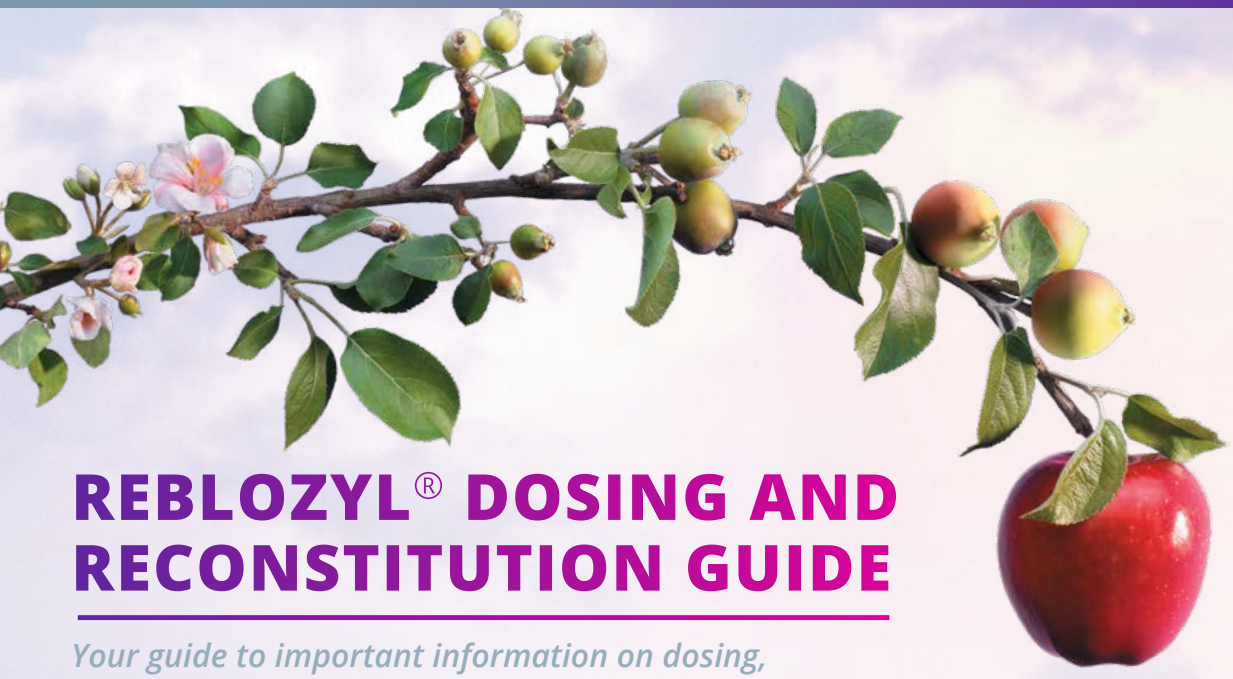

REBLOZYL® DOSING AND RECONSTITUTION GUIDE

Your guide to important information on dosing, reconstitution, and administration

THE FIRST AND ONLY ERYTHROID MATURATION AGENT INDICATED FOR ADULTS WITH TRANSFUSION-DEPENDENT ANEMIA RESULTING FROM VERY LOW- TO INTERMEDIATE-RISK MDS WITH RING SIDEROBLASTS WHO HAVE FAILED OR ARE NOT SUITABLE FOR EPO-BASED THERAPY*

REBLOZYL (luspatercept for injection) is an erythroid maturation agent indicated for the treatment of adult patients with transfusion-dependent anemia requiring at least two red blood cell (RBC) units over 8 weeks resulting from very low- to intermediate-risk myelodysplastic syndromes (MDS) who have ring sideroblasts and who have failed or are not suitable for erythropoietin-based therapy.

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.

*Comparative clinical significance is unknown.

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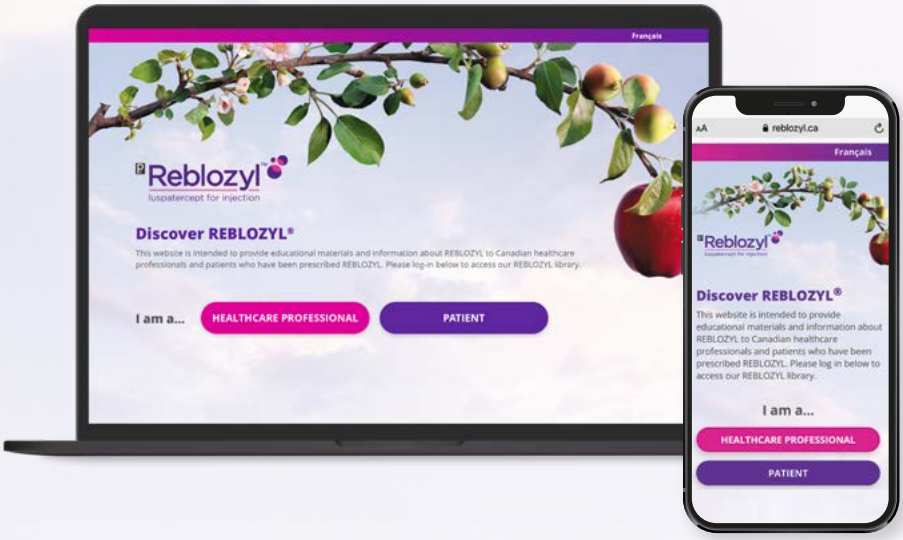
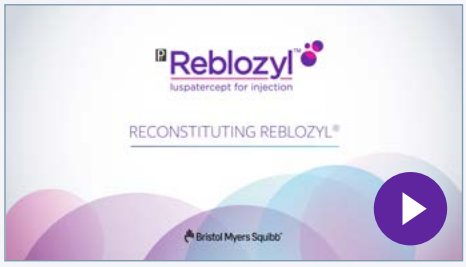
DISCOVER REBLOZYL.ca

REBLOZYL.ca is a one-stop digital hub, with downloadable tools to help support you and your patients during the REBLOZYL treatment journey.



Head out to REBLOZYL.ca to watch videos about:

Important information on dosing and administration



How to properly reconstitute REBLOZYL

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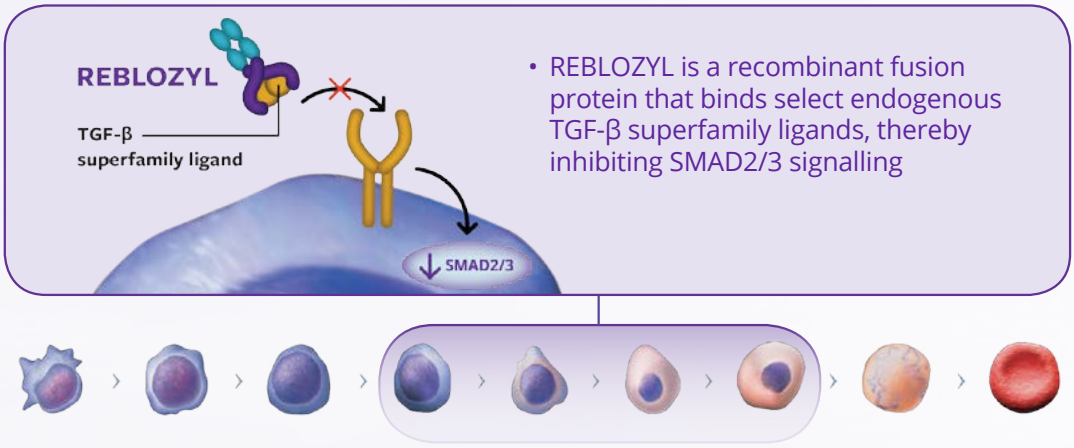
DISCOVER REBLOZYL

*The first and only erythroid maturation agent indicated for adults with transfusion-dependent anemia resulting from MDS with ring sideroblasts who have failed or are not suitable for EPO-based therapy**

A CLOSER LOOK AT THE REBLOZYL MOA FROM PRECLINICAL STUDIES WITH MICE†[1]



- 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)

Adapted from the REBLOZYL Product Monograph.

EPO: erythropoietin.
MDS-RS: MDS with ring sideroblasts.
TGF-β: Transforming growth factor beta.
*Comparative clinical significance is unknown.
†Clinical significance is unknown.

INITIATING REBLOZYL TREATMENT **IN PATIENTS WITH MDS-RS**

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
- If an RBC transfusion occurred prior to dosing, the pre-transfusion Hgb must be considered for dosing purposes
- If the pre-dose Hgb ≥11.5 g/dL (115 g/L) and the Hgb level is not influenced by recent transfusion, delay dosing until Hgb ≤11.0 g/dL (110 g/L)

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.

Dosing considerations

- There are limited clinical data in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) and therefore no dosing recommendations are available. No dose adjustments are required for patients with mild to moderate renal impairment (mild [eGFR 60–89 mL/min/1.73 m^2]; moderate [eGFR 30–59 mL/min/1.73 m^2])
- No starting dose adjustment is required for patients with mild to severe hepatic impairment (elevated total bilirubin [4–246 µmol/L] >ULN and ALT or AST <3 times ULN). Pharmacokinetic data are not available for patients with AST or ALT ≥3x ULN

ALT: Alanine aminotransferase.
AST: Aspartate aminotransferase.
eGFR: Estimated glomerular filtration rate.
MDS-RS: myelodysplastic syndrome with ring sideroblasts.
RBC: Red blood cell.
ULN: Upper limit of normal.

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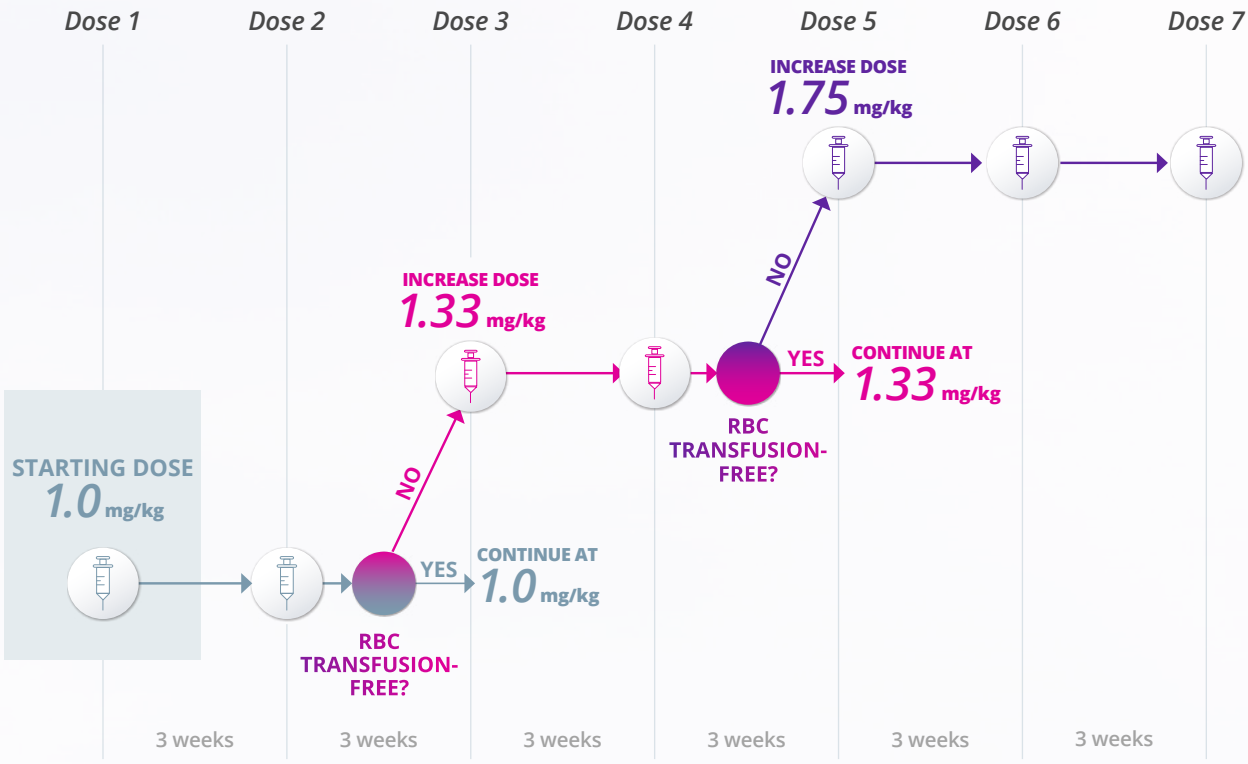
RECOMMENDATIONS FOR **DOSE MODIFICATIONS**

Consider dose titration for insufficient response from treatment initiation



DISCONTINUE

If no response is achieved after 9 weeks of treatment (3 doses) at the 1.75 mg/kg dose if no other causes are found, or if unacceptable toxicity occurs at any time

- REBLOZYL dose can be increased if the patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks)
- The dose should not be increased more frequently than every 6 weeks
- The dose should not exceed the maximum dose of 1.75 mg/kg

RECOMMENDATIONS FOR **DOSE MODIFICATIONS**

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

REBLOZYL DOSING RECOMMENDATIONS FOR MDS-RS

Current dose	Dosing recommendation
1.75 mg/kg	1.33 mg/kg
1.33 mg/kg	1.0 mg/kg
1.0 mg/kg	0.8 mg/kg
0.8 mg/kg	0.6 mg/kg
0.6 mg/kg	Discontinue REBLOZYL

Adapted from the REBLOZYL Product Monograph.

Modify dosing with REBLOZYL to help manage adverse events

Adverse events*	Dosing modifications
Any Grade 2 adverse 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 to ≤Grade 1. Discontinue if hematologic malignancy is confirmed
Other adverse events	Delay dose until resolved to ≤Grade 1

Adapted from the REBLOZYL Product Monograph.

MDS-RS: myelodysplastic syndrome with ring sideroblasts.
NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events.
*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 cells/μL.

RECONSTITUTING REBLOZYL

REBLOZYL should be reconstituted and administered by a healthcare professional

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.

Healthcare professionals should reconstitute:

- Using Sterile Water for Injection, USP only
- The number of REBLOZYL vials to achieve the appropriate dose based on the patient's weight
- Using a syringe with suitable graduations for reconstitution to ensure accurate dosage

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REBLOZYL **RECONSTITUTION INSTRUCTIONS**

Adhere to the following steps to properly reconstitute REBLOZYL

1 **Reconstitute with Sterile Water for Injection, USP,** *using volumes described in the Reconstitution Volumes table on page 8, with the stream directed into 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 subcutaneous injection.*

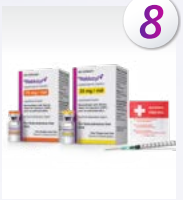
3 **Mix and wait.** *Gently swirl the vial in a circular motion for 30 seconds. Stop swirling and let the vial sit in upright position for 30 seconds.*

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 are 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, store 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.

CALCULATING A DOSE TO **ADMINISTER TO YOUR PATIENT**

Sample calculation for SC administration of REBLOZYL

- Average adult male aged 30 years and weighing 197 lb (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

ADMINISTERING REBLOZYL

- 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 8

Step 2 Plan and prep for injection

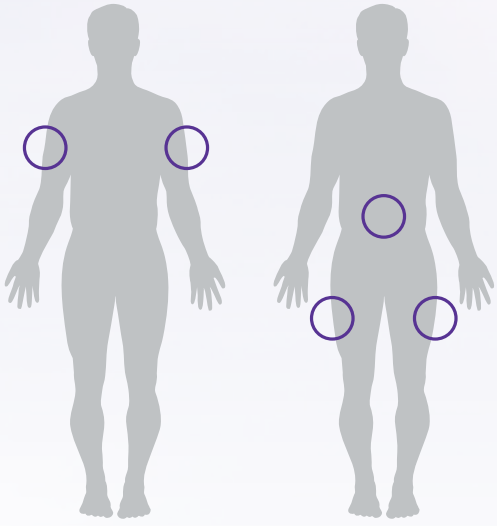
- Slowly withdraw the dosing volume of the reconstituted REBLOZYL solution from the single-dose vial(s) into a syringe
- Divide doses requiring larger reconstituted volumes (i.e., >1.2 mL) into separate similar volume injections and inject into separate sites

Step 3 Perform 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

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



Injection 1
Back

Injection 2
Front

Adapted from the REBLOZYL Product Monograph.

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

FOR MORE INFORMATION:

Consult the REBLOZYL Product Monograph at: https://www.bms.com/assets/bms/ca/documents/productmonograph/REBLOZYL_EN_PM.pdf for important information on contraindications, warnings, precautions, adverse reactions, drug interactions, and dosing information that have not been discussed in this piece.

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

VISIT
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TO FIND OUT MORE

REBLOZYL Product Monograph. Celgene Inc., February 11, 2021.