presence of ring sideroblasts is a favorable prognostic marker in MDS, whereas favorable response to ESAs is associated with baseline sEPO<500, lower percentage of blasts, and lower RBCT requirements at baseline. Because most subjects in this trial had ring sideroblasts (73%) and all had low sEPO (<500), the efficacy in ring-sideroblast negative ESA-naïve MDS-associated anemia is less clear.

Guidelines [5]

* Treatment goals for patients with lower-risk MDS include transfusion independence, improvement in hemoglobin levels, and maintenance of or improvement in quality of life.
* For initial management of MDS-associated anemia, iron, folate, and B12 replacement are used in combination with RBCTs.
* Erythropoiesis-stimulating agents (ESAs), epoetin alfa or darbepoetin, are a first-line medication treatment for anemia with lower-risk MDS, targeting early stages of erythropoiesis by inhibiting apoptosis and stimulating erythropoietin-responsive erythroid precursor proliferation (40-60% response rate). Lower baseline serum erythropoietin (sEPO) (<500), lower percentage of blasts, and lower pretreatment RBCTs (<2 per month) is associated with better response to ESAs. ESAs are dosed to a target Hgb of 10 to 12 g/dL (not to exceed 12). For lack of efficacy with ESAs, dose escalation is recommended. After 6-8 weeks,

treatment is stopped if ≤1.5 g/dL increase in Hgb or no reduction in RBCTs from baseline.

* Luspatercept (Reblozyl) is an option in anemic patients with ring sideroblasts if refractory to ESAs (or unlikely to respond to ESAs, namely those with sEPO above 500 at baseline).
* Other MDS-targeted options include chemotherapy (azacitidine, decitabine), targeted therapy (imatinib), immunosuppressive therapy (anti-thymocyte globulin, cyclosporine), and immunomodulators (lenalidomide).

Investigational Uses

- There is insufficient evidence to establish the efficacy of Reblozyl (luspatercept-aamt) for the treatment of other conditions, including non-proliferative chronic myelomonocytic leukemia, myelofibrosis, or non-transfusion dependent thalassemia. Data is limited to small, unpublished, phase 2 trials. Although the preliminary evidence is promising, larger, well controlled trials are needed to establish the safety and efficacy of Reblozyl (luspatercept-aamt) in these settings. Additional trials are ongoing. [7]

Safety [8]

- The most common adverse reactions associated with Reblozyl (luspatercept-aamt) include headache, bone pain, arthralgia, fatigue, cough, abdominal pain, diarrhea, and dizziness.

Dosing [8]

- The recommended dose of Reblozyl (luspatercept-aamt) in patients with beta thalassemia is 1 mg/kg (up to 1.25 mg/kg) every 3 weeks by subcutaneous injection. Safety and effectiveness of higher doses have not been established.
- In clinical trials of MDS, the dose of Reblozyl (luspatercept-aamt) was 1 mg/kg (up to 1.75 mg/kg) administered every 3 weeks by subcutaneous injection. The safety and effectiveness of higher doses have not been established.

Appendix 1: IPSS-R Prognostic Risk Categories/scores [10]	
Risk category	**Risk score**
Very low	≤ 1.5
Low	> 1.5 – 3
Intermediate	> 3 – 4.5
High	> 4.5 – 6
Very high	> 6

Appendix 2: Erythropoiesis-stimulating Agents (ESAs) [a]	
Aranesp	darbepoetin alfa
Epogen	epoetin alfa
Procrit	epoetin alfa
Retacrit	epoetin alfa-epbx

[a] For lack of efficacy with ESAs, dose escalation is recommended.[6]

Cross References
Site of Care Review, Medication Policy Manual, Policy No. dru408

Codes	Number	Description
HCPCS	J0896	Injection, luspatercept-aamt (Reblozyl), 0.25mg

References

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Revision History

Revision Date	Revision Summary
6/4/2026	• No change to coverage criteria with this annual review. • Revised the authorization length per state mandate. The authorization period has been updated to 12 months, whereas previously there was an initial authorization period for beta-thalassemia and MDS for 18 and 24 weeks respectively.
6/5/2025	Removed ESA-treatment naïve transfusion-dependent MDS from not medically necessary for administrative purposes. It is functionally covered in the coverage criteria after use of an ESA.
6/20/2024	No criteria changes with this annual review.
3/21/2024	Added the use in ESA-treatment-naïve transfusion-dependent MDS (a new FDA indication) as not medically necessary.
6/15/2023	No criteria changes with this annual update.
6/17/2022	No criteria changes with this annual update.
7/16/2021	No criteria changes with this annual update.
7/22/2020	Updated initial authorization periods to differentiate between beta-thalassemia and MDS and to be consistent with labeling.
4/22/2020	New policy (effective 5/15/2020). Limits coverage to patients with beta-thalassemia who require regular red blood cell transfusions. Coverage criteria also allows for patients with lower risk MDS who require regular red blood cell transfusions and are refractory, intolerant, or ineligible for ESA treatment, the settings in which luspatercept was studied.

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