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

REBLOZYL Dosing and Reconstitution Guide

REBLOZYL (luspatercept-aamt) is indicated for the treatment of anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions.

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%) of 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.

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Click here for REBLOZYL MDS Dosing Calculator

REBLOZYL is available in

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

25 mg

75 mg

Table of contents

Please see Important Safety Information throughout and full Prescribing Information for REBLOZYL.

Warnings and Precautions

Thrombosis/Thromboembolism

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Hypertension

Hypertension was reported in 11.4% (63/554) of REBLOZYL-treated patients. Across clinical studies, the incidence of Grade 3 to 4 hypertension ranged from 2% to 9.6%. In ESA-naïve adult patients with MDS with normal baseline blood pressure, 23 (36%) patients developed SBP ≥140 mm Hg and 11 (6%) 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.

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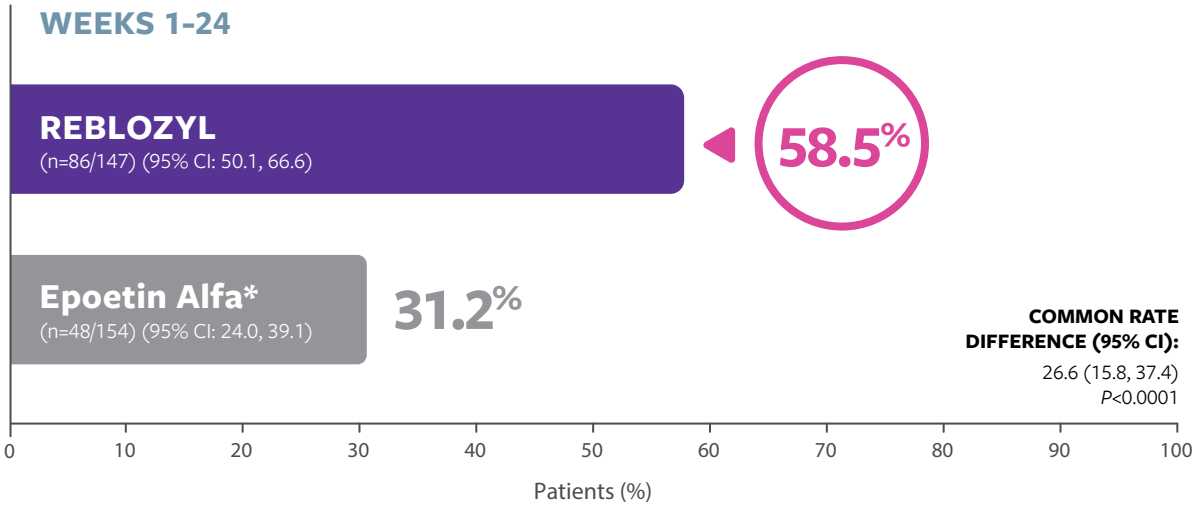
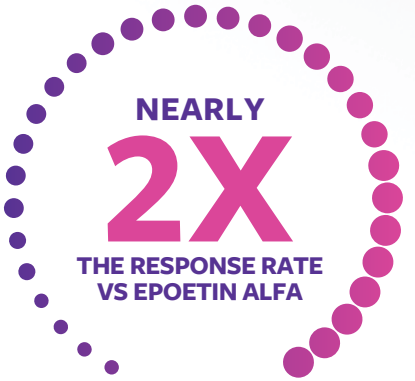
REBLOZYL nearly doubled the response rate in the COMMANDS trial[1]

PRIMARY COMPOSITE ENDPOINT: RBC-TI for at least 12 weeks with concurrent mean Hgb increase ≥1.5 g/dL[1]





This prespecified interim analysis included 301 patients who had either completed 24 weeks of treatment or discontinued prior to completing 24 weeks of treatment. This represents 85% of the total patient population contributing data for the primary endpoint.

STUDY DESIGN: COMMANDS (N=356) was a Phase 3, randomized, open-label, active-controlled trial comparing REBLOZYL vs epoetin alfa in adult patients with anemia due to IPSS-R very low-, low-, or intermediate-risk MDS, with or without ring-sideroblasts, who were ESA-naive (with endogenous sEPO levels <500 U/L) and required RBCT. Patients with del(5q) and those previously treated with disease-modifying agents or HMAs were excluded.

Patients were randomized to either REBLOZYL (n=178) 1 mg/kg SC Q3W, with titration up to max 1.75 mg/kg if needed to achieve response or epoetin alfa (n=178) 450 IU/kg SC QW max total dose 40K IU, with titration up to 1050 IU/kg max total dose 80K IU. The primary endpoint was RBC-TI with a mean improvement in Hgb by at least 1.5 g/dL for any consecutive 12-week period during Weeks 1-24.[1,2]

*>90% of study participants were outside of the United States and used non-licensed epoetin alfa product. Direct comparisons between REBLOZYL and US-licensed epoetin alfa product have not been established.

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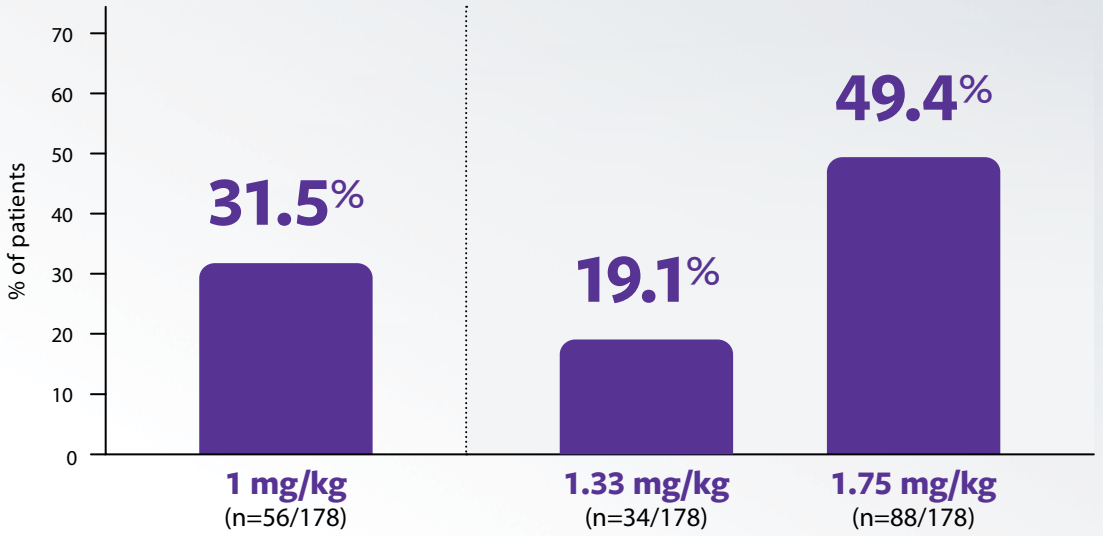
Highest dose level of REBLOZYL received by patients in the COMMANDS trial[3]



69%
OF ALL COMMANDS PATIENTS RECEIVING REBLOZYL HAD THEIR DOSE INCREASED AT LEAST ONCE[2]

- The majority of patients (49.4%, n=88/178) received 2 dose increases
- The median (min, max) time to first dose escalation was 45 days (43, 125)[4]

REBLOZYL has a well-established safety profile[1]

- The most common (>10%) all-grade adverse reactions included diarrhea, fatigue, hypertension, COVID-19, peripheral edema, nausea, and dyspnea[1]
- The most common (>2%) Grade >3 adverse reactions included hypertension and dyspnea[1]
- Selected laboratory abnormalities that changed from Grade 0-2 at baseline to Grades 2-3 at any time during the studies were glomerular filtration rate and total bilirubin increased[1]
- Other clinically relevant adverse reactions reported in <5% of patients are injection site reactions, including erythema, pruritus, and rash[1]

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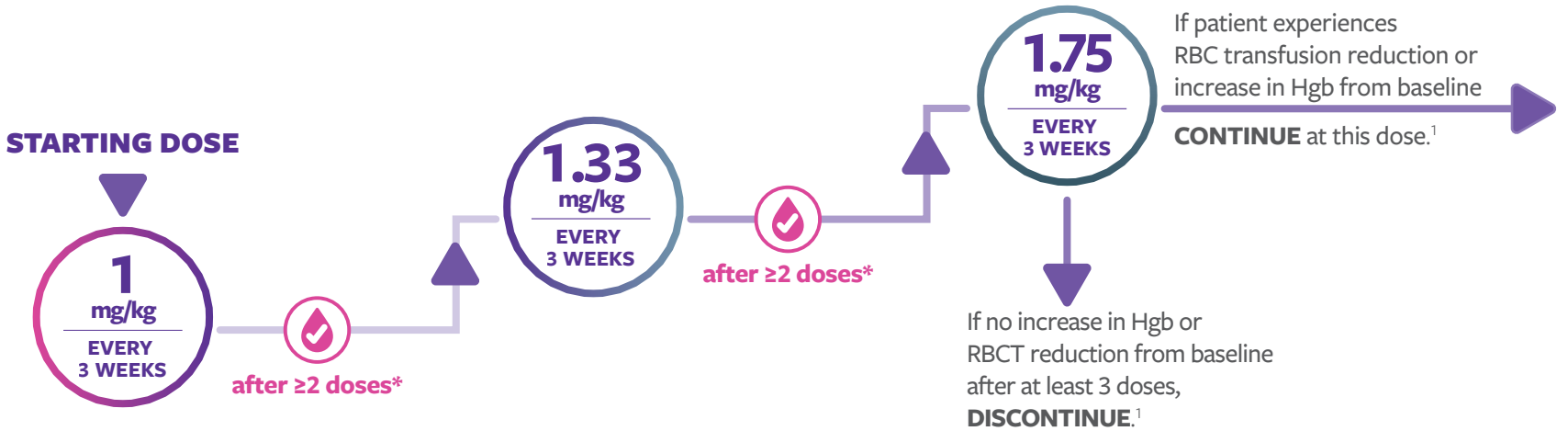
Dose-adjust to optimize patient response[1]

Expect to escalate dose to meet patient treatment goals[1]

- Prior to each REBLOZYL administration, assess if patient may require a dose adjustment. Review Hgb prior to administration. If RBC transfusion occurred, use pretransfusion Hgb
- Following at least 2 doses at the same level, dosing adjustments can be considered at any time during therapy
- **Do not continue treatment or increase dose if patient is experiencing unacceptable toxicity or an adverse event**

69% of all COMMANDS patients receiving REBLOZYL **had their dose increased at least once**[3]



DOSE ADJUSTMENT CRITERIA[1]
- Increase dose if **transfusion was required** since last assessment†
- Continue at current dose if patient has met treatment goals and has ongoing RBC-TI

Hgb=hemoglobin; RBCT=red blood cell transfusion; RBC-TI=red blood cell transfusion independence.
*Do not increase dose more frequently than every 6 weeks (2 doses); do not increase dose beyond maximum dose.
†In the absence of transfusion, if predose Hgb is ≥11.5 g/dL or if Hgb increases >2 g/dL within 3 weeks, interrupt or decrease dose. See instructions for modifications.

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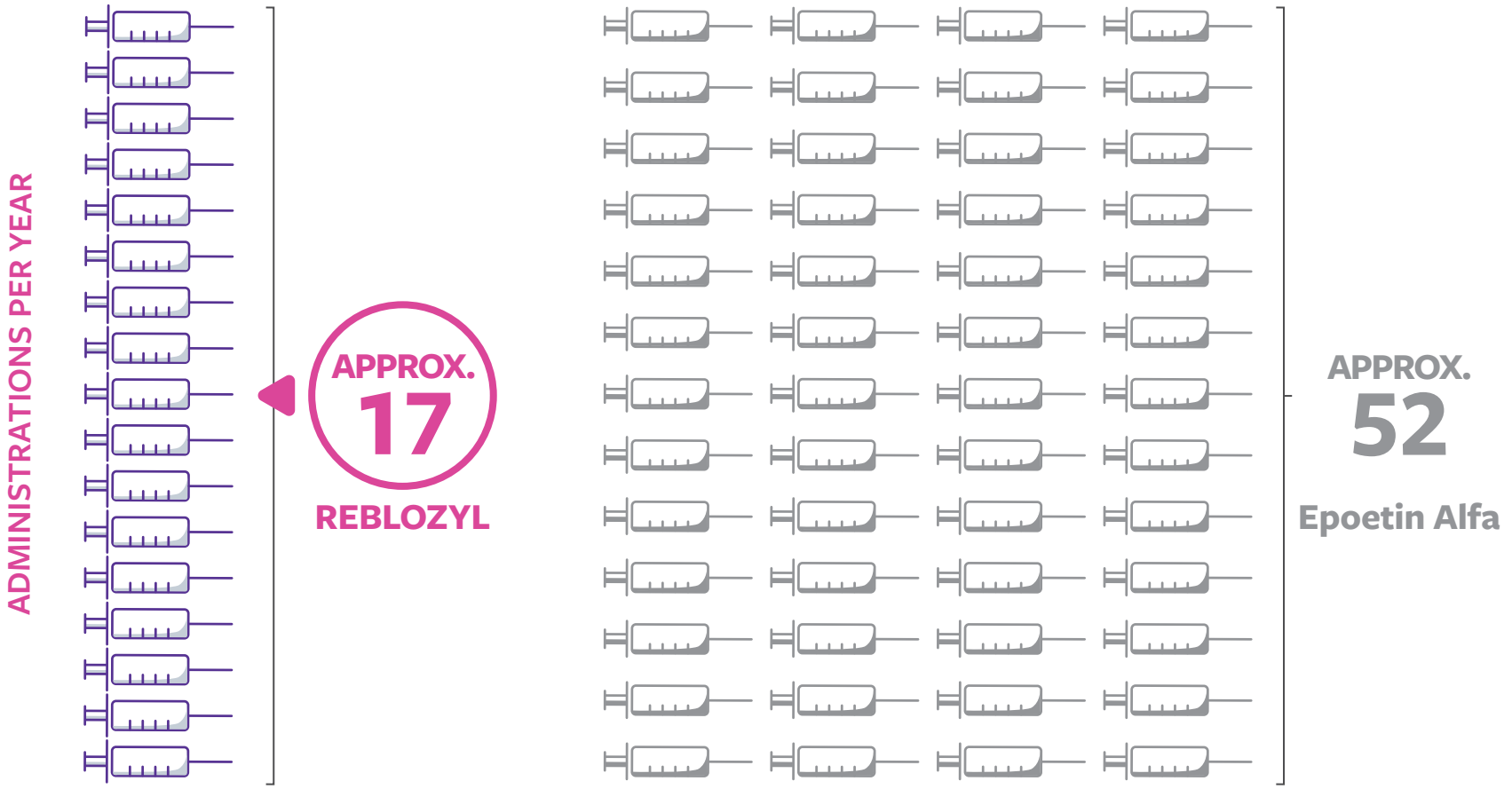
Dosing convenience[1,3‡]

Every 3 weeks vs once a week[§]



[‡]Timing of administration may be impacted by dose modifications (eg, AEs, rapid Hgb rise).
[§]Based on the COMMANDS dosing schedule for REBLOZYL (1 administration every 3 weeks=about 17 administrations per year) and epoetin alfa (1 injection every week=52 injections per year).

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Dose modifications when administering REBLOZYL[1]

DOSE MODIFICATIONS FOR PREDOSE HGB LEVELS OR RAPID HGB RISE[1]

SCENARIO	REBLOZYL Dosing recommendation
Predose Hgb **≥11.5 g/dL** is 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**	• Reduce dose to **1.33 mg/kg**
Current dose is **1.33 mg/kg**	• Reduce dose to **1 mg/kg**
Current dose is **1 mg/kg**	• Reduce dose to **0.8 mg/kg**
Current dose is **0.8 mg/kg**	• Reduce dose to **0.6 mg/kg**
Current dose is **0.6 mg/kg**	• Discontinue treatment

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 clinical benefit is observed[1]

- Discontinue REBLOZYL if no increase in Hgb or reduction in RBC transfusion burden from baseline after at least 3 consecutive doses (9 weeks) at 1.75 mg/kg 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

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Dose modifications when administering REBLOZYL[1]

DOSE MODIFICATIONS FOR ADVERSE REACTIONS[1]

SCENARIO	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 lower dose delay is >12 consecutive weeks, discontinue treatment

Patients requiring dose escalation[3]

- 69% of all COMMANDS patients receiving REBLOZYL had their dose increased at least once
- 49% of patients ultimately reached the maximum dose of 1.75 mg/kg

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

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Reconstituting REBLOZYL

REBLOZYL should be reconstituted and administered by a healthcare professional[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 (50 mg/mL)	0.5 mL
75 mg vial	1.6 mL	75 mg/1.5 mL (50 mg/mL)	1.5 mL

- 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

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Reconstitution instructions

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

STEP 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.

STEP 2

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

STEP 3

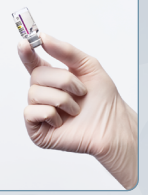
Mix and wait.
Gently swirl the vial in a circular motion for 30 seconds. Stop swirling and let the vial sit in an upright position for 30 seconds.

STEP 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.

STEP 5

Invert, 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.



STEP 6

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

STEP 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.

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Instructions for subcutaneous 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 prepare for injection

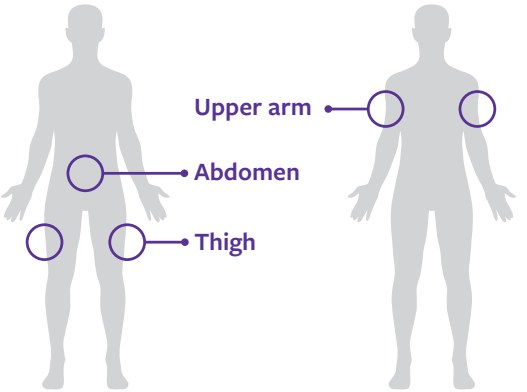
- Slowly withdraw the dosing volume of the reconstituted REBLOZYL solution from the single-dose vial(s) into a syringe
- Divide doses requiring larger reconstituted volumes (ie, >1.2 mL) into separate, similar-volume injections and inject into separate sites

STEP 3

Administer subcutaneously

- If multiple injections are required, use a new syringe and needle for each SC injection

Administer REBLOZYL into 1 or more of the following sites by SC injection:



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.[1]

SC=subcutaneous.

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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 aged 71 years and 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[1]

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 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

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Storing REBLOZYL

REBLOZYL requires cold storage[1]

Storage of unreconstituted vial	Storage of reconstituted solution
	
• Do not freeze • Store unreconstituted vials at 2°C to 8°C (36°F to 46°F) in original carton to protect from light	• Do not freeze • Store at 2°C to 8°C (36°F to 46°F) for up to 24 hours in the original vial — Discard if not used within 24 hours of reconstitution if refrigerated — Remove from refrigerated condition 15 to 30 minutes prior to injection to allow solution to reach room temperature for a more comfortable injection • 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 at room temperature

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Important Safety Information

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ADVERSE REACTIONS

Grade ≥3 (≥2%) adverse reactions included hypertension and dyspnea.

The most common (≥10%) all-grade adverse reactions included diarrhea, fatigue, hypertension, peripheral edema, nausea, and dyspnea.

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.

DRUG ABUSE POTENTIAL

Abuse: Abuse of REBLOZYL may be seen in athletes for the effects on erythropoiesis. Misuse of drugs that increase erythropoiesis, such as REBLOZYL, by healthy persons may lead to polycythemia, which may be associated with life-threatening cardiovascular complications.

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Learn more about REBLOZYL

Visit REBLOZYLPro.com to access additional resources.

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References: 1. REBLOZYL [US Prescribing Information]. Summit, NJ: Celgene Corporation; 2023. **2.** Platzbecker U, Della Porta MG, Santini V, et el. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial. *Lancet*. 2023;402(10399):373-385. **3.** Data on file. BMS-REF-ACE-536-0009. Princeton, NJ: Bristol-Myers Squibb Company; 2023. **4.** Platzbecker U, Della Porta MG, Santini V, et el. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial. *Lancet*. 2023;402(10399)(suppl):373-385.

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