Reblozyl®

(luspatercept-aamt)

for injection 25mg • 75mg

REBLOZYL DOSING AND RECONSTITUTION GUIDE

REBLOZYL is indicated for the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions.

REBLOZYL is indicated for the treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell 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).

REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Thrombosis/Thromboembolism

In adult patients with beta thalassemia, thromboembolic events (TEE) were reported in 8/223 (3.6%) REBLOZYL-treated patients. TEEs included deep vein thrombosis, pulmonary embolus, portal vein thrombosis, and ischemic stroke. Patients with known risk factors for thromboembolism (splenectomy or concomitant use of hormone replacement therapy) may be at further increased risk of thromboembolic conditions. Consider thromboprophylaxis in patients at increased risk of TEE. Monitor patients for signs and symptoms of thromboembolic events and institute treatment promptly.

Please click here for additional Important Safety Information and click here for full Prescribing Information for REBLOZYL.

Reblozyl®

(luspatercept-aamt)

for injection 25mg • 75mg

REBLOZYL IS AVAILABLE IN

2 strengths as single-dose vials for reconstitution[1]

25 mg

75 mg

Please click here for additional Important Safety Information and click here for full Prescribing Information for REBLOZYL.

TABLE OF CONTENTS

Reblozyl®

(luspatercept-aamt)

for injection 25mg • 75mg

WARNINGS AND PRECAUTIONS[1]

Thrombosis/Thromboembolism

In adult patients with beta thalassemia, thromboembolic events (TEE) were reported in 8/223 (3.6%) REBLOZYL-treated patients. TEEs included deep vein thrombosis, pulmonary embolus, portal vein thrombosis, and ischemic stroke. Patients with known risk factors for thromboembolism (splenectomy or concomitant use of hormone replacement therapy) may be at further increased risk of thromboembolic conditions. Consider thromboprophylaxis in patients at increased risk of TEE. Monitor patients for signs and symptoms of thromboembolic events and institute treatment promptly.

Hypertension

Hypertension was reported in 10.7% (61/571) of REBLOZYL-treated patients. Across clinical studies, the incidence of Grade 3 to 4 hypertension ranged from 1.8% to 8.6%. In patients with beta thalassemia with normal baseline blood pressure, 13 (6.2%) patients developed systolic blood pressure (SBP) ≥130 mm Hg and 33 (16.6%) patients developed diastolic blood pressure (DBP) ≥80 mm Hg. In adult patients with MDS with normal baseline blood pressure, 26 (29.9%) patients developed SBP ≥130 mm Hg and 23 (16.4%) patients developed DBP ≥80 mm Hg. Monitor blood pressure prior to each administration. Manage new or exacerbations of preexisting hypertension using anti-hypertensive agents.

Embryo-Fetal Toxicity

REBLOZYL may cause fetal harm when administered to a pregnant woman. REBLOZYL caused increased post-implantation loss, decreased litter size, and an increased incidence of skeletal variations in pregnant rat and rabbit studies. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 3 months after the final dose.

REBLOZYL DOSING FOR β-THALASSEMIA

Assess and review patients' hemoglobin (Hgb) and transfusion record prior to each administration[1]

- If an RBC transfusion occurred prior to dosing, use the pretransfusion Hgb for dose evaluation[1]
- If a patient experiences a dose delay due to Hgb increase, measure Hgb every week[2]

REBLOZYL dose titration for response: β-thalassemia[1]

	REBLOZYL Dosing recommendation*
STARTING DOSE	**1 mg/kg every 3 weeks**
↑ **Dose increases for insufficient response at initiation of treatment**	
No reduction in RBC transfusion burden after at least 2 consecutive doses (6 weeks) at the **1 mg/kg** starting dose	• Increase the dose to **1.25 mg/kg** every 3 weeks
No reduction in RBC transfusion burden after at least 3 consecutive doses (9 weeks) at **1.25 mg/kg**	• Discontinue treatment
↓ **Dose modifications for predose Hgb levels or rapid Hgb rise**	
Predose Hgb is **≥11.5 g/dL** in the absence of transfusions	• Interrupt treatment • Restart when the Hgb is no more than **11 g/dL**
Increase in Hgb **>2 g/dL** within 3 weeks in the absence of transfusions and • current dose is **1.25 mg/kg** • current dose is **1 mg/kg** • current dose is **0.8 mg/kg** • current dose is **0.6 mg/kg**	• Reduce dose to **1 mg/kg** • Reduce dose to **0.8 mg/kg** • Reduce dose to **0.6 mg/kg** • Discontinue treatment

*Do not increase the dose if the patient is experiencing an adverse reaction as described in the Dosing Modifications for Adverse Reactions table.

At least 5 doses (15 weeks of treatment) unless unacceptable toxicity occurs at any time

- Overall, 53% of patients in the BELIEVE trial had their dose increased to 1.25 mg/kg (46% REBLOZYL, n = 223; 66% placebo, n = 109)[1]

Reblozyl®
(luspatercept-aamt)
for injection 25mg • 75mg

Please click here for additional Important Safety Information and click here for full Prescribing Information for REBLOZYL.

REBLOZYL DOSING FOR β-THALASSEMIA (CONT'D)

Dose increases in the event of loss of response[1]

- A dose increase to 1.25 mg/kg may occur at any time during treatment after patients have received at least 2 consecutive doses of 1 mg/kg
- **Do not increase the dose beyond the maximum dose of 1.25 mg/kg**

Discontinue treatment if no reduction in transfusion burden from baseline is observed[1]

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

If a planned administration of REBLOZYL is delayed or missed[1]

- Administer REBLOZYL as soon as possible and continue dosing as prescribed, with at least 3 weeks between doses

IMPORTANT SAFETY INFORMATION (CONT'D)

ADVERSE REACTIONS

Beta-Thalassemia

- Serious adverse reactions occurred in 3.6% of patients on REBLOZYL. Serious adverse reactions occurring in 1% of patients included cerebrovascular accident and deep vein thrombosis. A fatal adverse reaction occurred in 1 patient treated with REBLOZYL who died due to an unconfirmed case of acute myeloid leukemia (AML)
- Most common adverse reactions (at least 10% for REBLOZYL and 1% more than placebo) were headache (26% vs 24%), bone pain (20% vs 8%), arthralgia (19% vs 12%), fatigue (14% vs 13%), cough (14% vs 11%), abdominal pain (14% vs 12%), diarrhea (12% vs 10%) and dizziness (11% vs 5%)

Please click here for additional Important Safety Information and click here for full Prescribing Information for REBLOZYL.

Reblozyl®
(luspatercept-aamt)
for injection 25mg • 75mg

REBLOZYL DOSING FOR β-THALASSEMIA (CONT'D)

REBLOZYL dosing modifications for adverse reactions[1]

	REBLOZYL Dosing recommendation*
Grade 3 or 4 hypersensitivity reactions	• **Discontinue treatment**
Other Grade 3 or 4 adverse reactions	• Interrupt treatment • Restart when the adverse reaction resolves to no more than Grade 1

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, and Grade 4 is life-threatening.

DISCONTINUATIONS AND DOSE MODIFICATIONS IN THE SAFETY POPULATION FOR β-THALASSEMIA

- The safety of REBLOZYL in patients with β-thalassemia (N = 223) was evaluated in the BELIEVE trial[1]

5.4% (12/223) of patients who received REBLOZYL discontinued treatment due to an adverse reaction[1,2]

15.2% (34/223) of patients who received REBLOZYL required a dose interruption due to an adverse reaction[1,2]

2.7% (6/223) of patients who received REBLOZYL required a dose reduction due to an adverse reaction[1,2]

Please click here for additional Important Safety Information and click here for full Prescribing Information for REBLOZYL.

Reblozyl®
(luspatercept-aamt)
for injection 25mg • 75mg

REBLOZYL DOSING FOR MDS-RS AND MDS/MPN-RS-T–ASSOCIATED ANEMIA

Assess and review patients' Hgb and transfusion record prior to each administration[1]

- If an RBC transfusion occurred prior to dosing, use the pretransfusion Hgb for dose evaluation[1]
- If a patient experiences a dose delay due to Hgb increase, measure Hgb every week[2]

REBLOZYL dose titration for response: MDS-RS and MDS/MPN-RS-T–associated anemia[1]

	REBLOZYL Dosing recommendation*
STARTING DOSE	**1 mg/kg every 3 weeks**
↑ **Dose increases for insufficient response at initiation of treatment**	
Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the **1 mg/kg** starting dose	• Increase the dose to **1.33 mg/kg** every 3 weeks
Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at **1.33 mg/kg**	• Increase the dose to **1.75 mg/kg** every 3 weeks
No reduction in RBC transfusion burden after at least 3 consecutive doses (9 weeks) at **1.75 mg/kg**	• Discontinue treatment
↓ **Dose modifications for predose Hgb levels or rapid Hgb rise**	
Predose Hgb is **≥11.5 g/dL** in the absence of transfusions	• Interrupt treatment • Restart when the Hgb is no more than **11 g/dL**
Increase in Hgb **>2 g/dL** within 3 weeks in the absence of transfusions and • current dose is **1.75 mg/kg** • current dose is **1.33 mg/kg** • current dose is **1 mg/kg** • current dose is **0.8 mg/kg** • current dose is **0.6 mg/kg**	 • Reduce dose to **1.33 mg/kg** • Reduce dose to **1 mg/kg** • Reduce dose to **0.8 mg/kg** • Reduce dose to **0.6 mg/kg** • Discontinue treatment

*Do not increase the dose if the patient is experiencing an adverse reaction as described in the Dosing Modifications for Adverse Reactions table.

At least 7 doses (21 weeks of treatment) unless unacceptable toxicity occurs at any time

- Overall, 77.1% (118/153) of patients in the MEDALIST trial had their dose of REBLOZYL increased at least once[2]
  - 58.8% of patients (90/153) had their REBLOZYL dose increased to a maximum dose of 1.75 mg/kg

Please click here for additional Important Safety Information and click here for full Prescribing Information for REBLOZYL.

Reblozyl®
(luspatercept-aamt)
for injection 25mg • 75mg

REBLOZYL DOSING FOR MDS-RS AND MDS/MPN-RS-T–ASSOCIATED ANEMIA (CONT'D)

Dose increases in the event of loss of response[1]

- If, upon dose reduction, the patient loses response (ie, requires a transfusion) or Hgb concentration drops by 1 g/dL or more in 3 weeks in the absence of transfusion, increase the dose by 1 dose level
- Wait a minimum of 6 weeks between dose increases
- Dose increases to 1.33 mg/kg and subsequently to 1.75 mg/kg may occur at any time during treatment after patients have received at least 2 consecutive doses at the prior lower dose level
- **Do not increase the dose more frequently than every 2 consecutive doses (6 weeks) or beyond the maximum dose of 1.75 mg/kg**

Discontinue treatment if no reduction in transfusion burden from baseline is observed[1]

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

If a planned administration of REBLOZYL is delayed or missed[1]

- Administer REBLOZYL as soon as possible and continue dosing as prescribed, with at least 3 weeks between doses

IMPORTANT SAFETY INFORMATION (CONT'D)

ADVERSE REACTIONS (CONT'D)

Myelodysplastic Syndromes

- Grade ≥3 (≥2%) adverse reactions included fatigue, hypertension, syncope and musculoskeletal pain. A fatal adverse reaction occurred in 5 (2.1%) patients
- The most common (≥10%) adverse reactions included fatigue, musculoskeletal pain, dizziness, diarrhea, nausea, hypersensitivity reactions, hypertension, headache, upper respiratory tract infection, bronchitis, and urinary tract infection

Please click here for additional Important Safety Information and click here for full Prescribing Information for REBLOZYL.

Reblozyl®
(luspatercept-aamt)
for injection 25mg • 75mg

REBLOZYL DOSING FOR MDS-RS AND MDS/MPN-RS-T–ASSOCIATED ANEMIA (CONT'D)

REBLOZYL dosing modifications for adverse reactions[1]

	REBLOZYL Dosing recommendation*
Grade 3 or 4 hypersensitivity reactions	• **Discontinue treatment**
Other Grade 3 or 4 adverse reactions	• Interrupt treatment • When the adverse reaction resolves to no more than Grade 1, restart treatment at the next lower dose level† • If the dose delay is >12 consecutive weeks, discontinue treatment

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, and Grade 4 is life-threatening.
†Per dose reductions on previous page.

DISCONTINUATIONS AND DOSE MODIFICATIONS IN THE SAFETY POPULATION FOR MDS-RS AND MDS/MPN-RS-T

- The safety of REBLOZYL at the recommended dose and schedule was evaluated in 242 patients with MDS with ring sideroblasts (n = 192) or other myeloid neoplasms (n = 50)[1]

Discontinuations due to adverse reactions

4.5%
(11/242)

of patients who received REBLOZYL discontinued treatment due to an adverse reaction[1]

Dose reductions due to adverse reactions

2.9%
(7/242)

of patients who received REBLOZYL required a dose reduction due to an adverse reaction[1]

Please click here for additional Important Safety Information and click here for full Prescribing Information for REBLOZYL.

Reblozyl®
(luspatercept-aamt)
for injection 25mg • 75mg

RECONSTITUTING REBLOZYL

REBLOZYL is available in 2 strengths as single-dose vials for reconstitution[1]

Reconstitution volumes			
Vial size	**Amount of Sterile Water for Injection, USP required for reconstitution**	**Final concentration**	**Deliverable volume**
25 mg vial	0.68 mL	25 mg/0.5 mL	0.5 mL
75 mg vial	1.6 mL	75 mg/1.5 mL (50 mg/mL)	1.5 mL

REBLOZYL should be reconstituted and administered by a healthcare professional[1]

- Reconstitute REBLOZYL with Sterile Water for Injection, USP only

Important considerations for REBLOZYL reconstitution[1]

- Reconstitute the number of REBLOZYL vials to achieve the appropriate dose based on the patient's weight
- Use a syringe with suitable graduations for reconstitution to ensure accurate dosage

Please click here for additional Important Safety Information and click here for full Prescribing Information for REBLOZYL.

Reblozyl®
(luspatercept-aamt)
for injection 25mg • 75mg

RECONSTITUTION INSTRUCTIONS

Adhere to the following steps to properly reconstitute REBLOZYL[1]

1. Add Sterile Water for Injection, USP.
Reconstitute with Sterile Water for Injection, USP using volumes described in the reconstitution volumes table on page 10 with the stream directed onto the lyophilized powder. Allow to stand for 1 minute.

2. Discard the needle and syringe used for reconstitution.
The needle and syringe used for reconstitution should not be used for SC injections.

3. Mix and wait.
Gently swirl the vial in a circular motion for 30 seconds. Stop swirling and let the vial sit in an upright position for 30 seconds.

4. Inspect.
Inspect the vial for undissolved particles in the solution. If undissolved powder is observed, repeat step 3 until the powder is completely dissolved.

5. Mix and wait.
Invert the vial and gently swirl in an inverted position for 30 seconds. Bring the vial back to the upright position, and let it sit for 30 seconds.

6. Repeat.
Repeat step 5 seven more times to ensure complete reconstitution of material on the sides of the vial.

7. Inspect.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. REBLOZYL is a colorless to slightly yellow, clear to slightly opalescent solution, which is free of foreign particulate matter. Do not use if undissolved product or foreign particulate matter is observed.

Please click here for additional Important Safety Information and click here for full Prescribing Information for REBLOZYL.

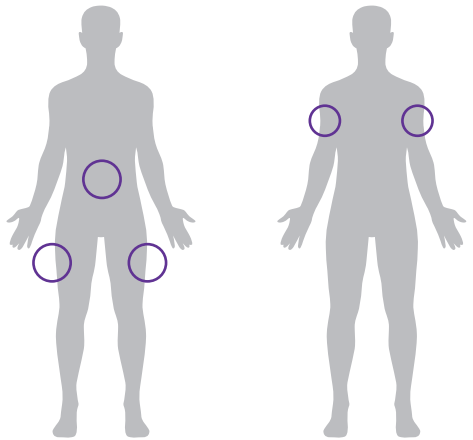
Reblozyl®
(luspatercept-aamt)
for injection 25mg • 75mg

INSTRUCTIONS FOR SUBCUTANEOUS (SC) ADMINISTRATION

REBLOZYL is administered subcutaneously and is available in 2 vial sizes (25 mg and 75 mg)[1]

- Prior to injection, allow solution to reach room temperature for a more comfortable injection

Step 1: **Verify correct dose for the patient**	• Calculate the exact total dosing volume of 50 mg/mL solution required for the patient
Step 2: **Plan and prep for injection**	• Slowly withdraw the dosing volume of the reconstituted REBLOZYL solution from the single-dose vial(s) into a syringe • Divide doses requiring larger reconstituted volumes (ie, >1.2 mL) into separate similar volume injections and inject into separate sites
Step 3: **Subcutaneous administration**	• If multiple injections are required, use a new syringe and needle for each SC injection • Administer the SC injection into the upper arm, thigh, and/or abdomen



Front Back

NOTE: Discard any unused portion. Do not pool unused portions from the vials. Do not administer more than 1 dose from a vial.

- **Do not mix** with other medications

Please click here for additional Important Safety Information and click here for full Prescribing Information for REBLOZYL.

Reblozyl®
(luspatercept-aamt)
for injection 25mg • 75mg

EXAMPLE: HOW TO CALCULATE AND DELIVER A DOSE

REBLOZYL should be reconstituted and administered by a healthcare professional[1]

Sample calculation for SC administration of REBLOZYL

- Average adult male weighing 197 pounds (89 kg)
- 1 mg of REBLOZYL per 1 kg = 89 mg starting dose

Total volume of reconstituted 50 mg/mL solution needed to administer 89 mg: 1.78 mL

Number of vials	REBLOZYL	Concentration after reconstitution	Solution needed for administration	Milligrams in solution
1	75 mg vial	75 mg/1.5 mL (50 mg/mL)	Use 1.5 mL	75 mg
1	25 mg vial	25 mg/0.5 mL	Use 0.28 mL	14 mg
			Total volume needed 1.78 mL	**89 mg**

Doses with reconstituted volumes larger than 1.2 mL should be divided into separate, similar-volume syringes for injection and injected into separate sites (upper arm, thigh, and/or abdomen)

Injection 1: 0.89 mL – upper arm

Injection 2: 0.89 mL – thigh or abdomen

STORING REBLOZYL

REBLOZYL requires cold storage[1]

STORAGE OF UNRECONSTITUTED VIAL

- Store unreconstituted vials refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light
- Do not freeze

STORAGE OF RECONSTITUTED SOLUTION

- If the reconstituted solution is not used immediately, store at room temperature at 20°C to 25°C (68°F to 77°F) in the original vial for up to 8 hours. Discard if not used within 8 hours of reconstitution
- Alternatively, store refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours in the original vial
  - — Remove from refrigerated condition 15 to 30 minutes prior to injection to allow solution to reach room temperature for a more comfortable injection
  - — Discard if not used within 24 hours of reconstitution
- Do not freeze the reconstituted solution

Please click here for additional Important Safety Information and click here for full Prescribing Information for REBLOZYL.

Reblozyl®
(luspatercept-aamt)
for injection 25mg • 75mg

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Thrombosis/Thromboembolism

In adult patients with beta thalassemia, thromboembolic events (TEE) were reported in 8/223 (3.6%) REBLOZYL-treated patients. TEEs included deep vein thrombosis, pulmonary embolus, portal vein thrombosis, and ischemic stroke. Patients with known risk factors for thromboembolism (splenectomy or concomitant use of hormone replacement therapy) may be at further increased risk of thromboembolic conditions. Consider thromboprophylaxis in patients at increased risk of TEE. Monitor patients for signs and symptoms of thromboembolic events and institute treatment promptly.

Hypertension

Hypertension was reported in 10.7% (61/571) of REBLOZYL-treated patients. Across clinical studies, the incidence of Grade 3 to 4 hypertension ranged from 1.8% to 8.6%. In patients with beta thalassemia with normal baseline blood pressure, 13 (6.2%) patients developed systolic blood pressure (SBP) ≥130 mm Hg and 33 (16.6%) patients developed diastolic blood pressure (DBP) ≥80 mm Hg. In adult patients with MDS with normal baseline blood pressure, 26 (29.9%) patients developed SBP ≥130 mm Hg and 23 (16.4%) patients developed DBP ≥80 mm Hg. Monitor blood pressure prior to each administration. Manage new or exacerbations of preexisting hypertension using anti-hypertensive agents.

Embryo-Fetal Toxicity

REBLOZYL may cause fetal harm when administered to a pregnant woman. REBLOZYL caused increased post-implantation loss, decreased litter size, and an increased incidence of skeletal variations in pregnant rat and rabbit studies. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 3 months after the final dose.

ADVERSE REACTIONS

Beta-Thalassemia

- Serious adverse reactions occurred in 3.6% of patients on REBLOZYL. Serious adverse reactions occurring in 1% of patients included cerebrovascular accident and deep vein thrombosis. A fatal adverse reaction occurred in 1 patient treated with REBLOZYL who died due to an unconfirmed case of acute myeloid leukemia (AML)

ADVERSE REACTIONS (CONT'D)

Beta-Thalassemia (cont'd)

- Most common adverse reactions (at least 10% for REBLOZYL and 1% more than placebo) were headache (26% vs 24%), bone pain (20% vs 8%), arthralgia (19% vs 12%), fatigue (14% vs 13%), cough (14% vs 11%), abdominal pain (14% vs 12%), diarrhea (12% vs 10%) and dizziness (11% vs 5%)

Myelodysplastic Syndromes

- Grade ≥3 (≥2%) adverse reactions included fatigue, hypertension, syncope and musculoskeletal pain. A fatal adverse reaction occurred in 5 (2.1%) patients
- The most common (≥10%) adverse reactions included fatigue, musculoskeletal pain, dizziness, diarrhea, nausea, hypersensitivity reactions, hypertension, headache, upper respiratory tract infection, bronchitis, and urinary tract infection

LACTATION

It is not known whether REBLOZYL is excreted into human milk or absorbed systemically after ingestion by a nursing infant. REBLOZYL was detected in milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because many drugs are excreted in human milk, and because of the unknown effects of REBLOZYL in infants, a decision should be made whether to discontinue nursing or to discontinue treatment. Because of the potential for serious adverse reactions in the breastfed child, breastfeeding is not recommended during treatment and for 3 months after the last dose.

Please click here for full Prescribing Information for REBLOZYL.

Reblozyl®
(luspatercept-aamt)
for injection 25mg • 75mg

LEARN MORE ABOUT REBLOZYL

Visit REBLOZYLpro.com/DosingGuide to access additional resources:

REBLOZYL reconstitution poster

Dosing and reconstitution videos

Patient brochures

Please click here for full Prescribing Information for REBLOZYL

Bristol Myers Squibb™ | ACCELERON

References: 1. REBLOZYL [Prescribing Information]. Summit, NJ: Celgene Corporation; 2020. **2.** Data on file. Celgene Corporation. Summit, New Jersey.

Reblozyl®
(luspatercept-aamt)
for injection 25mg • 75mg