THE FIRST AND ONLY
ERYTHROID MATURATION AGENT

NOW APPROVED FOR ANEMIA

IN MDS

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

for patients with ring sideroblasts who are failing an ESA and require ≥2 RBC units/8 weeks[1]

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

Myelodysplastic syndromes (MDS) are a heterogeneous group of myeloid malignancies characterized by multilineage cytopenias, including anemia[2]

THE WORLD HEALTH ORGANIZATION (WHO) CLASSIFIES MDS AS NEOPLASTIC AND THEREFORE CANCER[3]

- MDS are characterized by:
  - Bone marrow dysfunction[3,4]
  - Dysplasia[3,4]
  - Genomic instability[3]
  - Peripheral blood cytopenias[3,4]
  - Ineffective hematopoiesis[4]

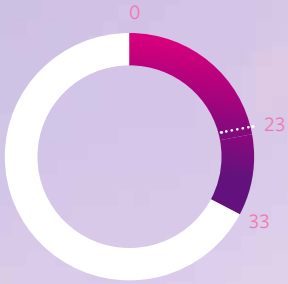
ANEMIA IS PRESENT IN THE MAJORITY OF PATIENTS WITH MDS[2]

- At diagnosis, anemia is the most common cytopenia present in patients with MDS*[2]
- 94% of patients with MDS received red blood cell (RBC) transfusions in the SEER-Sound registry of 783 patients from 2001 to 2007[5]
  - 13% of all patients with MDS requiring RBC transfusions had ring sideroblasts[5]

*Determined in a database analysis of 7012 patients with untreated MDS from 11 countries for the International Working Group for the Prognosis of MDS (IWG-PM) project.[2]

BASED ON THE NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®), MDS MANAGEMENT APPROACHES DIFFER ACCORDING TO MDS SUBTYPE AND SEVERITY OF DISEASE[6]

Patients with MDS may also have ring sideroblasts[7]



23%–33%

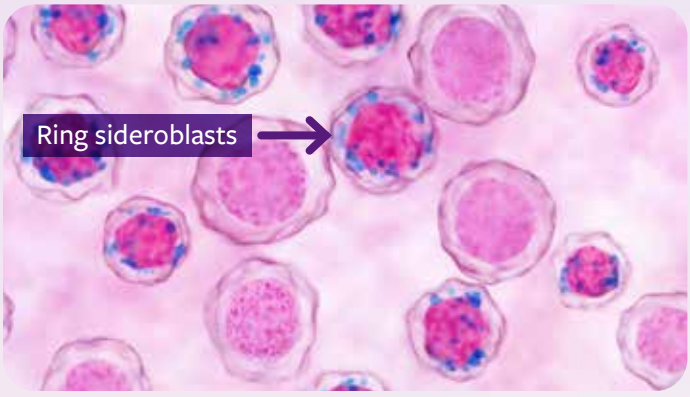
of patients with MDS have ring sideroblasts

RING SIDEROBLASTS ARE PART OF THE WHO 2016 CLASSIFICATION

- The WHO 2016 recognizes 2 MDS subtypes specific to ring sideroblasts[8]:
  - MDS-RS with single lineage dysplasia (MDS-RS-SLD)
  - MDS-RS with multilineage dysplasia (MDS-RS-MLD)
- MDS-RS subtype is identified with <5% bone marrow blasts and either[8]:
  - ≥15% ring sideroblasts in the bone marrow
  - ≥5% ring sideroblasts in the bone marrow and the presence of an *SF3B1* mutation (identified through molecular testing)
- MDS-RS is recognized as part of the ICD-10-CM coding system[9]
- Ring sideroblasts may also be present at any level in other subtypes of MDS[10]
- MDS/MPN-RS-T is a rare subtype recognized by the WHO 2016. It has similarities to MDS-RS but is characterized by specific clinical features[8,11]
  - These include anemia, bone marrow dysplasia with ring sideroblasts, and persistent thrombocytosis ≥450 × 10^9/L with proliferation of large and morphologically atypical megakaryocytes[8]

ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

RING SIDEROBLASTS ARE ERYTHROBLASTS WITH IRON-LOADED MITOCHONDRIA ASSOCIATED WITH ANEMIA[10]



For illustrative purposes only.

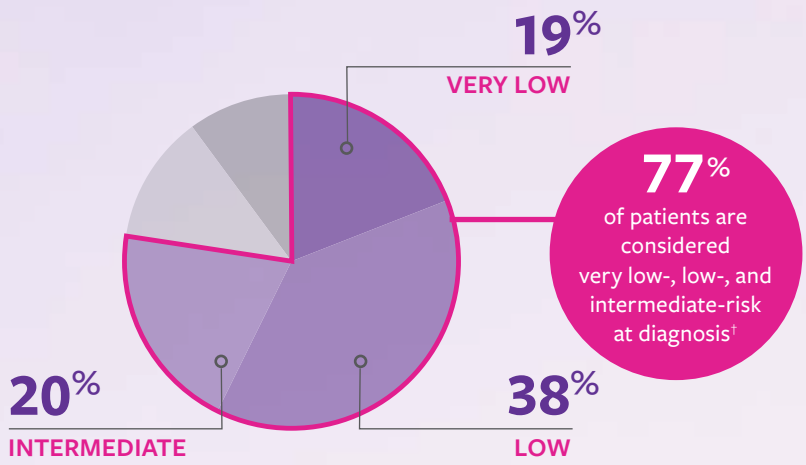
- Ring sideroblasts are identified by iron staining and the results can be found on pathology reports[10]
- There is variability in how pathologists describe the presence of ring sideroblasts in pathology reports[12]

Consult with your pathologist about how ring sideroblasts are reported in your patients with MDS

The IPSS-R categorization is the preferred* prognostic system of the NCCN Guidelines®[6]

THE MAJORITY OF PATIENTS WITH MDS HAVE IPSS-R VERY LOW- TO INTERMEDIATE-RISK DISEASE AT DIAGNOSIS[2]

Distribution of patients with MDS by IPSS-R risk status (N = 7012)†



*The NCCN Guidelines for MDS also note that other risk stratification systems have good value.[6]

†Distribution of the IPSS-R risk scores at time of diagnosis evaluated in the recently diagnosed patient cohort; (N = 7012) for the patient population included in the IPSS-R analysis.[2]

IPSS-R IS BASED ON BONE MARROW CYTOGENETICS, MARROW BLAST PERCENTAGE, AND PRESENCE AND DEPTH OF CYTOPENIAS[2]

Prognostic score values[2]							
Prognostic variable	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**
BM blasts, %	≤2	—	>2 to <5	—	5 to 10	>10	—
Cytogenetics	Very good	—	Good	—	Intermediate	Poor	Very poor
Hgb, g/dL	≥10	—	8 to <10	<8	—	—	—
Platelets, × 10^9 cells/L	≥100	50 to <100	<50	—	—	—	—
ANC, × 10^9 cells/L	≥0.8	<0.8	—	—	—	—	—

IPSS-R prognostic risk categories/scores[2]				
Very low	**Low**	**Intermediate**	**High**	**Very high**
≤1.5	>1.5–3	>3–4.5	>4.5–6	>6

AN IPSS-R SCORE IS CALCULATED BY ADDING THE VALUES FOR THE PROGNOSTIC FACTORS TOGETHER. AN EXAMPLE OF AN IPSS-R LOW-RISK SCORE:

- 2% blast count = 0
- Good cytogenetics = 1
- 8 g/dL Hgb = 1
- Platelets 75 x 10^9 cells/L = 0.5
- ANC 0.9 x 10^9 cells/L = 0

Total values added together = 2.5

ANC, absolute neutrophil count; BM, bone marrow; Hgb, hemoglobin; IPSS-R, Revised International Prognostic Scoring System.

Ineffective erythropoiesis is an underlying cause of anemia in MDS[13]

ANEMIA IN MDS IS LINKED TO BONE MARROW DYSFUNCTION CHARACTERIZED AS INEFFECTIVE ERYTHROPOIESIS[14]

- In MDS, stem cells lack the ability for differentiation and maturation, resulting in bone marrow dysfunction and poor blood cell production, in particular RBCs

INEFFECTIVE ERYTHROPOIESIS IN MDS MAY LEAD TO ANEMIA REQUIRING RBC TRANSFUSIONS, AND IS CHARACTERIZED BY[13,15]:

Increased proliferation of erythroid progenitors

Increased death of erythroid precursors

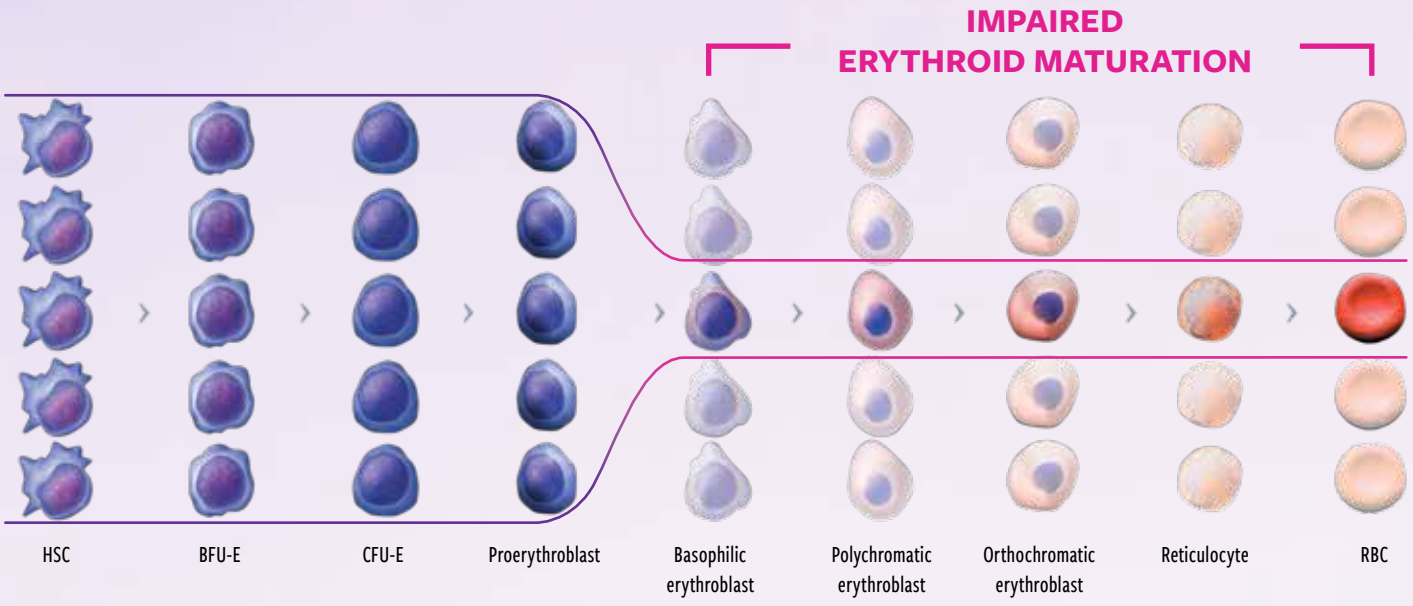
Impaired erythroid maturation

The presence of anemia despite increased proliferation of progenitor cells is indicative of ineffective erythropoiesis in MDS

There is a need to help address anemia due to ineffective erythropoiesis in patients with MDS requiring RBC transfusions

MECHANISM OF DISEASE

Impaired erythroid maturation contributes to ineffective erythropoiesis, resulting in low production of RBCs and anemia[16,17]



EARLY-STAGE ERYTHROPOIESIS[18]

Endogenous erythropoietin regulates proliferation

LATE-STAGE ERYTHROPOIESIS[1,19,20]

Select TGF-β superfamily ligands help regulate maturation

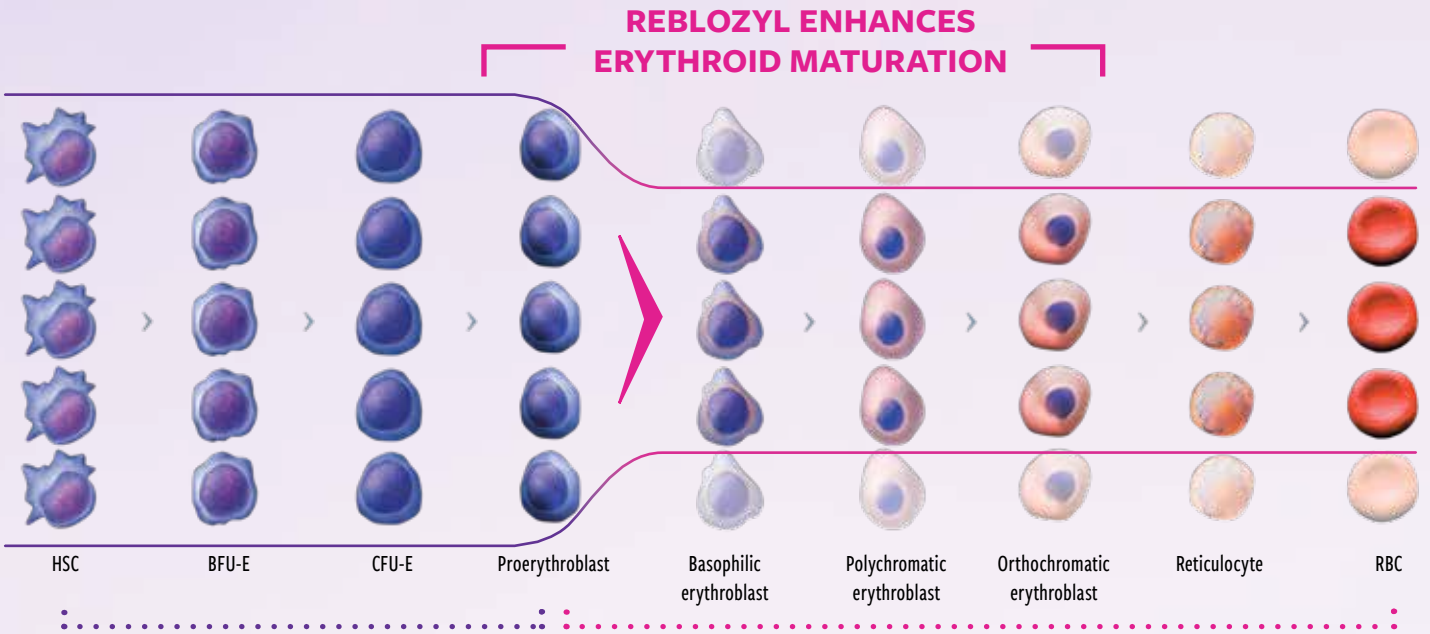
TGF-β superfamily signaling through Smad2/3 is abnormally high in diseases characterized by ineffective erythropoiesis, which leads to impaired erythroid maturation of RBCs

For illustrative purposes only.

BFU-E, burst-forming unit erythroid; CFU-E, colony-forming unit erythroid; HSC, hematopoietic stem cell; TGF-β, transforming growth factor beta.

MECHANISM OF ACTION

REBLOZYL restores erythropoiesis by increasing the number and improving the quality of mature RBCs[1,17]



For illustrative purposes only.

In preclinical models, REBLOZYL improved hemoglobin levels, RBC morphology, and other hematology parameters* associated with ineffective erythropoiesis[1,20,21]

*Other hematology parameters include reducing oxidative stress in erythrocytes, reducing accumulation of α-globin aggregates in erythrocyte membranes, and improving RBC life span.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

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 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.

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REBLOZYL was studied in the multicenter, randomized, double-blind, placebo-controlled, phase 3 MEDALIST trial[1,22]

Patient population (N = 229)[1,22]

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
- ESA exposure
  - — Inadequate response (response that is no longer maintained after at least 8 doses of recombinant human erythropoietin or 4 doses of darbepoetin alfa)
  - — Ineligible for ESAs (serum EPO >200 U/L)
  - — Intolerant of ESA treatment

Key exclusion criteria:

- del 5q MDS
- White blood cell count >13 Gi/L
- Neutrophils <0.5 Gi/L
- Platelets <50 Gi/L
- Prior use of a disease-modifying agent for treatment of MDS

Randomized 2:1[1]

REBLOZYL[1]

SC every 3 weeks (n = 153) for at least 24 weeks or until unacceptable toxicity, loss of efficacy, or disease progression*

- Starting dose: 1 mg/kg
- Patients could have dose increased to 1.33 mg/kg and then to 1.75 mg/kg

Placebo[1]

SC every 3 weeks (n = 76)

All patients received best supportive care (BSC), including RBC transfusions as needed[1]

*The primary efficacy assessment was conducted after completion of 24 weeks on study drug. Patients with a decrease in transfusion requirement or increase in Hgb could continue on blinded study drug thereafter until unacceptable toxicity, loss of efficacy, or disease progression.

del 5q, deletion 5q; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; SC, subcutaneous.

PRIMARY ENDPOINT[1]

- The efficacy of REBLOZYL was established based upon the proportion of adult patients who were red blood cell transfusion independent (RBC-TI), defined as the absence of any RBC transfusion during any consecutive 8-week period occurring entirely within weeks 1 through 24

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

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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Baseline characteristics in the phase 3 MEDALIST trial

BASELINE DISEASE CHARACTERISTICS OF PATIENTS IN MEDALIST[1,22]

Demographic and disease characteristics	REBLOZYL (n = 153)	Placebo (n = 76)
Age, years		
Median (min, max)	71.0 (26, 95)	72.0 (26, 91)
Time since original MDS diagnosis,[a] months		
Median (min, max)	44.0 (3, 421)	36.1 (4, 193)
Serum EPO (U/L) categories,[b] n (%)		
<200	88 (57.5)	50 (65.8)
200 to 500	43 (28.1)	15 (19.7)
>500	21 (13.7)	11 (14.5)
Missing	1 (0.7)	0
Diagnosis per WHO 2016 criteria,[c] n (%)		
MDS-RS[d]	135 (88.2)	65 (85.5)
MDS/MPN-RS-T	14 (9.2)	9 (11.8)
Other[e]	4 (2.6)	2 (2.6)

36% (83/229) of all patients in the trial were 75 years of age or older[1]*

While 39% of patients had serum EPO >200 U/L, 95.2% of all patients in the trial were ESA-exposed and only 4.8% were ESA-naive with serum EPO >200 U/L[1,22]*

All patients had ring sideroblasts[1]*

(continued on following page)

[a]Time since original MDS diagnosis was defined as the number of months from the date of original diagnosis to the date of informed consent.

[b]Baseline EPO was defined as the highest EPO value within 35 days of the first dose of study drug.

[c]MEDALIST enrolled patients with MDS with ring sideroblasts per the WHO 2008 criteria; however, these data are based on post hoc reclassification of patients by the FDA using the WHO 2016 diagnostic criteria (MDS-RS [n = 200; 87.3%], MDS/MPN-RS-T [n = 23; 10.0%], and Other [n = 6; 2.6%]).

[d]Includes MDS-RS-MLD and MDS-RS-SLD.

[e]Includes MDS-EB-1, MDS-EB-2, and MDS-U.

FDA, Food and Drug Administration; MDS-EB-1, myelodysplastic syndromes with excess blasts (5%–9% in the bone marrow or 2%–4% in the blood); MDS-EB-2, myelodysplastic syndromes with excess blasts (10%–19% in the bone marrow or 5%–19% in the blood); MDS-U, myelodysplastic syndromes, unclassifiable.

*Numbers in callouts are based on the entire clinical trial population.

IMPORTANT SAFETY INFORMATION (CONT'D)

ADVERSE REACTIONS

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.

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Baseline characteristics in the phase 3 MEDALIST trial (cont'd)

BASELINE DISEASE CHARACTERISTICS OF PATIENTS IN MEDALIST (CONT'D)[1,22]

Demographic and disease characteristics	REBLOZYL (n = 153)	Placebo (n = 76)
***SF3B1*, n (%)**		
Mutated	141 (92.2)	65 (85.5)
Nonmutated	12 (7.8)	10 (13.2)
Missing	0	1 (1.3)
IPSS-R classification risk category, n (%)		
Very low	18 (11.8)	6 (7.9)
Low	109 (71.2)	57 (75)
Intermediate	25 (16.3)	13 (17.1)
High	1 (0.7)	0
RBC transfusions/8 weeks over 16 weeks, n (%)		
<4 units	46 (30.1)	20 (26.3)
≥4 and <6 units	41 (26.8)	23 (30.3)
≥6 units	66 (43.1)	33 (43.4)

The majority of patients had an *SF3B1* mutation[22]*

All patients except 1 had very low- to intermediate-risk MDS[1]*

57% of patients had <6 RBC units/8 weeks[1]*

*Numbers in callouts are based on the entire clinical trial population.

PATIENT POPULATION CHARACTERISTICS[1]

- The median age was 71 years (range, 26–95)
- 63% of patients were male
- 69% of patients were white

IMPORTANT SAFETY INFORMATION (CONT'D)

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.

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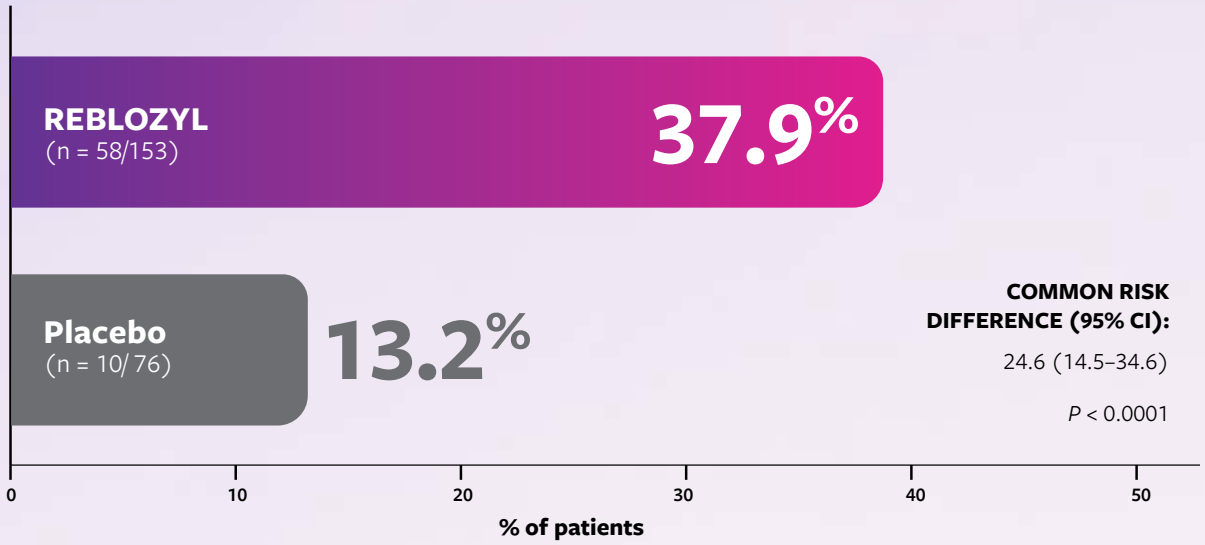
REBLOZYL significantly improved rates of RBC transfusion independence vs placebo[1]

PRIMARY ENDPOINT: RBC-TI ≥8 WEEKS DURING WEEKS 1 TO 24[1]



APPROXIMATELY

3X greater percentage of patients receiving REBLOZYL achieved RBC transfusion independence (primary endpoint) than placebo

In patients requiring ≥2 RBC units/8 weeks, start REBLOZYL after at least 2 to 3 months of an inadequate response to ESAs[1,22]

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.

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REBLOZYL provided RBC-TI vs placebo in patients with MDS-RS and MDS/MPN-RS-T[1]

KEY SECONDARY ENDPOINTS: RBC TRANSFUSION INDEPENDENCE ≥12 WEEKS[1]

Endpoint	REBLOZYL (n = 153) n, %	Placebo (n = 76) n, %	Common risk difference (95% CI)	*P* value
Weeks 1–24	43 (28.1%)	6 (7.9%)	20.0 (10.9, 29.1)	0.0002
Weeks 1–48[a]	51 (33.3%)	9 (11.8%)	21.4 (11.2, 31.5)	0.0003

[a]The median (range) duration of treatment was 49 weeks (6–114 weeks) on the REBLOZYL arm and 24 weeks (7– 89 weeks) on the placebo arm.

RBC-TI ≥8 WEEKS DURING WEEKS 1 TO 24 BY DIAGNOSIS AND BASELINE TRANSFUSION BURDEN IN MEDALIST[1]

	Responders/N		% Response (95% CI)	
	REBLOZYL	Placebo	REBLOZYL	Placebo
WHO 2016 diagnosis				
MDS-RS	46/135	8/65	34.1% (26.1, 42.7)	12.3% (5.5, 22.8)
MDS/MPN-RS-T	9/14	2/9	64.3% (35.1, 87.2)	22.2% (2.8, 60.0)
Other[a]	3/4	0/2	75.0% (19.4, 99.4)	0.0% (0.0, 84.2)
Baseline RBC transfusion burden				
2–3 units/8 weeks[b]	37/46	8/20	80.4% (66.1, 90.6)	40.0% (19.1, 63.9)
4–5 units/8 weeks[c]	15/41	1/23	36.6% (22.1, 53.1)	4.3% (0.1, 21.9)
≥6 units/8 weeks	6/66	1/33	9.1% (3.4, 18.7)	3.0% (0.1, 15.8)

[a]Includes MDS-EB-1, MDS-EB-2, and MDS-U.
[b]Includes patients who received 3.5 units.
[c]Includes patients who received 5.5 units.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

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 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.

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Adverse reactions with REBLOZYL

- The median time on treatment with REBLOZYL was 50.4 weeks (range, 3–221 weeks); 67% of patients were exposed for 6 months or longer and 49% were exposed for >1 year[1]
- Among the 242 patients treated with REBLOZYL, 5 (2.1%) had a fatal adverse reaction[1]
- The most common (≥2%) Grade ≥3 adverse reactions included fatigue, hypertension, syncope, and musculoskeletal pain[1]
- Selected laboratory abnormalities that changed from Grade 0–1 at baseline to Grade ≥2 at any time during the studies in at least 10% of patients included creatinine clearance decreased, total bilirubin increased, and alanine aminotransferase increased[1]
- Other clinically relevant adverse reactions reported in <5% of patients included bronchitis, urinary tract infection, and hypertension[1]

The majority of adverse reactions with REBLOZYL were Grade 1 or 2 (mild to moderate)[1]

ADVERSE REACTIONS (≥5%) IN PATIENTS RECEIVING REBLOZYL WITH A DIFFERENCE BETWEEN ARMS OF >2% IN MEDALIST TRIAL THROUGH CYCLE 8[1]

Body system/adverse reaction	REBLOZYL (n = 153)		Placebo (n = 76)	
	All Grades n (%)	Grade 3 n (%)	All Grades n (%)	Grade 3 n (%)
General disorders and administration site conditions				
Fatigue[a,b]	63 (41)	11 (7)	17 (22)	2 (3)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[b]	30 (20)	3 (2)	11 (14)	0 (0)
Nervous system disorders				
Dizziness/vertigo	28 (18)	1 (<1)	5 (7)	1 (1)
Headache[b]	21 (14)	0 (0)	5 (7)	0 (0)
Syncope/presyncope	8 (5)	5 (3)	0 (0)	0 (0)
Gastrointestinal disorders				
Nausea[b]	25 (16)	1 (<1)	8 (11)	0 (0)
Diarrhea[b]	25 (16)	0 (0)	7 (9)	0 (0)
Respiratory, thoracic, and mediastinal disorders				
Dyspnea[b]	20 (13)	2 (1)	4 (5)	1 (1)
Immune system disorders				
Hypersensitivity reactions[b]	15 (10)	1 (<1)	5 (7)	0 (0)
Renal and urinary disorders				
Renal impairment[b]	12 (8)	3 (2)	3 (4)	0 (0)
Cardiac disorders				
Tachycardia[b]	12 (8)	0 (0)	1 (1)	0 (0)
Injury poisoning and procedural complications				
Injection site reactions	10 (7)	0 (0)	3 (4)	0 (0)
Infections and infestations				
Upper respiratory tract infection	10 (7)	1 (<1)	2 (3)	0 (0)
Influenza/influenza-like illness	9 (6)	0 (0)	2 (3)	0 (0)

[a]Includes asthenic conditions.
[b]Reaction includes similar/grouped terms.

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Liver function abnormalities and immunogenicity

SELECTED GRADES 2 TO 4 TREATMENT-EMERGENT LABORATORY ABNORMALITIES THROUGH CYCLE 8 IN THE MEDALIST TRIAL[1]

Parameter	REBLOZYL		Placebo	
	N[a]	n (%)	N[a]	n (%)
ALT elevated	151	13 (9)	74	5 (7)
AST elevated	152	6 (4)	76	0 (0)
Total bilirubin elevated	140	17 (12)	66	3 (5)
Creatinine clearance reduced	113	30 (27)	62	13 (21)

[a]Number of patients at Grades 0 to 1 at baseline.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

IMMUNOGENICITY[1]

- Of 260 patients with MDS who were treated with REBLOZYL and evaluable for the presence of anti-luspatercept-aamt antibodies, 23 patients (8.9%) tested positive for treatment-emergent anti-luspatercept-aamt antibodies, including 9 patients (3.5%) who had neutralizing antibodies
- Luspatercept-aamt serum concentration tended to decrease in the presence of neutralizing antibodies
- There were no severe acute systemic hypersensitivity reactions reported for patients with anti-luspatercept-aamt antibodies in REBLOZYL clinical trials, and there was no association between hypersensitivity type reaction or injection site reaction and presence of anti-luspatercept-aamt antibodies

Discontinuations and dose modifications in the safety population

- 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]

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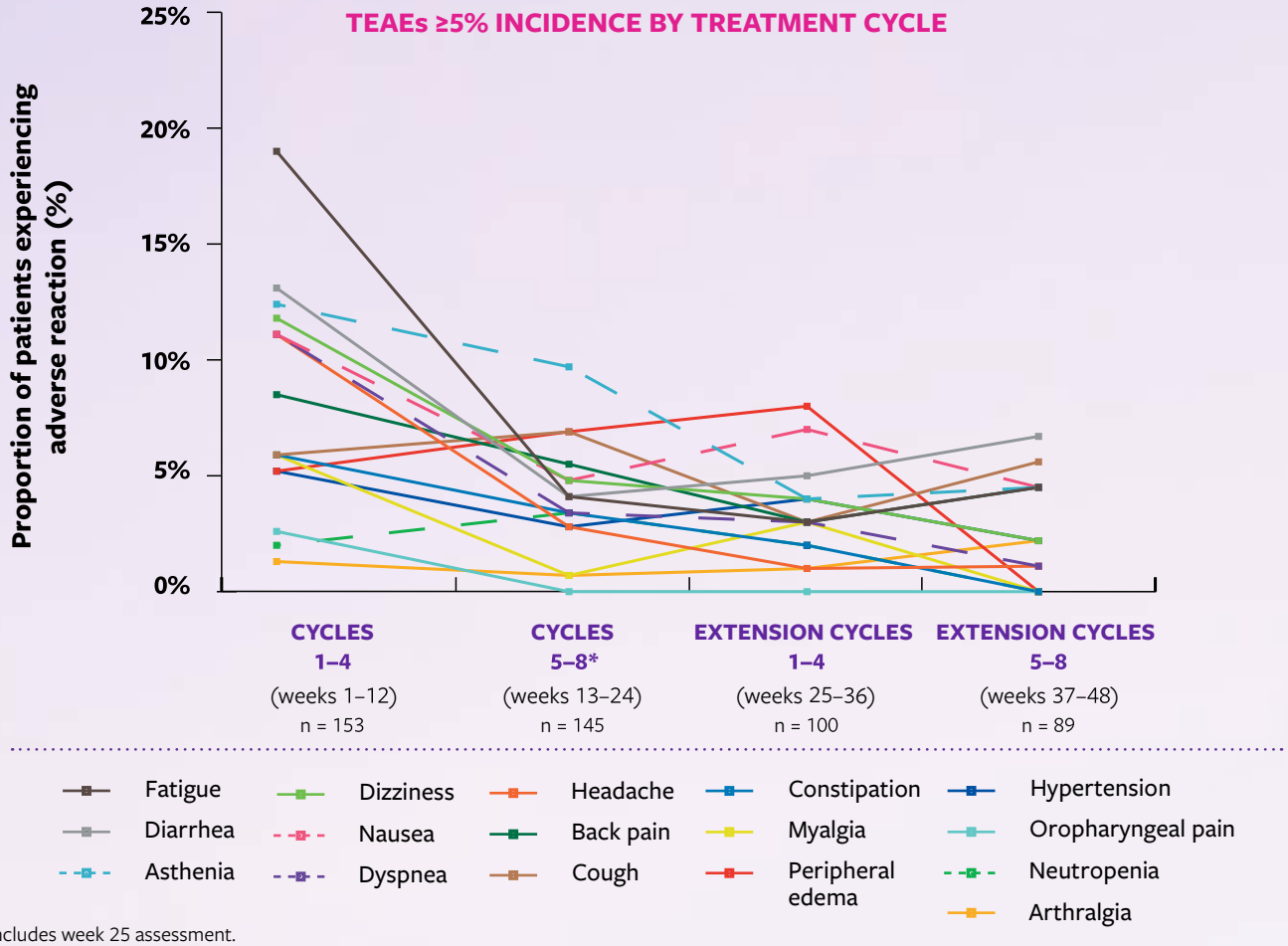
Additional analysis of treatment-emergent adverse events (TEAEs) by REBLOZYL treatment cycle[23]



*Includes week 25 assessment.

ANALYSIS LIMITATIONS

- All patients in both arms were eligible to receive BSC, including RBC transfusions as needed[1]
- Adverse events (AEs) with a duration overlapping multiple cycles were only counted in the first overlapped cycle. If an AE occurred multiple times in different cycles, it was counted once in each cycle. If an AE occurred multiple times within the same cycle, it was counted only once. If a patient experienced multiple events under the same MedDRA 20.0 preferred term, then the patient was counted only once for the preferred term[23]
- Patients who met the criteria and remained on double-blind treatment after completion of week 25 assessment may have continued dosing in the extension phase of the treatment period until the subject experienced unacceptable toxicities, disease progression, withdrew consent, or met any other discontinuation criteria[1,23]
- Fatigue TEAE does not include broader asthenic conditions adverse drug reactions (ADRs)

ADDITIONAL ANALYSIS INFORMATION

- Analysis is based on data through week 48[22]
- The chart displays TEAEs independent of attribution of treatment or disease. The percentage shown in this graph does not match the Adverse Reactions table on page 13
- TEAEs are undesirable events not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the treatment

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REBLOZYL dosing information

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

REBLOZYL DOSE TITRATION FOR RESPONSE[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.

At least 7 doses (21 weeks of treatment) unless unacceptable toxicity occurs at any time[1]

- Overall, 77.1% (118/153) of patients in the MEDALIST trial had their dose of REBLOZYL increased at least once[22]
  - 58.8% of patients (90/153) had their REBLOZYL dose increased to a maximum dose of 1.75 mg/kg

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

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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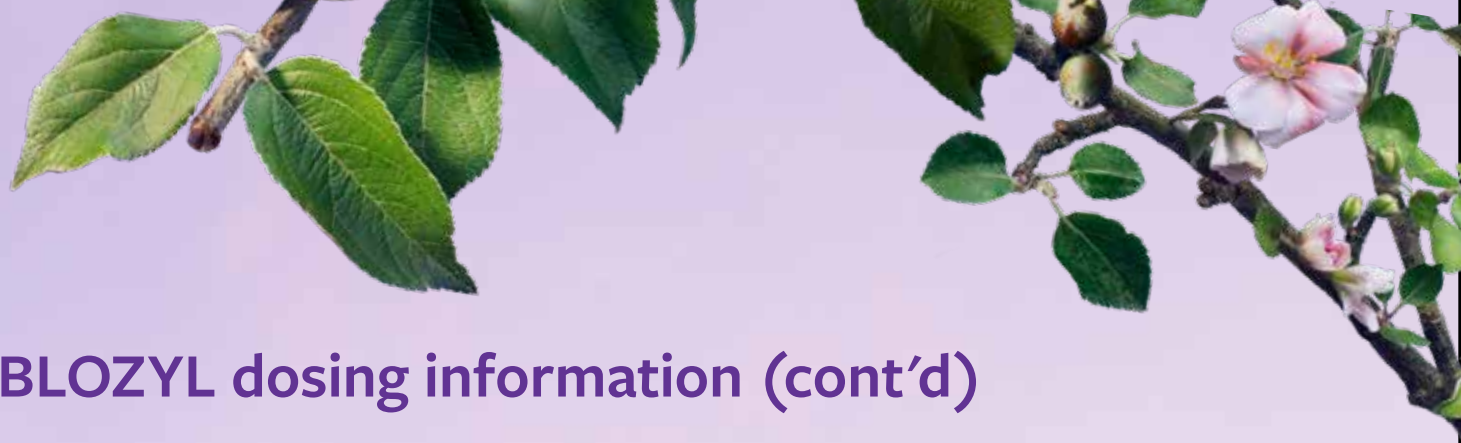

REBLOZYL dosing information (cont'd)

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 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

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.

IMPORTANT SAFETY INFORMATION (CONT'D)

ADVERSE REACTIONS

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.

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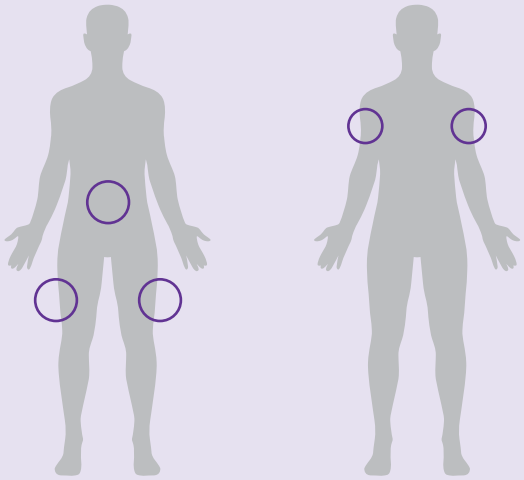
Instructions for subcutaneous administration

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

REBLOZYL SHOULD BE RECONSTITUTED AND ADMINISTERED BY A HEALTHCARE PROFESSIONAL[1]

Step 1: **Verify correct dose for the patient[1]**	• Calculate the exact total dosing volume of 50 mg/mL solution required for the patient
Step 2: **Plan and prep for injection[1]**	• 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[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  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.[1]

- Do not mix with other medications

IMPORTANT SAFETY INFORMATION (CONT'D)

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.

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Storing REBLOZYL

REBLOZYL REQUIRES COLD STORAGE

STORAGE OF UNRECONSTITUTED VIAL[1]

- 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[1]

- 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

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.

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Please click here for full Prescribing Information for REBLOZYL.

References: 1. REBLOZYL [Prescribing Information]. Summit, NJ: Celgene Corporation; 2020. **2.** Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood.* 2012;120(12):2454-2465. **3.** Steensma DP, Komrokji RS, Stone RM, et al. Disparity in perceptions of disease characteristics, treatment effectiveness, and factors influencing treatment adherence between physicians and patients with myelodysplastic syndromes. *Cancer.* 2014;120(11):1670-1676. **4.** Varney ME, Melgar K, Niederkorn M, Smith M, Barreyro L, Starczynowski DT. Deconstructing innate immune signaling in myelodysplastic syndromes. *Exp Hematol.* 2015;43(8):587-598. **5.** Ramsey SD, McCune JS, Blough DK, et al. Patterns of blood product use among patients with myelodysplastic syndrome. *Vox Sang.* 2012;102(4):331-337. **6.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myelodysplastic Syndromes V.2.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed February 28, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **7.** Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. *Blood.* 2013;122(22):3616-3627. **8.** Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood.* 2016;127(20):2391-2405. **9.** US Government Printing Office. The International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM): D-46.B refractory cytopenia with multilineage dysplasia and ring sideroblasts. https://www.icd10data.com/ICD10CM/Codes/C00-D49/D37-D48/D46-/D46. Accessed March 10, 2020. **10.** Malcovati L, Cazzola M. Recent advances in the understanding of myelodysplastic syndromes with ring sideroblasts. *Br J Haematol.* 2016;174(6):847-858. **11.** Aoyama Y, Sakai K, Kodaka T, et al. Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN with RS-T) complicated by hyperleukocytosis and gene analysis in relation to leukocytosis. *J Clin Exp Hematop.* 2019;59(1):29-33. **12.** Sever C, Abbott CL, de Baca ME. Bone marrow synoptic reporting for hematologic neoplasms: guideline from the College of American Pathologists Pathology and Laboratory Quality Center. *Arch Pathol Lab Med.* 2016;140(9):932-949. **13.** Santini V. Anemia as the main manifestation of myelodysplastic syndromes. *Semin Hematol.* 2015;52(4):348-356. **14.** Cazzola M, Malcovati L. Myelodysplastic syndromes—coping with ineffective hematopoiesis. *N Engl J Med.* 2005;352(6):536-538. **15.** Fontenay-Roupie M, Bouscary D, Guesnu M, et al. Ineffective erythropoiesis in myelodysplastic syndromes: correlation with Fas expression but not with lack of erythropoietin receptor signal transduction. *Br J Haematol.* 1999;106(2):464-473. **16.** Liang R, Ghaffari S. Advances in understanding the mechanisms of erythropoiesis in homeostasis and disease. *Br J Haematol.* 2016;174(5):661-673. **17.** Ponka P, Koury MJ, Sheftel AD. Erythropoiesis, hemoglobin synthesis, and erythroid mitochondrial iron homeostasis. In: Ferreira GC, ed. *Handbook of Porphyrin Science: with Applications to Chemistry, Physics, Materials Science, Engineering, Biology and Medicine.* Vol 27. Singapore: World Scientific Publishing Co.; 2014. **18.** Lodish H, Flygare J, Chou S. From stem cell to erythroblast: regulation of red cell production at multiple levels by multiple hormones. *IUBMB Life.* 2010;62(7):492-496. **19.** Fortunel NO, Hatzfeld A, Hatzfeld JA. Transforming growth factor-b: pleiotropic role in the regulation of hematopoiesis. *Blood.* 2000;96(6):2022-2036. **20.** Suragani RN, Cadena SM, Cawley SM, et al. Transforming growth factor-β superfamily ligand trap ACE-536 corrects anemia by promoting late-stage erythropoiesis. *Nat Med.* 2014;20(4):408-414. **21.** Suragani RM, Cawley SM, Li R. Modified activin receptor IIB ligand trap mitigates ineffective erythropoiesis and disease complications in murine β-thalassemia. *Blood.* 2014;123(25):3864-3872. **22.** Data on file. Celgene Corporation. Summit, New Jersey. **23.** Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Engl J Med.* 2020;382(2 suppl):140-151.

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Celgene Patient Support® provides

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A single source for access support

- A single Specialist assigned to help patients in your geographic area
- An Access Reimbursement Manager in each region with information on payer policies, billing, and coding for REBLOZYL
- Assistance with understanding patient insurance coverage for REBLOZYL
- Information about financial assistance for REBLOZYL

FINANCIAL ASSISTANCE

There are programs and organizations that may help pay for REBLOZYL, depending on a patient's insurance situation:

Celgene Commercial Co-pay Program

Co-pay responsibility for REBLOZYL is reduced to $0 (subject to annual benefit limits) for eligible patients with commercial or private insurance (including healthcare exchanges).*

Celgene Patient Assistance Program (PAP)

REBLOZYL may be available at no cost for qualified patients who are uninsured or underinsured.†

Independent Third-Party Organizations

Patients who are unable to afford their medication (including patients with Medicare, Medicaid, or other government-sponsored insurance) may be able to receive help from independent third-party organizations.‡

INSURANCE-RELATED ASSISTANCE

Our Specialists are available to assist with each of the following steps in the insurance approval process for REBLOZYL§:

- Benefits investigation
- Prior authorization/precertification assistance¶
- Appeals assistance¶
- Educating patients about insurance coverage or other programs for which they may qualify

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†Patients must meet specified financial and insurance eligibility requirements to qualify for assistance. Please see Eligibility Requirements on the Celgene Patient Support® website.

‡Financial and medical eligibility requirements vary by organization.

§Celgene cannot provide insurance advice or make insurance decisions.

¶Celgene provides a facilitation service and will not provide any medical input into a prior authorization or an appeal.

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NEW INDICATION

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THE NCCN GUIDELINES RECOMMEND

luspatercept-aamt (REBLOZYL) for anemia in very low- to intermediate-risk MDS with ring sideroblasts after 2 months of no response to ESAs (Category 2A)[6]

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.

SELECT WARNINGS AND PRECAUTIONS

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