A GUIDE FOR MANAGING REBLOZYL® THERAPY

DISCOVER REBLOZYL

The first and only erythroid maturation agent indicated in adult patients 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.[1]

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.[1]

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*Comparative clinical significance is unknown.

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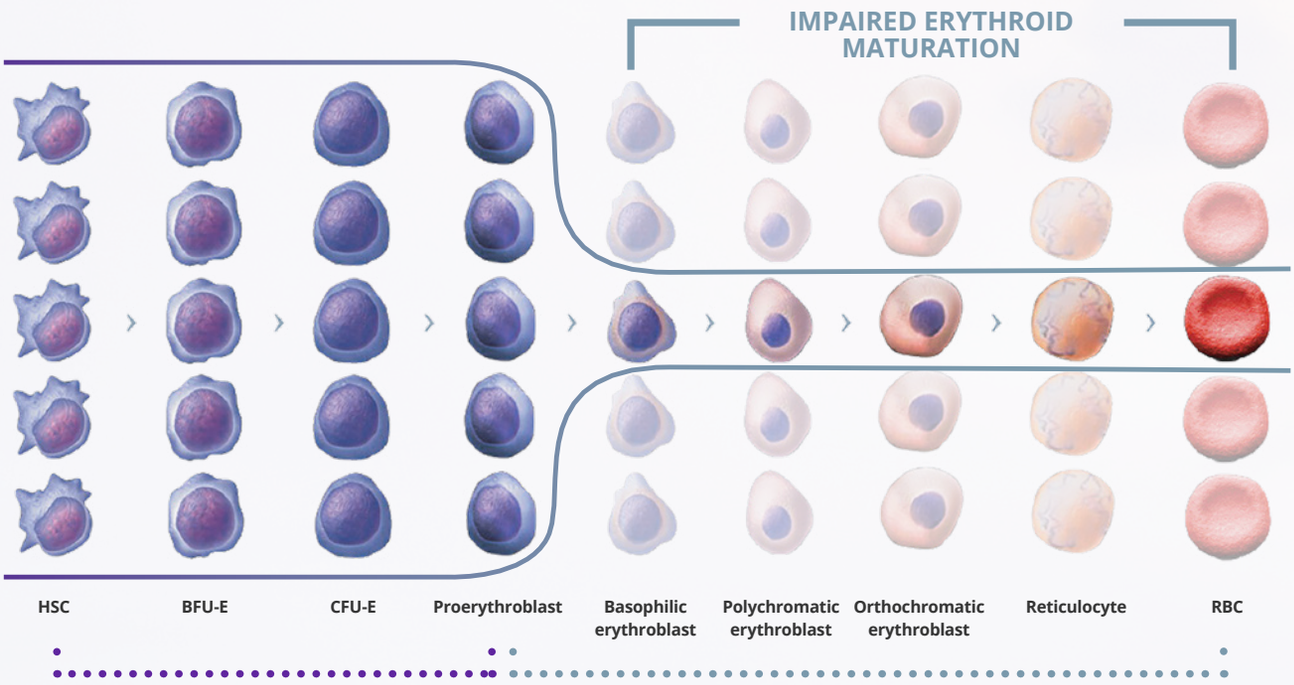
IMPAIRED ERYTHROID MATURATION CONTRIBUTES TO INEFFECTIVE ERYTHROPOIESIS, **RESULTING IN LOW PRODUCTION OF RBCs AND ANEMIA**[2]



Adapted from Lodish *et al*, 2010; Fortunel *et al*, 2000; Suragani *et al*, 2014.

MDS-RS is classified as lower-risk MDS that is often characterized by ineffective erythropoiesis[6,7,11]

- The hallmark of MDS-RS is the presence of **ring sideroblasts**
  - These are erythroblasts in the bone marrow characterized by iron-rich mitochondria around the nucleus[8]

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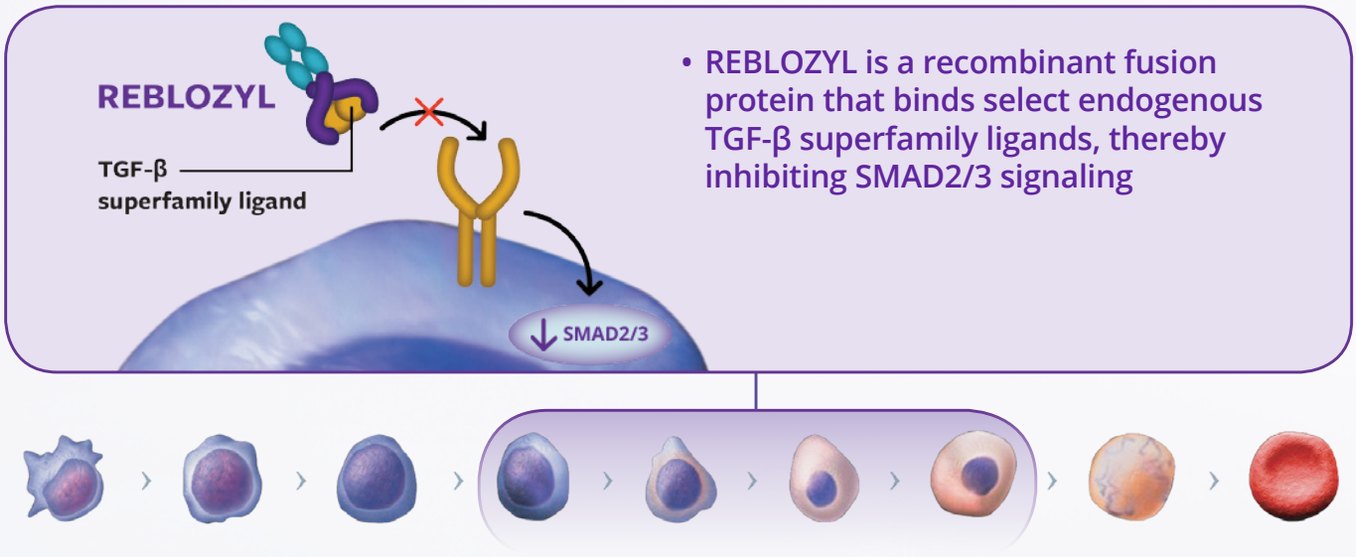
*The first and only erythroid maturation agent indicated in adult patients with transfusion-dependent anemia resulting from very low- to intermediate-risk MDS with ring sideroblasts who have failed or are not suitable for EPO-based therapy**

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 signaling

REBLOZYL promoted erythroid maturation
through differentiation of late-stage erythroid precursors (normoblasts)

Adapted from the REBLOZYL Product Monograph.

*Comparative clinical significance is unknown.
†Clinical significance is unknown.
BFU-E: Burst-forming unit erythroid.
CFU-E: Colony-forming unit erythroid.
HSC: Hematopoietic stem cell.
MDS-RS: Myelodysplastic syndrome with ring sideroblasts.
TGF-β: Transforming growth factor beta.

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REBLOZYL WAS **STUDIED IN THE PHASE 3,** RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED MEDALIST TRIAL[1,9,10]

PATIENT POPULATION (N = 229)

Key inclusion criteria:

- Adults ≥18 years of age
- IPSS-R very low-, low-, or intermediate-risk MDS
- <5% bone marrow blasts
- Presence of ring sideroblasts
  - ≥15% ring sideroblasts or ≥5% ring sideroblasts with an *SF3B1* mutation
- RBC transfusion burden ≥2 units over 8 weeks during the 16-week period prior to randomization
- Received prior treatment with an erythropoiesis-stimulating agent (ESA) or determined to be unlikely to respond to ESA treatment with serum erythropoietin (EPO) (>200 U/L)

Key exclusion criteria:

- Deletion 5q (del 5q) MDS
- White blood cell count ≥13 x 10^9/L
- Neutrophils <0.5 x 10^9/L
- Platelets <50 x 10^9/L
- Prior use of a disease-modifying agent for treatment of MDS

Randomized
2:1

REBLOZYL + BSC

REBLOZYL 1 mg/kg subcutaneous (SC) every 3 weeks + BSC for 48 weeks (n = 153)

Placebo + BSC

Placebo SC every 3 weeks + BSC for 48 weeks (n = 76)

All patients were eligible to receive BSC as needed, including:

- RBC transfusions
- Iron-chelating agents
- Use of antibiotic, antiviral and antifungal therapy
- Nutritional support

Adapted from the REBLOZYL Product Monograph and Fenaux, *et al* (2020).

BSC: Best supportive care.
IPSS-R: International Prognostic Scoring System-Revised.

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THE MEDALIST TRIAL INCLUDED PATIENTS WITH VERY **LOW- TO INTERMEDIATE-RISK** MDS WITH RING SIDEROBLASTS[1]

Baseline demographics and disease characteristics of patients in the phase 3 MEDALIST trial

Disease characteristic	REBLOZYL (n = 153)	Placebo (n = 76)
Age (years) median (min, max)	71 (40, 95)	72 (26, 91)
Age categories, n (%)		
<65 years	29 (19.0)	16 (21.1)
65–74 years	72 (47.1)	29 (38.2)
≥75 years	52 (34.0)	31 (40.8)
Time since original MDS diagnosis* (months)		
Mean (SD)	57.8 (56.6)	52.7 (42.3)
Median (min, max)	44.0 (3, 421)	36.1 (4, 193)
Serum EPO (U/L) categories†, n (%)		
<100	51 (33.3)	31 (40.8)
100 to <200	37 (24.2)	19 (25.0)
200 to 500	43 (28.1)	15 (19.7)
>500	21 (13.7)	11 (14.5)
Missing	1 (0.7)	0 (0.0)
Hemoglobin (g/L)		
Mean (SD)	7.7 (0.8)	7.7 (0.8)
Median (min, max)	7.6 (6, 10)	7.6 (5, 9)
Ring sideroblasts, n (%)		
≥15%	153 (100.0)	76 (100.0)
MDS classification‡, n (%)		
MDS RARS	7 (4.6)	2 (2.6)
MDS RCMD-RS	145 (94.8)	74 (97.4)
Other§	1 (0.7)	0 (0.0)

Disease characteristic	REBLOZYL (n = 153)	Placebo (n = 76)
IPSS-R classification risk category, n (%)		
Very low	18 (11.8)	6 (7.9)
Low	109 (71.2)	57 (75.0)
Intermediate	25 (16.3)	13 (17.1)
High	1 (0.7)	0 (0.0)
***SF3B1*, n (%)**		
Mutated	141 (92.2)	65 (85.5)
Nonmutated	12 (7.8)	10 (13.2)
Missing	0 (0.0)	1 (1.3)
ECOG performance status, n (%)		
0	54 (35.3)	33 (43.4)
1	91 (59.5)	32 (42.1)
2	8 (5.2)	11 (14.5)
RBC transfusions/8 weeks over 16 weeks categories, n (%)		
≥6 units	66 (43.1)	33 (43.4)
<6 units	87 (56.9)	43 (56.6)
≥4 and <6 units	41 (26.8)	23 (30.3)
<4 units	46 (30.1)	20 (26.3)
Prior ESA, n (%)	148 (96.7)	70 (92.1)

Adapted from the REBLOZYL Product Monograph.

Patient population characteristics[1]

- 62.9% of patients were male and 69% were Caucasian
- Race was not recorded for 29.7% of patients

REBLOZYL is only indicated in adult patients 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.

* Time since original MDS diagnosis was defined as the number of years from the date of original diagnosis to the date of informed consent.
† Baseline EPO was defined as the highest EPO value within 35 days of the first dose of study drug.
‡ Per the World Health Organization (WHO) 2008 criteria.
§ Locally diagnosed MDS-RS and multilineage dysplasia.
ECOG: Eastern Cooperative Oncology Group.
IPSS-R: International Prognostic Scoring System-Revised.
RARS: Refractory anemia with ring sideroblasts.
RCMD-RS: Refractory cytopenia with multilineage dysplasia with ring sideroblasts.
SD: Standard deviation.

ADVERSE **EVENTS**[1]

- TEAEs in the MEDALIST trial reflected a median treatment duration of 49.0 weeks (range 6–114) in the REBLOZYL arm vs 24.0 weeks (range 7–89) in the placebo arm

All TEAEs observed in ≥5% of the REBLOZYL-treated patients and Grade 3 or 4 TEAEs observed in ≥1% of the REBLOZYL-treated patients†[1]*

System organ class/ preferred term	REBLOZYL N = 153		Placebo N = 76	
	All grades n (%)	Grades 3–4‡ n (%)	All grades n (%)	Grades 3–4 n (%)
Ear and labyrinth disorders				
Vertigo and vertigo positional	9 (6)	0 (0)	1 (1)	1 (1)
Gastrointestinal disorders				
Diarrhea	34 (22)	0 (0)	7 (9)	0 (0)
Nausea‡	31 (20)	1 (1)	6 (8)	0 (0)
Constipation	17 (11)	0 (0)	7 (9)	0 (0)
General disorders and administration site conditions				
Fatigue§	70 (46)	11 (7)	19 (25)	2 (3)
Infections and infestations				
Bronchitis‡	17 (11)	1 (1)	1 (1)	0 (0)
Urinary tract infection‡	17 (11)	2 (1)	4 (5)	3 (4)
Upper respiratory tract infection	15 (10)	1 (1)	3 (4)	0 (0)
Viral upper respiratory tract infection	12 (8)	0 (0)	4 (5)	0 (0)
Influenza	10 (7)	0 (0)	0 (0)	0 (0)
Investigations				
Alanine aminotransferase increased	9 (6)	3 (2)	3 (4)	0 (0)
Metabolism and nutrition disorders				
Decreased appetite	10 (6)	0 (0)	3 (4)	0 (0)
Hyperglycemia	8 (5)	0 (0)	3 (4)	1 (1)

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System organ class/ preferred term	REBLOZYL N = 153		Placebo N = 76	
	All grades n (%)	Grades 3–4‡ n (%)	All grades n (%)	Grades 3–4 n (%)
Musculoskeletal and connective tissue disorders				
Back pain‡	29 (19)	3 (2)	5 (7)	0 (0)
Myalgia	13 (8)	1 (1)	5 (7)	2 (3)
Nervous system disorders				
Dizziness	30 (20)	0 (0)	4 (5)	0 (0)
Headache	24 (16)	1 (1)	5 (7)	0 (0)
Syncope/presyncope	10 (7)	7 (5)	1 (1)	1 (1)
Renal and urinary disorders				
Renal impairment‡‖	11 (7)	4 (3)	2 (3)	1 (1)
Respiratory, thoracic and mediastinal disorders				
Cough	27 (18)	0 (0)	10 (13)	0 (0)
Dyspnea‡	23 (15)	1 (1)	5 (7)	0 (0)
Vascular disorders				
Hypertension¶	13 (9)	5 (3)	7 (9)	3 (4)

Adapted from the REBLOZYL Product Monograph.

- Serious TEAEs occurred in 31.4% of patients treated with REBLOZYL and 30.3% of patients given placebo[1]
- Serious TEAEs reported in ≥1% of patients treated with REBLOZYL include[1]:
  - Pneumonia
  - Urinary tract infection
  - Transformation to AML
  - Back pain
  - Syncope
  - Sepsis
  - Basal cell carcinoma
  - Cardiac failure
  - Angina pectoris
  - Atrioventricular block
  - Femur fracture
  - Anemia
  - Acute kidney injury

* Grade 3 or 4 TEAEs included have ≥1% greater frequency versus placebo.
† TEAEs are included without regard to causality.
‡ At least 1 event was reported as serious.
§ Grouped terms include: fatigue and asthenia.
‖ Grouped terms include: renal failure, acute kidney injury, chronic kidney disease, renal impairment.
¶ Grouped terms include: essential hypertension, hypertension, hypertensive crisis.
AML: Acute myelogenous leukemia.
TEAE: Treatment emergent adverse event.

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REBLOZYL HAS A DEMONSTRATED **SAFETY PROFILE**

Treatment discontinuations and dose modifications due to adverse events[1]

8.5% REBLOZYL vs **7.9%** PLACEBO

Discontinuations due to an adverse event

The most common adverse events leading to discontinuation of REBLOZYL were transformation to AML (1.3%), fatigue (1.3%) and sepsis (1.3%)

15% REBLOZYL vs **5.3%** PLACEBO

Dose delay/interruption due to an adverse event

The most common adverse events leading to dose delay/interruption in the REBLOZYL arm were urinary tract infection (1.3%), aspartate aminotransferase increased (1.3%), neutropenia (1.3%) and muscle weakness (1.3%)

4.6% REBLOZYL vs **0%** PLACEBO

Dose reductions due to an adverse event

Adverse events leading to dose reduction were based on single patient experiences of: asthenia, fatigue, back pain, myalgia, neutropenia, vomiting, and aminotransferase increased.

Adapted from the REBLOZYL Product Monograph.

SELECTED LABORATORY ABNORMALITIES REPORTED IN THE **MEDALIST TRIAL**[1]

Lab shift	**REBLOZYL** N = 153 n (%)	**Placebo** N = 76 n (%)
ALT ≥3 x ULN	23 (15)	6 (8)
AST ≥3 x ULN	11 (7)	0 (0)
ALP ≥2 x ULN	2 (1)	1 (2)
Total bilirubin ≥2 x ULN	13 (8)	9 (12)
Direct bilirubin ≥ 2 x ULN	2 (1)	0 (0)
Creatine clearance <0.5 x baseline	4 (3)	1 (1)

Adapted from the REBLOZYL Product Monograph.

ALP: Alkaline phosphate.
ALT: Alanine aminotransferase.
AML: Acute myeloid leukemia.
AST: Aspartate aminotransferase.
ULN: Upper limit of normal.

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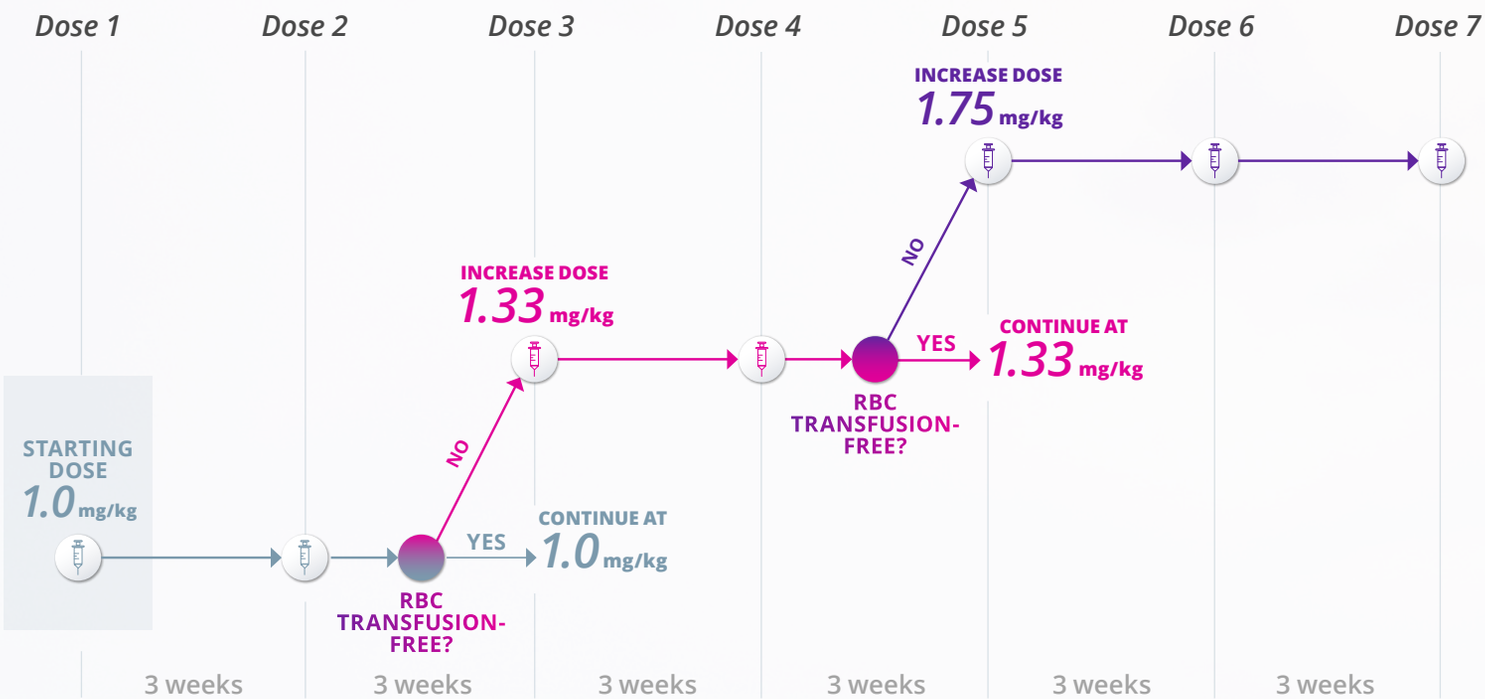
DOSE ADJUSTMENT RECOMMENDATIONS

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

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DOSE ADJUSTMENT RECOMMENDATIONS

Assess and review hemoglobin (Hgb) results prior to each administration[1]

- 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/1.73m^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]). Pharmacokinetic data are not available for patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2)
- No dose adjustment is required for patients with mild to severe hepatic impairment (elevated 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
- No dose adjustments are required for geriatric patients (≥65 years of age)

Adapted from the REBLOZYL Product Monograph.

ALT: Alanine aminotransferase.
AST: Aspartate aminotransferase.
eGFR: Estimated glomerular filtration rate.
RBC: Red blood cells.
ULN: Upper limit of normal.

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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.

Hgb: Hemoglobin.
MDS-RS: Myelodysplastic syndrome with ring sideroblasts

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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.

*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 WBC/μL.

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RECONSTITUTING REBLOZYL

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

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[1]:

- 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]

1 **Reconstitute with Sterile Water for Injection, USP** using volumes described in the Reconstitution Volumes table on page 16, 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 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.** Parental 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

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ADMINISTERING REBLOZYL

- Prior to injection, allow solution to reach room temperature for a more comfortable injection[1]

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 16

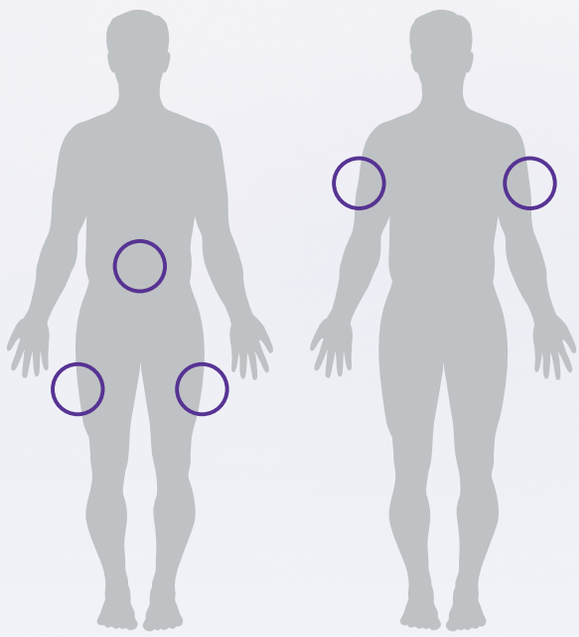
Step 2 Plan and prep for injection

- Slowly withdraw the dosing volume of the reconstituted REBLOZYL solution from the single-use 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[1]

- 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.[1]



Front Back

Adapted from the REBLOZYL Product Monograph.

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STORING REBLOZYL

REBLOZYL requires refrigerated storage[1]

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.

RELEVANT WARNINGS AND PRECAUTIONS:

- Hypertension: Monitor blood pressure prior to each administration.
- Thrombosis/Thromboembolic events (TEEs), including deep vein thrombosis, pulmonary emboli, and ischemic stroke.
- 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 at: https://www.bms.com/assets/bms/ca/documents/productmonograph/REBLOZYL_EN_PM.pdf for important information relating to 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.

DISCOVER REBLOZYL

REBLOZYL promoted erythroid maturation through differentiation of late-stage erythroid precursors (normoblasts) in mice*[1]

- REBLOZYL binds select endogenous TGF-β superfamily ligands, thereby inhibiting SMAD2/3 signalling

REBLOZYL safety profile was assessed in the phase 3 MEDALIST trial[1]

- The most common TEAEs in patients treated with REBLOZYL (≥10% and with ≥1% frequency vs placebo) were fatigue, diarrhea, asthenia, nausea, dizziness, back pain, cough, headache, dyspnea, urinary tract infection, bronchitis, constipation
- Serious TEAEs occurred in 31.4% of patients treated with REBLOZYL and 30.3% of patients on placebo

The recommended starting dose of REBLOZYL is 1 mg/kg once every 3 weeks by SC injection[1]

- Doses with REBLOZYL can be titrated upwards according to individual response to treatment
- Discontinue REBLOZYL 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

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*Clinical significance is unknown.

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