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 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]

* Comparative clinical significance is unknown.

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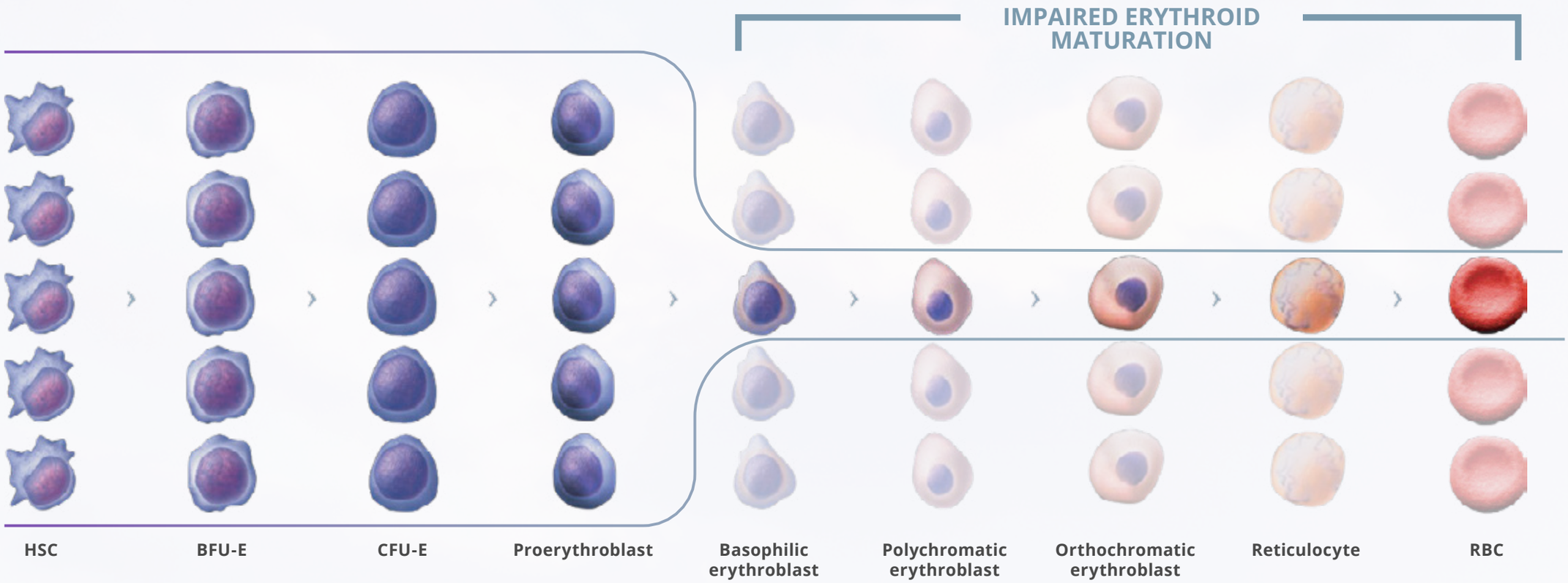
TO FIND OUT MORE

Bristol Myers Squibb™

Pr Reblozyl™
luspatercept for injection

Pr Reblozyl™ luspatercept for injection

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



EARLY-STAGE ERYTHROPOIESIS[3]

Endogenous erythropoietin (EPO) regulates proliferation

LATE-STAGE ERYTHROPOIESIS[4,5]

Select TGF-β superfamily ligands help regulate maturation

TGF-β superfamily signalling through SMAD2/3 is abnormally high in diseases characterized by ineffective erythropoiesis, which leads to impaired erythroid maturation of RBCs

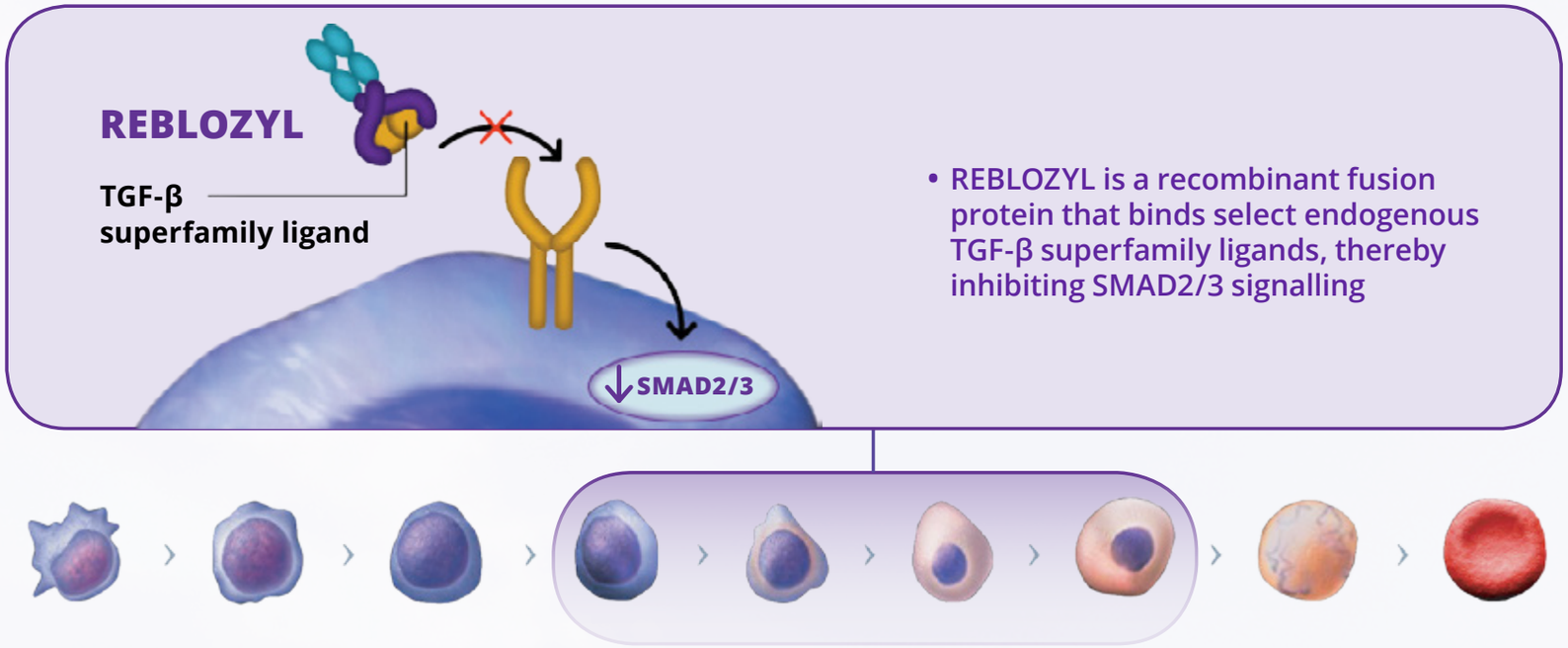
Adapted from Lodish, *et al* (2010), Fortunel, *et al* (2000) and Suragani, *et al* (2014).

BFU-E: Burst-forming unit erythroid. CFU-E: Colony-forming unit erythroid. HSC: Hematopoietic stem cell. RBC: Red blood cell. TGF-ß: Transforming growth factor beta.

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[1]*

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.

REBLOZYL (luspatercept for injection) is 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]

* Comparative clinical significance is unknown.
† Clinical significance is unknown.
TGF-β: Transforming growth factor beta.

CARL

Did not respond to ESA

DOROTHY

Lost response to ESA

ERIC

Unlikely to respond to ESA

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IDENTIFYING THE REBLOZYL MDS PATIENT[1,6,7]

1	**Has very low-, low-, to intermediate-risk MDS (based on IPSS-R)**	Represented in 77% of MDS patients
+		
2	**Experienced ESA failure or not suitable**	Nonresponse or response that is no longer maintained Unlikely to respond to ESA treatment with serum erythropoietin (EPO) (>200 U/L)
+		
3	**Receives red blood cell (RBC) transfusions**	≥2 RBC units per 8 weeks
+		
4	**Has ring sideroblasts (RS)**	WHO definition: >15% or 5%–14% with *SF3B1* mutation

Adapted from the REBLOZYL Product Monograph, Greenberg, *et al*. (2012) and Fenaux, *et al* (2020).

ESA: erythropoietin-stimulating agents; IPSS-R: International Prognostic Scoring System, revised; MDS: myelodysplastic syndromes; - U: Units; WHO: World Health Organization.

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CARL*

Has very low-, low-, to intermediate-risk MDS	ESA failure or not suitable for ESA	Receives red blood cell (RBC) transfusions	Has ring sideroblasts (RS)
IPSS-R Low-risk MDS (risk score: 3.0)	Serum EPO 300 U/L	3 RBC U/8 weeks	RS +28%

Carl is transfusion-dependent and failed EPO-based therapy

Would you consider a patient like Carl a candidate for REBLOZYL?

* Carl is a hypothetical patient and not from a clinical trial. Actual patient experiences may vary.
EPO: Erythropoietin; ESA: Erythropoiesis-stimulating agents; IPSS-R: International Prognostic Scoring System, revised; MDS: Myelodysplastic syndromes; RBC: Red blood cell; U: Units.

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CARL*

1 — 2 — 3 — 4

Diagnosis

- 70-year-old male with anemia diagnosed with MDS-RS

Treatment

- ESA treatment for 2 months
- RBC transfusions (3 U/8 weeks)

ESA-treatment status

- Carl failed EPO-based therapy

A NEW OPTION

- Carl begins treatment with REBLOZYL

* Carl is a hypothetical patient and not from a clinical trial. Actual patient experiences may vary.
EPO: Erythropoietin; ESA: Erythropoiesis-stimulating agents; MDS-RS: Myelodysplastic syndromes with ring sideroblasts; RBC: Red blood cell; U: Units.

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DOROTHY*

Has very low-, low-, to intermediate-risk MDS	ESA failure or not suitable for ESA	Receives red blood cell (RBC) transfusions	Has ring sideroblasts (RS)
IPSS-R Very low-risk MDS (risk score: 1.5)	Serum EPO 190 U/L	2 RBC U/8 weeks	RS +12% with *SF3B1* mutation

Dorothy's healthcare team has now determined that she has failed EPO-based therapy after being on ESA treatment for 17 months

Would you consider a patient like Dorothy a candidate for REBLOZYL?

* Dorothy is a hypothetical patient and not from a clinical trial. Actual patient experiences may vary.
EPO: Erythropoietin; ESA: Erythropoiesis-stimulating agents; IPSS-R: International Prognostic Scoring System, revised; MDS: Myelodysplastic syndromes; RBC: Red blood cell; U: Units.

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DOROTHY*

1 — 2 — 3 — 4

Diagnosis

- 67-year-old female presents with MDS-RS-associated symptomatic anemia

Treatment

- RBC transfusion dependence (2 U/8 weeks)
- ESA therapy started 17 months ago

ESA-treatment status

- Dorothy failed EPO-based therapy

A NEW OPTION

- Dorothy begins treatment with REBLOZYL

* Dorothy is a hypothetical patient and not from a clinical trial. Actual patient experiences may vary.
EPO: Erythropoietin; ESA: Erythropoiesis-stimulating agents; MDS-RS: Myelodysplastic syndromes with ring sideroblasts; RBC: Red blood cell.

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ERIC*

Has very low-, low-, to intermediate-risk MDS	ESA failure or not suitable for ESA	Receives red blood cell (RBC) transfusions	Has ring sideroblasts (RS)
IPSS-R Intermediate-risk MDS (risk score: 3.5)	Serum EPO 510 U/L	5 RBC U/8 weeks	RS +17%

Based on his high EPO level, ESAs may not be appropriate for Eric[8-10]

Would you consider a patient like Eric a candidate for REBLOZYL?

* Eric is a hypothetical patient and not from a clinical trial. Actual patient experiences may vary.
EPO: Erythropoietin; ESA: Erythropoiesis-stimulating agents; IPSS-R: International Prognostic Scoring System, revised; MDS: Myelodysplastic syndromes; RBC: Red blood cell; U: Units.

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ERIC*

1 — 2 — 3 — 4

Diagnosis

- 65-year-old male presents with MDS-RS-associated symptomatic anemia

Treatment

- RBC transfusions (5 U/8 weeks)

ESA-treatment status

- Eric is not suitable for EPO-based therapy

A NEW OPTION

- Eric begins treatment with REBLOZYL

* Eric is a hypothetical patient and not from a clinical trial. Actual patient experiences may vary.
EPO: Erythropoietin; ESA: Erythropoiesis-stimulating agents; MDS-RS: Myelodysplastic syndromes with ring sideroblasts; RBC: Red blood cell; U: Units.

DISCOVER MEDALIST

REBLOZYL was studied in the phase 3, randomized, double-blind, placebo-controlled MEDALIST trial[1,10]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes

P. Fenaux, U. Platzbecker, G.J. Mufti, G. Garcia-Manero, R. Buckstein, V. Santini, M. Díez-Campelo, C. Finelli, M. Cazzola, O. Ilhan, M.A. Sekeres, J.F. Falantes, B. Arrizabalaga, F. Salvi, V. Giai, P. Vyas, D. Bowen, D. Selleslag, A.E. DeZern, J.G. Jurcic, U. Germing, K.S. Götze, B. Quesnel, O. Beyne-Rauzy, T. Cluzeau, M.-T. Voso, D. Mazure, E. Vellenga, P.L. Greenberg, E. Hellström-Lindberg, A.M. Zeidan, L. Adès, A. Verma, M.R. Savona, A. Laadem, A. Benzohra, J. Zhang, A. Ramtpersad, D.R. Dunshee, P.G. Linde, M.L. Sherman, R.S. Komrokji, and A.F. List

ABSTRACT

BACKGROUND

Patients with anemia and lower-risk myelodysplastic syndromes in whom erythropoiesis-stimulating agent therapy is not effective generally become dependent on red-cell transfusions. Luspatercept, a recombinant fusion protein that binds transforming growth factor β superfamily ligands to reduce SMAD2 and SMAD3 signaling, showed promising results in a phase 2 study.

METHODS

In a double-blind, placebo-controlled, phase 3 trial, we randomly assigned patients with very-low-risk, low-risk, or intermediate-risk myelodysplastic syndromes (defined according to the Revised International Prognostic Scoring System) with ring sideroblasts who had been receiving regular red-cell transfusions to receive either luspatercept (at a dose of 1.0 up to 1.75 mg per kilogram of body weight) or placebo, administered subcutaneously every 3 weeks. The primary end point was transfusion independence for 8 weeks or longer during weeks 1 through 24, and the key secondary end point was transfusion independence for 12 weeks or longer, assessed during both weeks 1 through 24 and weeks 1 through 48.

RESULTS

Of the 229 patients enrolled, 153 were randomly assigned to receive luspatercept and 76 to receive placebo; the baseline characteristics of the patients were balanced. Transfusion independence for 8 weeks or longer was observed in 38% of the patients in the luspatercept group, as compared with 13% of those in the placebo group ($P<0.001$). A higher percentage of patients in the luspatercept group than in the placebo group met the key secondary end point (28% vs. 8% for weeks 1 through 24, and 33% vs. 12% for weeks 1 through 48; $P<0.001$ for both comparisons). The most common luspatercept-associated adverse events (of any grade) included fatigue, diarrhea, asthenia, nausea, and dizziness. The incidence of adverse events decreased over time.

CONCLUSIONS

Luspatercept reduced the severity of anemia in patients with lower-risk myelodysplastic syndromes with ring sideroblasts who had been receiving regular red-cell transfusions and who had disease that was refractory to or unlikely to respond to erythropoiesis-stimulating agents or who had discontinued such agents owing to an adverse event. (Funded by Celgene and Acceleron Pharma; MEDALIST ClinicalTrials.gov number, NCT02631070; EudraCT number, 2015-003454-41.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Fenaux at Hôpital Saint-Louis, 1 Ave. Claude Vellefaux, 75475 Paris, France, or at pierre.fenaux@aphp.fr; or to Dr. Platzbecker at Medical Clinic and Policlinic 1, Hematology and Cellular Therapy, Leipzig University Hospital, Johannisallee 32 A, 04103 Leipzig, Germany, or at uwe.platzbecker@medizin.uni-leipzig.de.

Drs. Fenaux and Platzbecker and Drs. Komrokji and List contributed equally to this article.

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N ENGL J MED 382;2 NEJM.ORG JANUARY 9, 2020

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MEDALIST STUDY DESIGN

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).

Primary endpoint[1]

- RBC transfusion independence (RBC-TI) ≥8 weeks from week 1 through week 24*

Key secondary endpoints[1]

- RBC-TI ≥12 weeks from week 1 through week 24†
- RBC-TI ≥12 weeks from week 1 through week 48‡

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 characteristics	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)
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)

Patient population characteristics[1]

- Patients were required to have received prior ESA treatment, or determined to be unlikely to respond to ESAs

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.

Adapted from the REBLOZYL Product Monograph.

* RBC-TI was defined as the absence of any RBC transfusion during any consecutive 56-day (8-week) period during the primary phase of the treatment period (first 24 weeks of double-blind treatment).
† RBC-TI was defined as the absence of any RBC transfusion during any consecutive 84-day (12-week) period during the primary phase of the treatment period (first 24 weeks of double-blind treatment).
‡ RBC-TI was defined as the absence of any RBC transfusion during any consecutive 84-day (12-week) period.
§ 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.

BSC: Best supportive care. ECOG: Eastern Cooperative Oncology Group.
ESA: Erythropoiesis-stimulating agent. IPSS-R: International Prognostic Scoring System-Revised.
RARS: Refractory anemia with ring sideroblasts. RCMD-RS: Refractory cytopenia with multilineage dysplasia. SD: Standard deviation.

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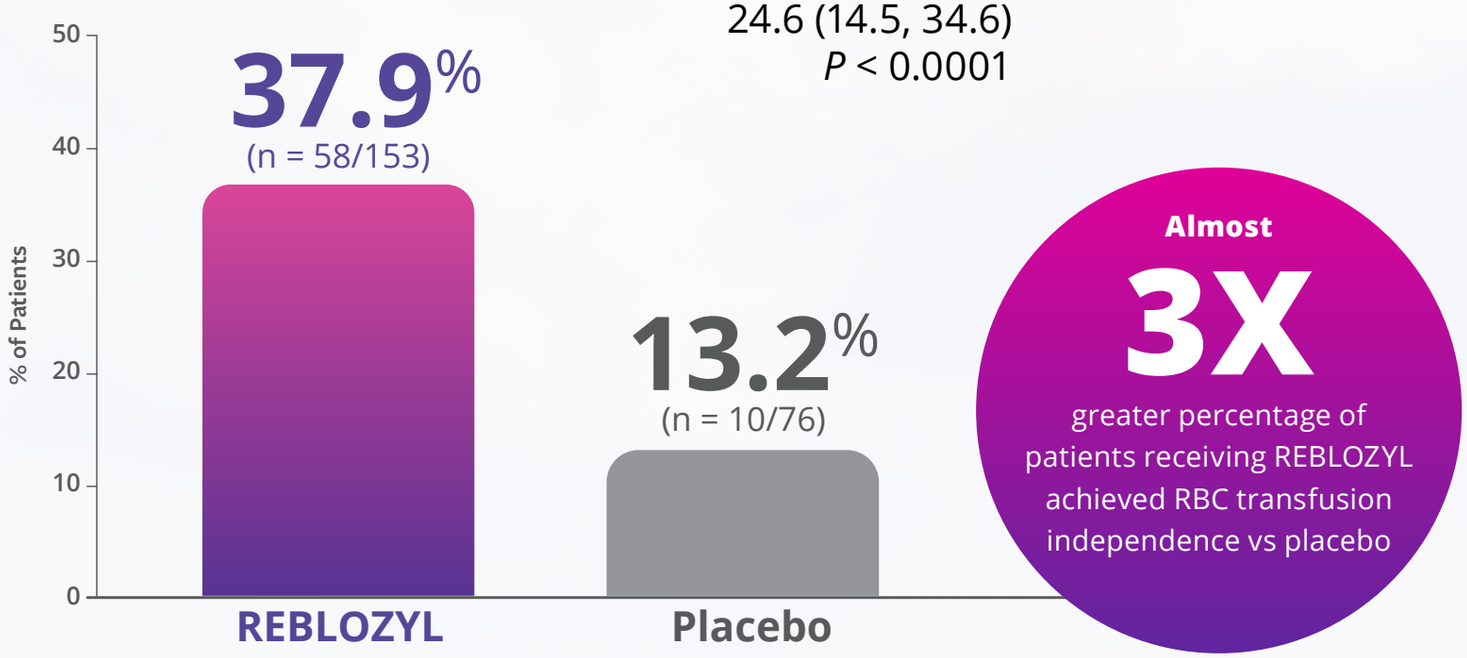
REBLOZYL PROVIDED A **SIGNIFICANT INCREASE IN THE PROPORTION OF PATIENTS WHO WERE RBC TRANSFUSION INDEPENDENT (RBC-TI)** COMPARED TO PLACEBO*[1]

- RBC transfusion independence (RBC-TI) is defined as the absence of any RBC transfusion during any consecutive 8-week period within the first 24 weeks of treatment

PRIMARY ENDPOINT:

RBC-TI ≥ 8 WEEKS FROM WEEK 1 THROUGH WEEK 24[1]



62% (36/58) of patients treated with REBLOZYL who achieved the primary endpoint had more than 1 episode of RBC-TI during the treatment period.[1]

Adapted from the REBLOZYL Product Monograph.

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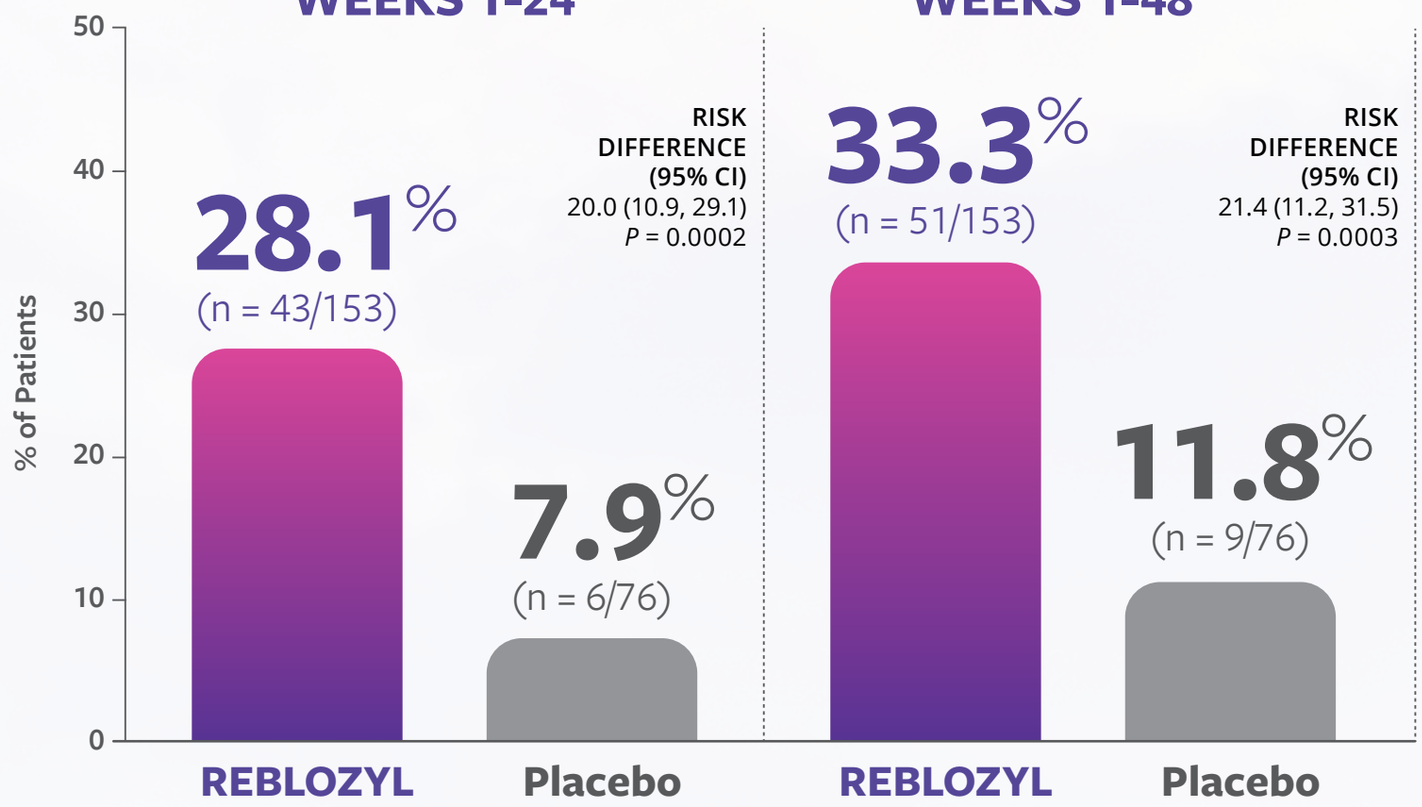
REBLOZYL HAD A SIGNIFICANTLY HIGHER RATE OF RBC TRANSFUSION INDEPENDENCE (RBC-TI) VS PLACEBO FOR ≥12 WEEKS[1,10]

- RBC-TI is defined as the absence of any RBC transfusion during any consecutive 12- or 16- week period as recorded during weeks 1-24 and weeks 1-48

SECONDARY ENDPOINTS:
RBC-TI ≥12 WEEKS



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

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REBLOZYL HAS A **PROVEN SAFETY PROFILE**[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 REBLOZYL-treated patients including Grades 3 or 4 TEAEs reported in ≥1% of 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)

* 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.
TEAE: Treatment-emergent adverse event.

SAFETY PROFILE *(cont.)*

All TEAEs observed in ≥5% of REBLOZYL-treated patients including Grades 3 or 4 TEAEs reported in ≥1% of REBLOZYL-treated patients*†[1] *(cont.)*

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:
  - 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 myeloid leukemia
TEAE: Treatment emergent adverse event.

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.

AML: Acute myeloid leukemia.

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

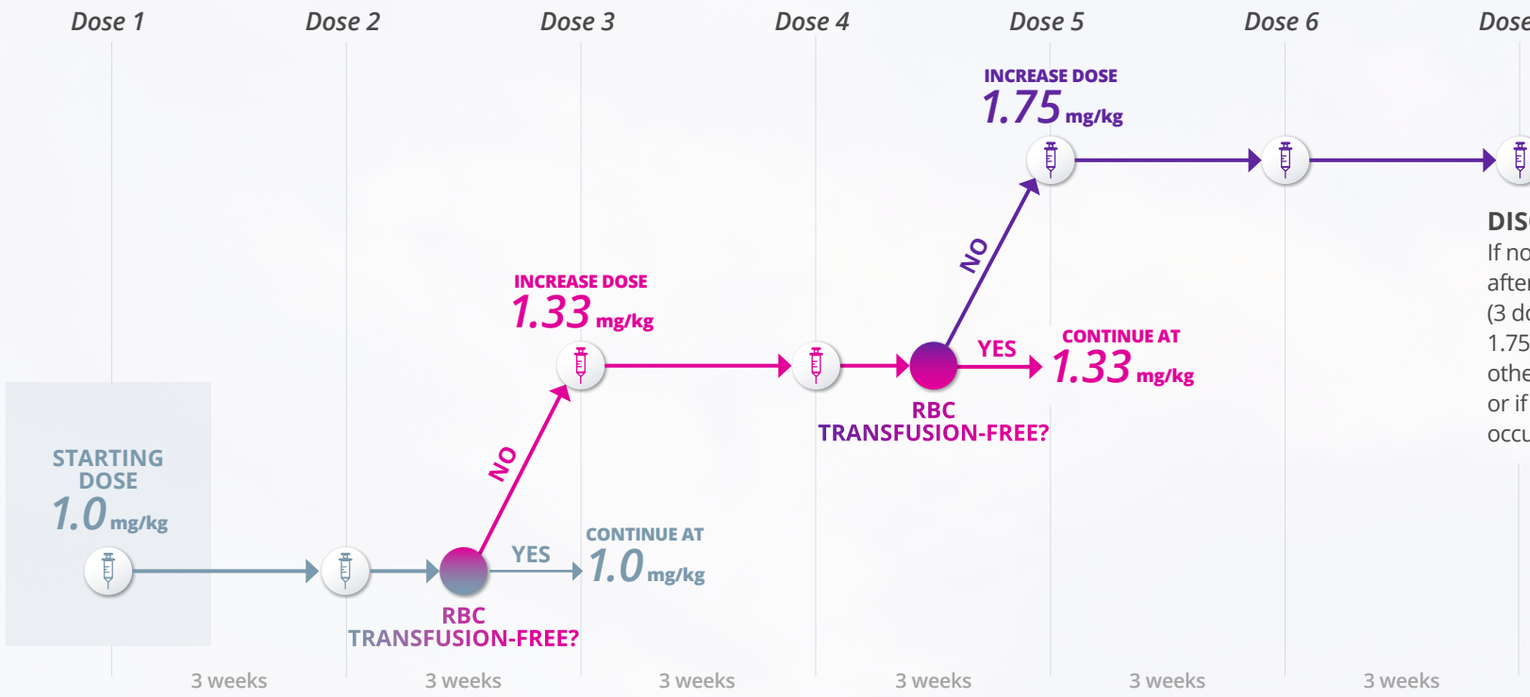
Lab shift	REBLOZYL N = 153 n (%)	Placebo N = 76 n (%)
ALT ≥3 x ULN	23 (15)	6 (8)
AST ≥3 x ULN	11 (7)	0 (0)
ALP ≥2 x ULN	2 (1)	1 (2)
Total bilirubin ≥2 x ULN	13 (8)	9 (12)
Direct bilirubin ≥2 x ULN	2 (1)	0 (0)
Creatinine clearance <0.5 x baseline	4 (3)	1 (1)

Adapted from the REBLOZYL Product Monograph.

ALP: Alkaline phosphate. ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. ULN: Upper limit of normal.

REBLOZYL DOSING RECOMMENDATIONS

Consider dose titration for insufficient response from treatment initiation[1]



- 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

Adapted from the REBLOZYL Product Monograph.

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 is ≥11.5 g/dL (115 g/L) and the Hgb level is not influenced by recent transfusion, delay dosing until the Hgb is ≤11.0 g/dL (110 g/L)

Dosing considerations[1]

- 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 x ULN). Pharmacokinetic data are not available for patients with AST or ALT ≥3 x ULN
- No dose adjustments are required for geriatric patients (≥65 years of age) by recent transfusion, delay dosing until the Hgb is ≤11.0 g/dL (110 g/L)

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

DOSE ADJUSTMENT RECOMMENDATIONS

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*	**Dose 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.
MDS-RS: myelodysplastic syndromes with ring sideroblasts.

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REBLOZYL SHOULD BE RECONSTITUTED AND **ADMINISTERED BY A HEALTHCARE PROFESSIONAL**

Available in 2 strengths as single-use vials for reconstitution[1]

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

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 22, 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 is observed.

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

- Store at room temperature at 20°C to 25°C in the original vial for up to 8 hours. Discard if not used within 8 hours of reconstitution.
- Alternatively, 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.

REBLOZYL **SC ADMINISTRATION**[1]

- 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 22

STEP **2** **Plan and prep for injection**

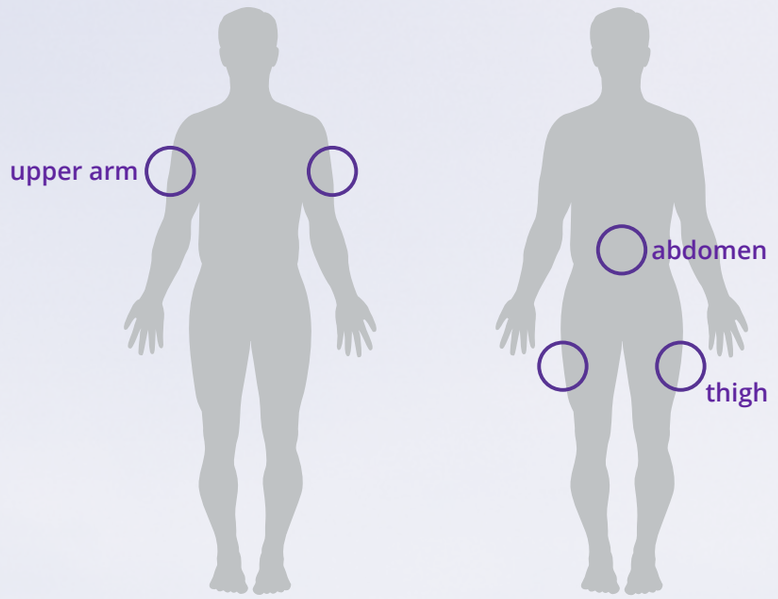
- Slowly withdraw the dosing volume of the reconstituted REBLOZYL solution from the single-use vial(s) into a syringe
- Divide doses requiring larger reconstituted volumes (i.e., >1.2 mL) into separate similar volume injections and inject into separate sites

STEP **3** **Perform subcutaneous administration**

- 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.

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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 the 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

Pr Reblozyl™
luspatercept for injection

REBLOZYL provided significant increase in the proportion of patients who were RBC-TI vs placebo[1]

- 37.9% of patients treated with REBLOZYL achieved RBC-TI for ≥8 weeks from week 1 to week 24 compared to 13.2% of patients with placebo (p<0.0001) (primary endpoint)

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

REBLOZYL has a proven safety profile[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
- Treatment discontinuation due to an adverse event occurred in 8.5% of REBLOZYL-treated and 7.9% of placebo-treated patients
  - The most common adverse events leading to discontinuation were transformation to AML, fatigue, and sepsis (1.3% each)

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 PROMOTED ERYTHROID MATURATION through differentiation of late-stage erythroid precursors (normoblasts) in mice*[1]

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REBLOZYL.ca
TO FIND OUT MORE

REBLOZYL (luspatercept for injection) is 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]

AML: Acute myeloid leukemia.
* Clinical significance is unknown.
† RBC-TI was defined as the absence of any RBC transfusion during any consecutive 56-day (8-week) period during the primary phase of the treatment period (first 24 weeks of double-blind treatment).

REFERENCES

Reblozyl™ luspatercept for injection

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

CLOSE ×

REFERENCES:

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