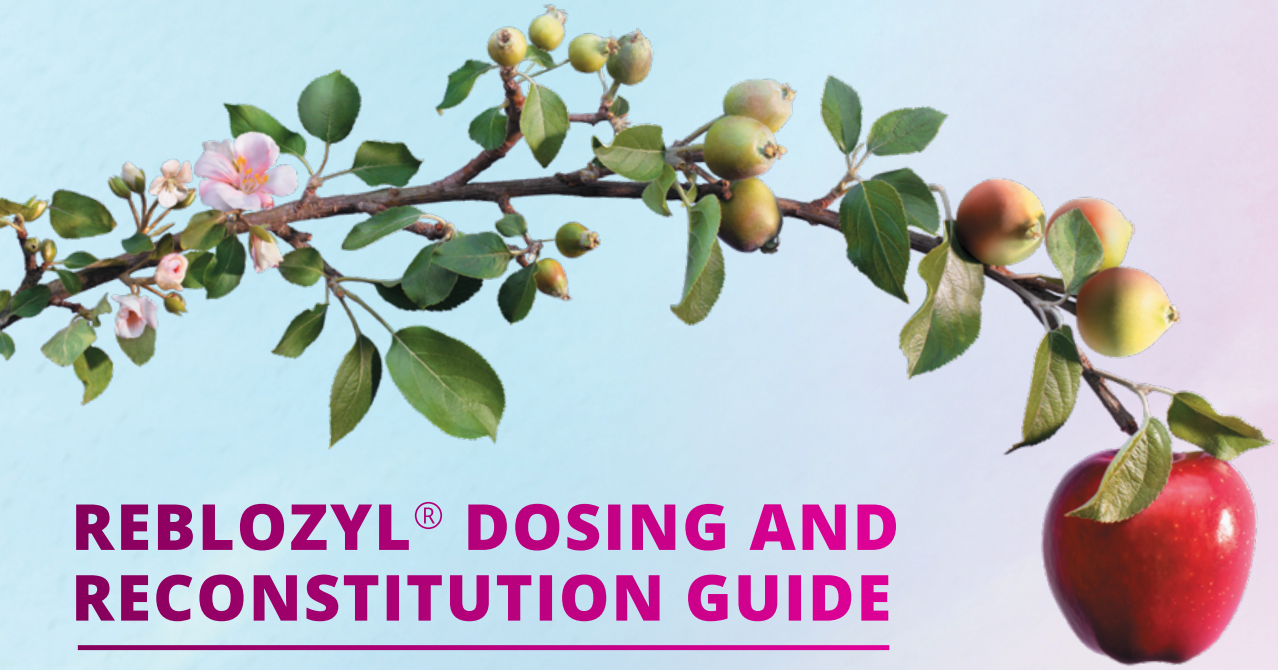


REBLOZYL® DOSING AND RECONSTITUTION GUIDE

Use this guide to find important information on dosing, reconstitution, and administration

The first and only erythroid maturation agent* indicated for adults with RBC transfusion-dependent anemia associated with β-thalassemia

REBLOZYL (luspatercept for injection) is indicated for the treatment of adult patients with red blood cell (RBC) transfusion-dependent anemia associated with beta(β)-thalassemia.

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

No clinically meaningful change in liver iron concentration was observed in β-thalassemia patients treated with REBLOZYL + best supportive care (BSC) compared to patients treated with placebo + BSC at 48 weeks.

VISIT
REBLOZYL.ca
TO FIND OUT MORE

Pr Reblozyl®
luspatercept for injection

* Comparative clinical significance has not been established.

Pr Reblozyl®
luspatercept for injection

TABLE OF **CONTENTS**

Mechanism of action (MOA)

REBLOZYL MOA 03

Dosing

REBLOZYL dosing recommendations 04

Reconstitution

Reconstituting REBLOZYL 07

Reconstitution instructions 08

Administration

How to calculate and deliver a dose 09

REBLOZYL subcutaneous (SC) administration 10

Safety Profile

Adverse events 11

Discontinuations and dose modifications 12

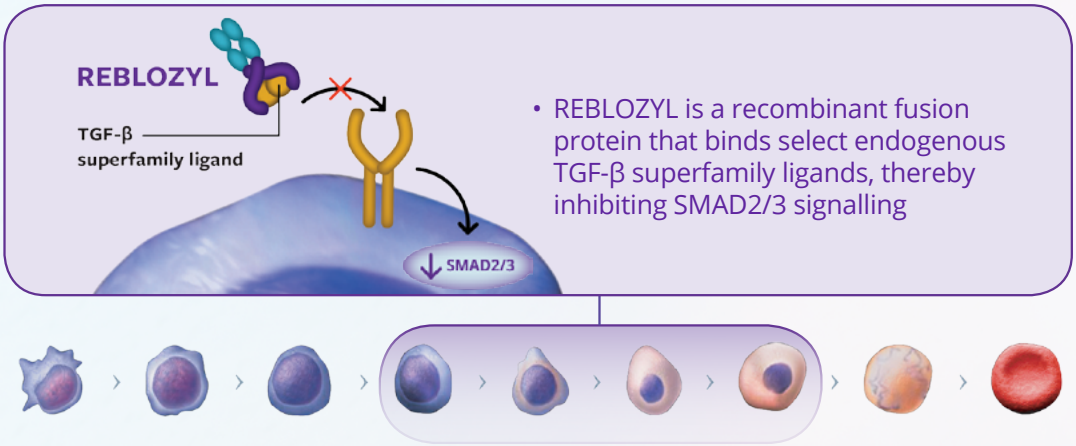
Storage

Storing REBLOZYL 13

MECHANISM OF **ACTION (MOA)**

*REBLOZYL is the **first and only erythroid maturation agent*** indicated for adults with RBC transfusion-dependent anemia associated with β-thalassemia*

THE REBLOZYL MOA IS BASED ON PRECLINICAL STUDIES WITH MICE†



- REBLOZYL is a recombinant fusion protein that binds select endogenous TGF-β superfamily ligands, thereby inhibiting SMAD2/3 signalling

REBLOZYL PROMOTED ERYTHROID MATURATION through differentiation of late-stage erythroid precursors (normoblasts)

In a model of β-thalassemia, REBLOZYL:

- Decreased abnormally elevated SMAD2/3 signalling
- Improved hematology parameters associated with ineffective erythropoiesis in mice

Adapted from the REBLOZYL Product Monograph.

RBC: Red blood cell; TGF-β: Transforming growth factor beta.
* Comparative clinical significance has not been established.
† Clinical significance is unknown.

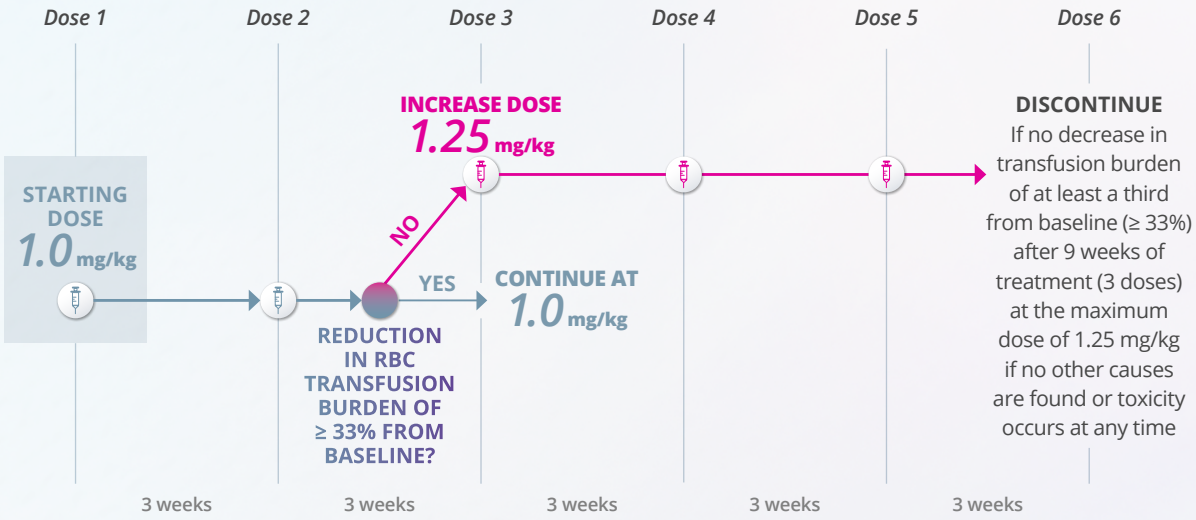
REBLOZYL
DOSING RECOMMENDATIONS

Assess and review hemoglobin (Hgb) results prior to each administration

- Start patients at the recommended starting dose of 1 mg/kg by subcutaneous (SC) injection once every 3 weeks
- Hemoglobin results prior to each administration must be considered for dosing purposes. If an RBC transfusion occurred prior to dosing, the pre-transfusion Hgb must be considered for dosing purposes
- If the pre-dose Hgb is ≥ 115 g/L and the Hgb level is not influenced by recent transfusion, delay dosing until the Hgb is ≤ 110 g/L

No reduction in transfusion burden after at least 6 weeks?

Increase dose to 1.25 mg/kg (maximum dose) if patient does not achieve a response, defined as a reduction in transfusion burden of at least a third from baseline (≥ 33%) after at least 2 consecutive doses at 1 mg/kg (6 weeks)



Adapted from the REBLOZYL Product Monograph.

DOSING **CONSIDERATIONS**

- There are no dosing recommendations available for patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) due to limited clinical data
- Consider the risk of REBLOZYL use in β-thalassemia patients excluded from clinical trials, i.e., patients with uncontrolled hypertension, a deep vein thrombosis or stroke in the previous 24 weeks, or use of an erythropoiesis-stimulating agent (ESA) within the previous 24 weeks
- Discontinue REBLOZYL in case of extramedullary hematopoietic (EMH) masses causing serious complications

If a planned administration of REBLOZYL is missed, administer REBLOZYL as soon as possible and continue dosing as prescribed, with at least 3 weeks between doses.

ESA: Erythropoiesis-stimulating agent; Hgb: Hemoglobin; RBC: Red blood cell.

DOSE ADJUSTMENT **RECOMMENDATIONS***

Pre-dose hemoglobin ≥ 115 g/L or rapid hemoglobin rise

- If the pre-dose Hgb is ≥ 115 g/L in the absence of transfusions, delay dose and restart only when Hgb is ≤ 110 g/L

Reduce dose if there is an increase in Hgb > 20 g/L within 3 weeks of previous dose, and in the absence of transfusion

REBLOZYL DOSE RECOMMENDATIONS FOR β-THALASSEMIA

Current dose	Dosing recommendation
1.25 mg/kg	1 mg/kg
1 mg/kg	0.8 mg/kg
0.8 mg/kg	0.6 mg/kg
0.6 mg/kg	Discontinue REBLOZYL

Dose modifications to help manage adverse events

Adverse events†	Dose modification
Any Grade 2 event	Delay dose until resolved to ≤ Grade 1
Grade 3 or 4	
Hypersensitivity reactions	Discontinue REBLOZYL
Leukocytosis‡ or suspected hematologic malignancy	Delay dose until resolved. Discontinue if hematologic malignancy is confirmed
Other adverse reactions	Delay dose until resolved

Adapted from the REBLOZYL Product Monograph.

* 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.
† Grades as per NCI-CTCAE or when not defined Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, and Grade 4 is life-threatening.
‡ Leukocytosis is defined as >100,000 white blood cell/μL.

RECONSTITUTING REBLOZYL

REBLOZYL is available in 2 strengths as single-use vials for reconstitution

RECONSTITUTION VOLUMES			
Vial size	**Amount of sterile water for injection, USP required for reconstitution**	**Approximate deliverable volume**	**Nominal concentration per mL**
25-mg vial	0.68 mL	0.5 mL	25 mg/0.5 mL (50 mg/mL)
75-mg vial	1.6 mL	1.5 mL	75 mg/1.5 mL (50 mg/mL)

Adapted from the REBLOZYL Product Monograph.

REBLOZYL should be reconstituted and administered by a healthcare professional

- Reconstitute REBLOZYL with sterile water for injection, USP only

Important considerations for REBLOZYL reconstitution

- 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

Pr Reblozyl®
luspatercept for injection

RECONSTITUTION **INSTRUCTIONS**

Adhere to the following steps to properly reconstitute REBLOZYL

1 **Add sterile water for injection, USP.** Reconstitute with sterile water for injection, USP, using volumes described in the reconstitution volumes table on page 7 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 discolouration prior to administration whenever solution and container permit. REBLOZYL is a colourless 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.

8 **Storage.** If the reconstituted solution is not used immediately:

- Store at room temperature at 20°C to 25°C in the original vial for up to 8 hours. Discard if not used within 8 hours of reconstitution.
- Alternatively, the reconstituted solution can be refrigerated at 2°C to 8°C for up to 24 hours in the original vial. Remove from refrigerated conditions 15–30 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.**

Adapted from the REBLOZYL Product Monograph.
SC: Subcutaneous.

HOW TO CALCULATE AND DELIVER A DOSE

Sample calculation for SC administration of REBLOZYL

- Average adult male aged 30 years and weighing 197 pounds (89 kg)
- 1 mg of REBLOZYL per 1 kg = 89 mg starting dose
- Hgb of 100 g/L

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 (50 mg/mL)	Use 0.28 mL	14 mg
			Total volume needed is 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

SC: Subcutaneous.

REBLOZYL
SC ADMINISTRATION

- Prior to injection, allow the 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 according to the table on page 9

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 (i.e., > 1.2 mL) into separate similar volume injections and inject into separate sites

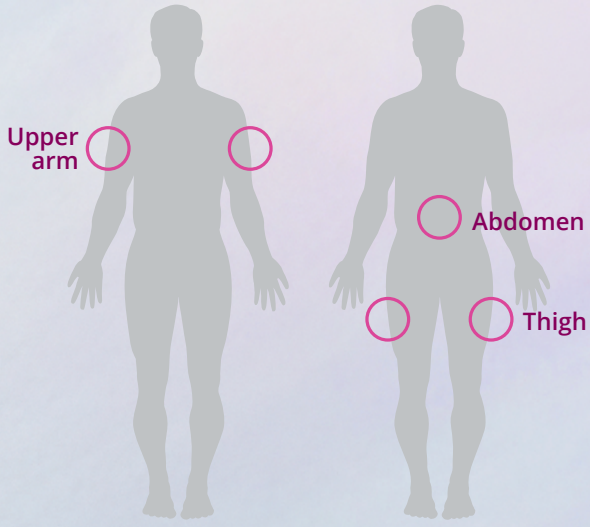
STEP 3

Perform SC 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

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.***

Sample administration of a REBLOZYL dose larger than 1.2 mL



Adapted from the REBLOZYL Product Monograph.
SC: Subcutaneous.

ADVERSE EVENTS

In the BELIEVE trial (N = 332) – A phase III, double-blind, randomized, placebo-controlled study

- Treatment emergent adverse events (TEAEs) reflected a median treatment duration of 64.1 weeks (range 3–97) in the REBLOZYL arm vs 64.0 weeks (range 9–92) in the placebo arm
- The most common TEAEs in patients treated with REBLOZYL (≥ 10% and with ≥ 1% frequency compared to placebo) were:
  - Headache (26%)
  - Bone pain (20%)
  - Arthralgia (19%)
  - Fatigue (14%)
  - Cough (14%)
  - Abdominal pain (14%)
  - Diarrhea (12%)
  - Dizziness (11%)
- Serious TEAEs occurred in 15.2% of patients treated with REBLOZYL compared to 5.2% of patients treated with placebo
  - Serious TEAEs of infections occurred in 5.8% of patients treated with REBLOZYL compared to 2.8% of patients treated with placebo

TREATMENT DISCONTINUATION AND **DOSE MODIFICATIONS** DUE TO ADVERSE EVENTS

5.4% REBLOZYL vs **0.9%** PLACEBO

PERMANENT DISCONTINUATIONS DUE TO AN ADVERSE EVENT

Most common adverse events leading to discontinuation of REBLOZYL included arthralgia (0.9%), back pain (0.9%), and deep vein thrombosis (0.9%)

2.7% REBLOZYL vs **2.8%** PLACEBO

DOSE REDUCTIONS DUE TO AN ADVERSE EVENT

The most common adverse event leading to dose reduction of REBLOZYL was hypertension (0.9%)

15.2% REBLOZYL vs **10.1%** PLACEBO

DOSE DELAY/INTERRUPTIONS DUE TO AN ADVERSE EVENT

Most common adverse events leading to dose delay/interruption of REBLOZYL included, upper respiratory tract infection (1.8%), alanine aminotransferase increase (1.3%), and cough (1.3%)

Adapted from the REBLOZYL Product Monograph.

ALT: Alanine aminotransferase.

STORING REBLOZYL

REBLOZYL requires refrigerated storage

Storage of unreconstituted vial

- Store unreconstituted vials refrigerated at 2°C to 8°C 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 in the original vial for up to 8 hours. Discard if not used within 8 hours of reconstitution
- Alternatively, the reconstituted solution can be refrigerated at 2°C to 8°C for up to 24 hours in the original vial
  - Remove from refrigerated conditions 15–30 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

Clinical use:

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use.

Geriatrics (> 65 years of age): No differences in safety or effectiveness were observed between older (≥ 65 years) and younger patients when compared to placebo. Clinical studies in β-thalassemia did not include sufficient numbers of patients aged ≥ 65 to determine whether they respond differently.

Relevant warnings and precautions:

- Extramedullary hematopoietic (EMH) masses: Monitor patients with β-thalassemia. Not recommended for patients requiring treatment for EMH masses.
- Hypertension: Monitor blood pressure prior to each administration.
- Thrombosis/Thromboembolic events (TEEs), including deep vein thrombosis, pulmonary emboli, and ischemic stroke. Consider thromboprophylaxis in patients at higher risk for developing TEE.
- Monitoring and laboratory testing: Assess and review Hgb results prior to each administration of REBLOZYL.
- Pregnancy: Potential for fetal harm when administered to pregnant women. Females of childbearing potential should be advised to avoid becoming pregnant while receiving REBLOZYL treatment. They are also advised to use effective contraception during treatment and for at least 3 months after the last dose.
- The safe use of REBLOZYL during breast-feeding has not been established.

For more information:

Consult the REBLOZYL Product Monograph for important information relating to adverse reactions, drug interactions, and dosing information, which has not been discussed in this piece.

The Product Monograph is also available by calling our medical department at: **1-866-463-6267**.

SUMMARY

Start patients at the recommended starting dose of 1 mg/kg by subcutaneous (SC) injection once every 3 weeks

Continue treatment as long as reduction in transfusion burden from baseline is observed and is tolerated

Increase dose to 1.25 mg/kg (maximum dose) if there is no reduction in transfusion burden of at least a third from baseline (≥ 33%) after at least 2 consecutive doses at 1 mg/kg (6 weeks)

Discontinue REBLOZYL if there is no reduction in transfusion burden of at least a third from baseline (≥ 33%) after 9 weeks of treatment (administration of 3 doses) at the maximum dose level if no other causes are found, or if unacceptable toxicity occurs at any time

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

RECONSTITUTION VOLUMES

Vial size	Amount of sterile water for injection, USP required for reconstitution	Approximate deliverable volume	Nominal concentration per mL
25 mg vial	0.68 mL	0.5 mL	25 mg/0.5 mL (50 mg/mL)
75 mg vial	1.6 mL	1.5 mL	75 mg/1.5 mL (50 mg/mL)

Store vials refrigerated at 2–8°C in original carton to protect from light. Do not freeze. Reconstituted vials in the original container can be stored for up to 8 hours when stored at room temperature or for 24 hours when stored at 2–8°C.

VISIT REBLOZYL.ca TO FIND OUT MORE

REFERENCE: REBLOZYL Product Monograph. Celgene Inc.

Bristol Myers Squibb™

MEMBER OF INNOVATIVE MEDICINES CANADA

Pr Reblozyl® luspatercept for injection

2007-CA-2300020E