PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**REBLOZYL®**

luspatercept for injection

25 mg / vial, 75 mg / vial

lyophilized powder for solution for subcutaneous injection

Erythroid Maturation Agent

Bristol-Myers Squibb Canada
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Suite 300
Montreal, Canada
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Date of Initial Authorization:
September 25, 2020

Date of Revision:
March 26, 2024

Submission Control Number: 283802

RECENT MAJOR LABEL CHANGES

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Reblozyl® (luspatercept for injection) is indicated for:

- the treatment of adult patients with red blood cell (RBC) transfusion-dependent anemia associated with beta(β)-thalassemia
- the treatment of adult patients with transfusion-dependent anemia requiring at least two 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.

Limitation of Use:

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.

No clinically meaningful change in liver iron concentration was observed in β-thalassemia patients treated with Reblozyl® plus best supportive care (BSC) compared to patients treated with placebo plus BSC at 48 weeks.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age):
Clinical studies of Reblozyl® in β-thalassemia did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

2 CONTRAINDICATIONS

Reblozyl® is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- There are limited clinical data in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30mL/min/1.73m^2) and therefore no dosing recommendations are available.
- Consider the risk of use of Reblozyl® in β-thalassemia patients who were excluded from clinical trials i.e., patients with uncontrolled hypertension, a deep vein thrombosis or stroke in the previous 24 weeks, or use of an erythropoiesis-stimulating agent (ESA) within the previous 24 weeks (see **14 CLINICAL TRIALS**).

- No dose adjustments are required for geriatric patients (≥ 65 years of age), patients with mild to moderate renal impairment, or patients with mild to severe hepatic impairment, see **10.3 Pharmacokinetics**.
- Discontinue Reblozyl® in case of extramedullary hematopoietic (EMH) masses causing serious complications (see **7 WARNINGS AND PRECAUTIONS**).

4.2 Recommended Dose and Dosage Adjustment

The recommended starting dose of Reblozyl® is 1.0 mg/kg once every 3 weeks by subcutaneous (SC) injection.

Assess and review hemoglobin (Hgb) results prior to each administration. If an RBC transfusion occurred prior to dosing, the pre-transfusion Hgb must be considered for dosing purposes.

If the pre-dose Hgb is greater than or equal to 115 g/L and the Hgb level is not influenced by recent transfusion, delay dosing until Hgb is less than or equal to 110 g/L.

Recommended Dosage Adjustment in B-thalassemia:

If a patient does not achieve a response, defined as a reduction in RBC transfusion burden of at least a third from baseline (≥ 33%), after at least 2 consecutive doses (6 weeks) at the 1.0 mg/kg starting dose, increase the Reblozyl® dose to 1.25 mg/kg. Do not increase the dose beyond the maximum dose of 1.25 mg/kg.

If there is an increase in Hgb > 20 g/L within 3 weeks of the previous dose, and in the absence of transfusion, then dose reduce as per Table 1.

Discontinue Reblozyl® if a patient does not achieve a response (as defined above) after 9 weeks of treatment (administration of 3 doses) at the maximum dose level if no other causes are found, or if unacceptable toxicity occurs at any time.

Dosing recommendations and modifications in patients with β-thalasssemia are provided in Table 1.

Table 1: β-thalassemia - Reblozyl® Dose Titration, Dose Modifications, and Treatment Discontinuation Recommendations

Parameter	Reblozyl® Dosing Recommendation
Insufficient Response	
No reduction in RBC transfusion burden after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose	• Increase dose to 1.25 mg/kg every 3 weeks
No reduction in RBC transfusion burden after 3 consecutive doses (9 weeks) at 1.25 mg/kg	• Discontinue Reblozyl®
Pre-dose Hemoglobin ≥ 115 g/L or Rapid Hemoglobin Rise	
Pre-dose Hgb is ≥ 115 g/L in the absence of transfusions	• Delay dose and restart only when Hgb is ≤ 110g/L

Increase in hemoglobin > 20 g/L within 3 weeks in the absence of transfusion and • current dose is 1.25 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 mg/kg • Reduce to 0.8 mg/kg • Reduce dose to 0.6 mg/kg • Discontinue Reblozyl®
Adverse Events*	
Any Grade 2 adverse reaction	• Delay dose until resolved to ≤ Grade 1
Grade 3 or 4 hypersensitivity reactions	• Discontinue Reblozyl®
Grade 3 or 4 leukocytosis (>100,000 WBC/µL) or hematologic malignancy is suspected	• Delay dose until resolved to ≤ Grade 1 • Discontinue if hematologic malignancy is confirmed
Other Grade 3 or 4 adverse reactions	• Delay dose until resolved to ≤ Grade 1

*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.

Recommended Dosage Adjustment in Very Low- to Intermediate Risk MDS with Ring Sideroblasts:

If a patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1.0 mg/kg starting dose, increase the Reblozyl® dose to 1.33 mg/kg.

If the patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1.33 mg/kg dose, increase the Reblozyl® dose to 1.75 mg/kg.

Do not increase the dose more frequently than every 6 weeks (2 doses) or beyond the maximum dose of 1.75 mg/kg.

If there is an increase in Hgb > 20 g/L within 3 weeks of the previous dose, and in the absence of transfusion, then dose reduce as per Table 2.

Discontinue Reblozyl® if a patient does not achieve a response after 9 weeks of treatment (administration of 3 doses) at the maximum dose level if no other causes are found, or if unacceptable toxicity occurs at any time.

Dosing recommendations and modifications in patients with MDS are provided in Table 2.

Table 2: MDS - Reblozyl® Dose Titration, Dose Modifications, and Treatment Discontinuation Recommendations

Parameter	Reblozyl® Dosing Recommendation
Insufficient Response	
Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose	• Increase dose to 1.33 mg/kg every 3 weeks
Not RBC transfusion-free after at least 2	• Increase dose to 1.75 mg/kg every 3 weeks

consecutive doses (6 weeks) at 1.33 mg/kg	
No reduction in RBC transfusion burden after at least 3 consecutive doses (9 weeks) at 1.75 mg/kg	• Discontinue Reblozyl®
Pre-dose Hemoglobin ≥ 115 g/L or Rapid Hemoglobin Rise	
Pre-dose Hgb is ≥ 115 g/L in the absence of transfusions	• Delay dose and restart only when Hgb is ≤ 110g/L
Increase in hemoglobin > 20 g/L within 3 weeks in the absence of transfusion and • current dose is 1.75 mg/kg • current dose is 1.33 mg/kg • current dose is 1.0 mg/kg • current dose is 0.8 mg/kg • current dose is 0.6 mg/kg	 • Reduce dose to 1.33 mg/kg • Reduce to 1.0 mg/kg • Reduce dose to 0.8 mg/kg • Reduce dose to 0.6 mg/kg • Discontinue Reblozyl®
Adverse Events*	
Any Grade 2 adverse reaction	• Delay dose until resolved to ≤ Grade 1
Grade 3 or 4 hypersensitivity reactions	• Discontinue Reblozyl®
Grade 3 or 4 leukocytosis (>100,000 WBC/µL) or hematologic malignancy is suspected	• Delay dose until resolved to ≤ Grade 1 • Discontinue if hematologic malignancy is confirmed
Other Grade 3 or 4 adverse reactions	• Delay dose until resolved to ≤ Grade 1

*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.

4.3 Reconstitution

Reblozyl® should be reconstituted and administered by a healthcare professional.

Reconstitute Reblozyl® with Sterile Water for Injection, USP only.

Table 3 - Reconstitution Volumes

Vial Size	Amount of Sterile Water for Injection, USP required for reconstitution	Approximate Available 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	75mg/1.5 mL (50 mg/mL)

Reconstitute the number of Reblozyl® vials to achieve the appropriate dose based on the patient's weight. Use a syringe with suitable graduations for reconstitution to ensure accurate dosage.

Once reconstituted the solution has a pH of 6.5.

Reconstitution Instructions:

1. Reconstitute with Sterile Water for Injection, USP using volumes described in Table 3 with the stream directed into the lyophilized powder. Allow to stand for one 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. 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 the vial for undissolved particles in the solution. If undissolved powder is observed, repeat step 3 until the powder is completely dissolved.
5. 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 step 5 seven more time to ensure complete reconstitution of material on the sides of the vial.
7. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit. Reblozyl® is a colourless to slightly yellow, clear to slightly opalescent solution which is free of foreign particulate matter. Do not use if undissolved product or foreign particulate matter are observed.
8. 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.

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.

4.4 Administration

Reblozyl® should be reconstituted and administered by a healthcare professional.

Calculate the exact total dosing volume of 50 mg/mL solution required for the patient as per Table 3.

Slowly withdraw the dosing volume of the reconstituted Reblozyl® solution from the single-dose vial(s) into a syringe. Divide doses requiring larger reconstituted volumes (i.e., greater than 1.2 mL) into separate similar volume injections and inject into separate sites. If multiple injections are required, use a new syringe and needle for each subcutaneous injection.

Administer the injection subcutaneously into the upper arm, thigh, and/or abdomen.

4.5 Missed Dose

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.

5 OVERDOSAGE

Overdosage may cause hemoglobin levels to increase above the desired level. In the event of an overdose, assess Hgb level 7 days after the overdose and once a week thereafter. Treatment should be delayed until Hgb ≤ 110 g/L.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, health professionals should recognize the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Reblozyl® is available in 2 vial strengths, 1 vial / carton (see Table 4).

Table 4 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
subcutaneous injection	25 mg luspatercept off-white lyophilized powder for reconstitution / single-use vial	citric acid monohydrate, hydrochloric acid, polysorbate 80, sodium hydroxide, sucrose, tri-sodium citrate dihydrate
subcutaneous injection	75 mg luspatercept off-white lyophilized powder for reconstitution / single-use vial	citric acid monohydrate, hydrochloric acid, polysorbate 80, sodium hydroxide, sucrose, tri-sodium citrate dihydrate

7 WARNINGS AND PRECAUTIONS

General

Extramedullary hematopoietic (EMH) masses

In adult patients with transfusion-dependent β-thalassemia from the BELIEVE and longer-term follow-up study, extramedullary hematopoietic (EMH) masses were observed in 10/315 (3.2%) Reblozyl®-treated patients and in no placebo-treated patient. Spinal compression symptoms due to EMH masses occurred in 6/315 (1.9%) Reblozyl®-treated patients. β-thalassemia patients with EMH masses had known risk factors such as medical history of EMH masses at baseline or comorbidity of splenectomy, splenomegaly, hepatomegaly or low baseline hemoglobin (<8.5 g/dL). Signs and symptoms may vary

depending on the anatomical location. Monitor β-thalassemia patients at initiation and during treatment for symptoms and signs or complications resulting from the EMH masses and treat according to clinical guidelines. Discontinue treatment with Reblozyl® in case of serious complications due to EMH masses (see **4.1 Dosing Considerations**). Reblozyl® is not recommended for patients requiring treatment to control the growth of EMH masses.

Cardiovascular

Hypertension

In controlled clinical trials, adult patients treated with Reblozyl® had an average increase in systolic and diastolic blood pressure of 5 mm Hg from baseline, which was not observed in patients who received placebo. In the Phase III, BELIEVE (ACE-536-B-THAL-001) β-thalassemia trial, hypertension was reported as an adverse event in more patients treated with Reblozyl® compared to placebo (see **8 ADVERSE REACTIONS**). Monitor blood pressure prior to each administration. Treat new-onset hypertension or exacerbations of pre-existing hypertension as per current guidelines.

Thrombosis / Thromboembolism

In the BELIEVE β-thalassemia trial, thromboembolic events (TEE) were reported as an adverse event in more patients treated with Reblozyl® compared to placebo (see **8 ADVERSE REACTIONS**). Reported TEEs included deep vein thrombosis, pulmonary emboli, and ischemic stroke. The potential benefit of treatment with Reblozyl® should be weighed against the potential risk of thromboembolic events in β-thalassemia patients with a splenectomy and other risk factors for developing TEE. Consider thromboprophylaxis in patients with β-thalassemia at higher risk at increased risk of TEE. Monitor patients receiving Reblozyl® for signs and symptoms of TEE and institute treatment promptly as per standard clinical practice.

Monitoring and Laboratory Tests

Assess and review Hgb results prior to each administration of Reblozyl®. If an RBC transfusion occurred prior to dosing, the pretransfusion Hgb must be considered for dosing purposes, see **4.2 Recommended Dose and Dosage Adjustment**.

Monitor blood pressure prior to each administration, see **7 WARNINGS AND PRECAUTIONS, Cardiovascular**.

Reproductive Health: Female and Male Potential

- **Fertility**

  There are no data on the effects of Reblozyl® on human fertility.

  In a fertility and early embryonic development study in rats, there were significant reductions in the average numbers of corpora lutea, implantations, and viable embryos in female rats receiving luspatercept. There was no effect on mating, fertility, or litter parameters when male rats treated with luspatercept were mated with untreated female rats. Effects on fertility in female rats were reversible after a 14-week recovery period. Based on findings in animals, female fertility may be compromised with Reblozyl® (see **16 NON-CLINICAL TOXICOLOGY**).

7.1 Special Populations

7.1.1 Pregnant Women

Embryo-fetal toxicity

There are no available human data to inform the drug-associated risk; however, based on findings in animals, Reblozyl® may cause fetal harm when administered to a pregnant woman. Luspatercept was a selective development toxicant in the rat, and a maternal and fetal development toxicant in the rabbit. In both species, effects included increased resorptions and post-implementation loss, decreased litter size, and an increased incidence of skeletal alterations. See **16 NON-CLINICAL TOXICOLOGY**.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Reblozyl®.

Pregnancy testing is recommended for females of childbearing potential prior to initiating treatment with Reblozyl®.

Advise females of childbearing potential to use effective contraception during treatment with Reblozyl® and for at least 3 months after the last dose. If Reblozyl® is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be informed of the potential for hazard to the fetus.

7.1.2 Breast-feeding

Luspatercept was detected in the milk of lactating rats following a single subcutaneous dose of luspatercept (30 mg/kg); mean lacteal transfer was 12% (see **16 NON-CLINCIAL TOXICOLOGY)**. The safe use of Reblozyl® during breast-feeding has not been established.

It is unknown if the drug is excreted in human milk or absorbed systemically after ingestion by a nursing infant. As many drugs are excreted in human milk, and because of the unknown effects of luspatercept in infants, taking into account the importance of the drug to the mother, a decision should be made whether to discontinue breast-feeding during treatment with Reblozyl® and for 3 months after the final dose or to discontinue Reblozyl®.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (> 65 years of age):

Clinical studies of Reblozyl® in β-thalassemia did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

Clinical studies of Reblozyl® in MDS included patients with ages ranging from 18 to 95 years old, with a median age of 72 years. No differences in safety or effectiveness were observed between older (≥65 years) and younger patients when compared to placebo.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

β-thalassemia:

In the double-blind, randomized, placebo-controlled, multicentre, Phase III, BELIEVE trial, 332 adult patients with transfusion-dependent (TD) β-thalassemia were included in the Safety Population: 223 in the Reblozyl® arm and 109 in the placebo arm following a 2:1 randomization scheme.

The most common treatment emergent adverse events (TEAEs) in patients treated with Reblozyl® (≥ 10% and with ≥ 1% frequency versus placebo) were: headache, bone pain, arthralgia, fatigue, cough, abdominal pain, diarrhea, and dizziness.

Serious TEAEs occurred in 15.2% of patients treated with Reblozyl® compared to 5.2% of patients treated with placebo. More patients treated with Reblozyl® experienced serious TEAEs of infections compared to patients treated with placebo (5.8% vs. 2.8%), including septic shock (1% vs. none), cellulitis (1% vs. none) and cholangitis (1% vs. none). Other serious TEAEs reported in ≥ 1% of patients treated with Reblozyl® were anemia (1.3%), cerebrovascular accident, deep vein thrombosis, and pyrexia (1% each).

Dose delay/interruption due to an adverse event occurred in 15.2% of Reblozyl® and 10.1% of placebo treated patients. In the Reblozyl® arm, the most common adverse events leading to dose delay/interruption were upper respiratory tract infection (1.8%), alanine aminotransferase increased (1.3%), and cough (1.3%). Dose reduction due to an adverse event occurred in 2.7% of Reblozyl® and 2.8% of placebo-treated patients. In the Reblozyl® arm the most common adverse event leading to dose reduction of Reblozyl® was hypertension (0.9%).

Treatment discontinuation due to an adverse event occurred in 5.4% of Reblozyl® and 0.9% of placebo treated patients. The most common adverse events leading to discontinuation of Reblozyl® were arthralgia (0.9%), back pain (0.9%), and deep vein thrombosis (0.9%).

Hypersensitivity reactions (systemic including eyelid edema, drug hypersensitivity, swelling face, periorbital edema, hypersensitivity, face edema, lip swelling, drug eruption) were reported in 4.5% of patients receiving Reblozyl®. All events were Grade 1-2 and non-serious.

Injection site reactions (including injection site erythema, injection site pruritus, injection site swelling, and injection site rash) were reported in 2.2% of Reblozyl® and 1.8% of placebo treated patients. All events were Grade 1.

Very Low- to Intermediate Risk MDS with Ring Sideroblasts:

In the double-blind, randomized, placebo-controlled, multicentre, Phase III, MEDALIST trial, 229 adult patients with RBC transfusion-dependent (TD) very low-, low-, or intermediate-risk MDS with ring sideroblasts were included in the Safety Population: 153 in the Reblozyl® arm and 76 in the placebo arm.

The most common TEAEs in patients treated with Reblozyl® (≥ 10% and with ≥ 1% frequency versus placebo) were: fatigue, diarrhea, asthenia, nausea, dizziness, back pain, cough, headache, dyspnea, urinary tract infection, bronchitis, and constipation. Asthenia, fatigue, dizziness and headache occurred

more frequently during the first 3 months of treatment.

Serious TEAEs occurred in 31.4% of patients on Reblozyl® and 30.3% of patients on placebo. Serious TEAEs reported in ≥ 1% of patients treated with Reblozyl® were pneumonia, urinary tract infection, transformation to AML, back pain, syncope (2% each), and sepsis, basal cell carcinoma, cardiac failure, angina pectoris, atrioventricular block, femur fracture, anemia, and acute kidney injury (1.3% each).

Dose delay/interruption due to an adverse event occurred in 15.0% of Reblozyl® and 5.3% of placebo-treated patients. In the Reblozyl® arm, the most common adverse events leading to dose delay/interruption were urinary tract infection, aspartate aminotransferase increased, neutropenia, and muscle weakness (1.3% each).

Dose reduction due to an adverse event occurred in 4.6% of Reblozyl®-treated patients compared to none for placebo-treated patients. Adverse events leading to dose reduction were based on single patient experiences of: asthenia, fatigue, back pain, myalgia, neutropenia, vomiting, and aminotransferase increased.

Treatment discontinuation due to an adverse event occurred in 8.5% of Reblozyl® and 7.9% of placebo-treated patients. The most common adverse events leading to discontinuation of Reblozyl® were transformation to AML, fatigue, and sepsis (1.3% each).

Hypersensitivity reactions (systemic including eyelid edema, drug hypersensitivity, swelling face, periorbital edema, hypersensitivity, face edema) were reported in 4.6% of patients receiving Reblozyl®. All events were Grade 1-2 and non-serious.

Injection site reactions (including injection site erythema, injection site pruritus, injection site rash, injection site swelling) were reported in 4.6% of Reblozyl® and 2.6% of placebo-treated patients. All events were Grade 1 and non-serious.

Transformation to AML was reported in 2.0% of Reblozyl® treated patients and 1.3% of placebo patients.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

β-thalassemia:

The TEAEs reported in adult patients enrolled in the BELIEVE trial are listed in Table 5 and reflect a median treatment duration of 64.1 weeks (range 3-97) in the Reblozyl® arm, compared with 64.0 weeks (range 9-92) 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 are included in the table (≥ 1% greater frequency versus placebo is applied). TEAEs are included without regard to causality.

Table 5 - Treatment Emergent Adverse Events (≥ 5%) Reported in Patients with β-thalassemia Treated with Reblozyl® from the BELIEVE Trial (safety population)

System Organ Class/Preferred Term	Reblozyl® N = 223		Placebo N= 109	
	All Grades n (%)	Grades 3-4[a] n (%)	All Grades n (%)	Grades 3-4 n (%)
Gastrointestinal disorders	**80 (36)**	**4 (2)**	**36 (33)**	**0 (0)**
Abdominal pain[b]	31 (14)	0 (0)	13 (12)	0 (0)
Diarrhea	27 (12)	1 (<1)	11 (10)	0 (0)
Nausea	20 (9)	0 (0)	6 (6)	0 (0)
General disorders and administration site conditions	105 (47)	4 (2)	45 (41)	0 (0)
Fatigue	30 (14)	0 (0)	14 (13)	0 (0)
Pain	13 (6)	0 (0)	4 (4)	0 (0)
Metabolism and nutrition disorders	**34 (15)**	**10 (5)**	**7 (6.4)**	**1 (1)**
Hyperuricemia[c]	19 (9)	9 (4)	1 (1)	0 (0)
Musculoskeletal and connective tissue disorders	**137 (61)**	**9 (4)**	**61 (56)**	**1 (1)**
Bone Pain	44 (20)	3 (1)	9 (8)	0 (0)
Arthralgia	43 (19)	0 (0)	13 (12)	0 (0)
Pain in extremity	21 (9)	0 (0)	9 (8)	0 (0)
Infections and infestations	**141 (63)**	**15 (7)**	**63 (58)**	**6 (6)**
Influenza	19 (9)	0 (0)	6 (6)	0 (0)
Viral Upper Respiratory Infection	14 (6)	1 (0.4)	2 (2)	0 (0)
Nervous system disorders	**90 (40)**	**9 (4)**	**32 (29)**	**1 (1)**
Headache	56 (26)	1 (<1)	26 (24)	1 (1)
Dizziness	25 (11)	0 (0)	5 (5)	0 (0)
Respiratory, thoracic and mediastinal disorders	**71 (32)**	**0 (0)**	**29 (27)**	**0 (0)**
Cough	32 (14)	0 (0)	12 (11)	0 (0)
Oropharyngeal pain	28 (13)	0 (0)	12 (11)	0 (0)

Vascular disorders	**25 (11)**	**4 (2)**	**6 (6)**	**0 (0)**
Hypertension[d]	18 (8)	4 (2)	3 (3)	0 (0)

[a]Limited to Grade 3 reactions with the exception of 4 events of Grade 4 hyperuricemia
[b]Grouped term includes: abdominal pain and abdominal pain upper
[c]Grouped term includes: hyperuricemia and blood uric acid increased
[d]Grouped term includes: essential hypertension, hypertension, and hypertensive crisis

Very Low- to Intermediate Risk MDS with Ring Sideroblasts:

The TEAEs reported in adult patients enrolled in the MEDALIST trial are listed in Table 6 and reflect a median treatment duration of 49.0 weeks (range 6-114) in the Reblozyl® arm compared with 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 are included in the table (≥ 1% greater frequency versus placebo is applied). TEAEs are included without regard to causality.

Table 6 - Treatment Emergent Adverse Events (≥ 5%) Reported in Patients with MDS Reported with Reblozyl® from Trial ACE-536-MDS-001 (safety population)

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 + vertigo positional	9 (6)	0 (0)	1 (1)	1 (1)
Gastrointestinal Disorders				
Diarrhea	34 (22)	0 (0)	7 (9)	0 (0)
Nausea[a]	31 (20)	1 (1)	6 (8)	0 (0)
Constipation	17 (11)	0 (0)	7 (9)	0 (0)
General disorders and administration site conditions				
Fatigue[b]	70 (46)	11 (7)	19 (25)	2 (3)
Infections and Infestations				
Bronchitis[a]	17 (11)	1 (1)	1 (1)	0 (0)
Urinary tract infection[a]	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)
Musculoskeletal and connective tissue disorders				
Back pain[a]	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[a,c]	11 (7)	4 (3)	2 (3)	1 (1)
Respiratory, thoracic, and mediastinal disorders				
Cough	27 (18)	0 (0)	10 (13)	0 (0)
Dyspnea[a]	23 (15)	1 (1)	5 (7)	0 (0)
Vascular Disorders				
Hypertension[d]	13 (9)	5 (3)	7 (9)	3 (4)

[a]At least 1 event was reported as serious
[b]Grouped terms include: fatigue and asthenia
[c]Grouped terms include: renal failure, acute kidney injury, chronic kidney disease, renal impairment
[d]Grouped terms include: essential hypertension, hypertension, hypertensive crisis

8.3 Less Common Clinical Trial Adverse Reactions

β-thalassemia:
Less common clinically significant adverse events (<5%, all grades with incidence greater than placebo) in the BELIEVE trial include:

Blood and Lymphatic disorders: anemia (4.5%), EMH masses (3.2%)
Ear and labyrinth disorders: vertigo (3%)
Eye disorders: eyelid edema (1%), periorbital edema (1%)
Gastrointestinal disorders: lip swelling (0.4%)
General disorders and administration site conditions: face edema (0.4%), injection site reaction (2%), injection site swelling (0.4%)

Hepatobiliary Disorders: cholangitis (1%), drug-induced liver injury (0.4%), portal vein thrombosis (0.4%)
Immune System Disorders: drug hypersensitivity (0.4%), hypersensitivity (0.4%)
Infections and infestations: cellulitis (2%), septic shock (1%), urinary tract infection (2%)
Investigations: urine albumin/creatinine ratio increased (2%)
Nervous System Disorder: cerebrovascular accident (1%), Spinal cord compression (1.9%)
Respiratory, Thoracic, and Mediastinal Disorders: pulmonary embolism (0.4%)
Skin and subcutaneous tissue disorders: drug eruption (0.4%), swelling face (0.4%)
Vascular disorders: deep vein thrombosis (1%), thrombophlebitis superficial (1%)

Very Low- to Intermediate Risk MDS with Ring Sideroblasts:
Less common clinically significant adverse events (<5%, all grades with incidence greater than placebo) in the MEDALIST trial include:

Cardiac disorders: angina pectoris (4.6%), atrioventricular block (2.0%), cardiac failure (1.3%)
Infections and infestations: pneumonia (3.3%), sepsis (1.3%)
Injury, poisoning and procedural complications: femur fracture (1.3%)
Neoplasms benign, malignant and unspecified: basal cell carcinoma (1.3%)
Respiratory, Thoracic, and Mediastinal Disorders: pulmonary fibrosis (0.7%)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

β-thalassemia:

Changes in selected post-baseline laboratory parameters that were observed in the BELIEVE study are listed in Table 7.

Table 7 – Selected Laboratory Abnormalities Reported in the BELIEVE Trial (Safety Population)

Lab Shift	Reblozyl® N = 223 n (%)	Placebo N= 109 n (%)
ALT ≥ 3 x ULN	26 (12)	13 (12)
AST ≥ 3 x ULN	25 (11)	5 (5)
ALP ≥ 2 x ULN	17 (8)	1 (1)
Total bilirubin ≥ 2 x ULN	143 (64)	51 (47)
Direct bilirubin ≥ 2 x ULN	13 (6)	4 (4)
Creatine > 2 x baseline	6 (3)	0
Creatinine clearance < 0.5 x baseline	7 (3)	0
Leukocytes > 2 x baseline and >	11 (5)	2 (2)

ULN		

ALP = alkaline phosphate; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

Very Low- to Intermediate Risk MDS with Ring Sideroblasts:

Changes in selected post-baseline laboratory parameters that were observed in the MEDALIST trial are listed in Table 8.

Table 8 – Selected Laboratory Abnormalities Reported in Trial ACE-536-MDS-001 (Safety Population)

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)

ALP = alkaline phosphate; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal drug interaction studies have been conducted with Reblozyl®.

9.4 Drug-Drug Interactions

Iron-chelating agents: No clinically significant differences in luspatercept PK parameters were observed when used concomitantly with iron-chelating agents.

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Luspatercept is a recombinant fusion protein that binds select endogenous TGF-β superfamily ligands, thereby inhibiting Smad2/3 signaling. Luspatercept promoted erythroid maturation through differentiation of late-stage erythroid precursors (normoblasts) in mice. In models of β-thalassemia, luspatercept decreased abnormally elevated Smad2/3 signaling and improved hematology parameters associated with ineffective erythropoiesis in mice.

10.2 Pharmacodynamics

Increases in Hemoglobin

In patients having received < 4 units of RBC transfusion within 8 weeks prior to study, hemoglobin (Hgb) increased within 7 days of initiating Reblozyl® and correlated with the time to luspatercept maximum serum concentration (Cmax). The greatest Hgb increase occurred after the first dose with additional smaller increases observed after subsequent doses. Hemoglobin levels returned to baseline approximately 8 weeks from the last dose (0.6 to 1.25 mg/kg) in patients with β-thalassemia, and approximately 6 weeks from the last dose (0.75 to 1.75 mg/kg) in patients with MDS. Increasing luspatercept serum exposure (AUC) was associated with greater Hgb increase in patients with β-thalassemia and in patients with MDS.

Cardiac Electrophysiology

The potential for QTc prolongation with Reblozyl® was evaluated in 638 patients with either MDS (an unapproved indication) or β-thalassemia who were treated with multiple doses (0.125 to 1.75 mg/kg) of Reblozyl® (n=474) or placebo (n=164). At steady-state mean Cmax for the maximum therapeutic dose (1.75 mg/kg), the upper bound of the 2-sided 90% CI for the mean difference in QTc change from baseline between Reblozyl® and placebo was < 10ms. Therefore, Reblozyl ® does not cause any clinically meaningful prolongation of the QTc interval at therapeutic doses.

10.3 Pharmacokinetics

Luspatercept exhibited linear pharmacokinetics (PK) over the dose range of 0.2 to 1.25 mg/kg in patients with β-thalassemia, and over the dose range of 0.125 to 1.75 mg/kg in patients with MDS. Luspatercept serum concentration reached steady state after 3 doses when administered every 3 weeks. The accumulation ratio of luspatercept was approximately 1.5. Luspatercept PK parameters, in patients with β-thalassemia are summarized in Table 9, and in patients with MDS in Table 10.

Table 9 - Summary of Luspatercept Pharmacokinetic Parameters in Patients With β-Thalassemia

C_{max} at 1 mg/kg (µg/mL) (N = 6)	**AUC_{21d} at 1 mg/kg** (µg/mL*day) (N = 6)	**$t_{½}$** (day)[a] (N = 57)
5.9 (26.4%)	73.6 (30.3%)	10.8 (24.2%)

[a] Includes all dose groups (0.2 to1.25 mg/kg) in Phase II study

Data are based on non-compartmental analysis and all PK parameters are summarized by the arithmetic mean (% CV).

AUC_{21d} = area under the concentration-time curve during the first dosing interval (1-21 days); C_{max} = maximum concentration during the first dosing interval; CV = coefficient of variation; N = sample size; $t_{1/2}$ = elimination half-life.

Table 10 - Summary of Luspatercept Pharmacokinetic Parameters in Patients with MDS after Multiple Doses

	[a]$C_{max.ss}$ (µg/mL)	[a]AUC_{ss} (µg/mL*day)	[a]$t_{½}$ (day)
Starting dose of 1 mg/kg	9.2 (29.9%)	145 (38.3%)	13.0 (31.6%)

[a] All PK parameters are summarized by geometric mean (geometric CV%).
AUC_{ss} = area under the concentration-time curve at steady state for the starting dose (1 mg/kg); $C_{max.ss}$ = maximum concentration for at steady state (1 mg/kg); CV = coefficient of variation; $t_{1/2}$ = elimination half-life.

Absorption

The median (range) time to maximum concentration (Tmax) of luspatercept was observed at approximately 7 (6-10) days post-dose in patients with β-thalassemia and at approximately 7 (4-21) days post-dose in patients with MDS. The absorption of luspatercept was not significantly affected by the subcutaneous injection sites (upper arm, thigh, or abdomen).

Distribution:

In a population PK analysis, the mean (%CV) apparent volume of distribution (Vd/F) of luspatercept was estimated to be 7.1 (26.7%) L for patients with β-thalassemia and 9.7 (26.5%) L for patients with MDS.

Metabolism:

Luspatercept is expected to be catabolized into amino acids by general protein degradation processes in multiple tissues.

Elimination

The mean (%CV) half-life (t1/2) of luspatercept was approximately 11 (24.2%) days in patients with β-thalassemia. In a population PK analysis, the mean (%CV) apparent total clearance (CL/F) was estimated to be 0.44 (38.5%) L/day in patients with β-thalassemia. The mean (%CV) half-life (t1/2) of luspatercept was approximately 13 (31.6%) days and the mean (%CV) apparent total clearance (CL/F) was 0.52 (41.2%) L/day in patients with MDS.

Special Populations and Conditions

No clinically significant differences in the luspatercept PK was observed based on age (18 to 66 years), sex, baseline albumin (30 – 56 g/L), baseline serum erythropoietin (2.4 to 972 U/L), RBC transfusion burden (0 to 34 units/24 weeks), β-thalassemia genotype (β0/β0 vs. non-β0/β0), and splenectomy in patients with β-thalassemia. No clinically significant differences in luspatercept PK was observed in MDS patients based on age (27-95 years), sex, baseline albumin (31-53 g/L), baseline serum erythropoietin (10 to 2450 U/L), RBC transfusion burden (0-43 units/24 weeks), and ring sideroblasts status (negative vs. positive).

- **Pediatrics**

  Luspatercept pharmacokinetics in patients < 18 years of age has not been evaluated.

- **Geriatrics**

  Clinical studies of Reblozyl® in β-thalassemia did not include sufficient numbers of patients aged 65 years and older to determine if luspatercept pharmacokinetics are different from younger patients. No clinically significant differences in luspatercept PK were observed in MDS patients < 65, 65 – 74, and ≥ 75 years of age.

- **Sex**

  Gender had no clinically significant effect on luspatercept exposure (AUC or clearance).

- **Ethnic Origin**

  Race (Asian vs. Caucasian) had no clinically significant effect on luspatercept exposure (AUC or clearance).

- **Hepatic Insufficiency**

  No formal studies of Reblozyl® in patients with hepatic impairment have been conducted. No clinically important differences in luspatercept exposure were observed in patients with mild to severe hepatic impairment i.e. elevated liver enzymes (ALT or AST, up to 3 x ULN [upper limit of normal]) and elevated bilirubin (4-246 µmol/L). Pharmacokinetic data are not available for patients with AST or ALT ≥ 3x ULN.

- **Renal Insufficiency**

  No formal studies of Reblozyl® in patients with renal impairment have been conducted. Based on estimated eGFR, no clinically important differences in exposure to luspatercept were observed in 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).

- **Obesity**

  The apparent clearance (CL/F) and volume of distribution (Vd/F) of luspatercept increased with increasing body weight (34 to 97 Kg) in patients with β-thalassemia. The apparent CL/F and Vd/F of luspatercept increased with increasing body weight (46 to 124 Kg) in patients with MDS.

11 STORAGE, STABILITY AND DISPOSAL

Store vials refrigerated at 2-8˚C in original carton to protect from light. Do not freeze.

Reconstituted vials in the original container can be stored for up to 8 hours when stored at room temperature or for 24 hours when stored at 2-8˚C.

12 SPECIAL HANDLING INSTRUCTIONS

Do not freeze. Avoid aggressive shaking.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: luspatercept

Molecular mass: Approximately 76 kD

Structural: Luspatercept is a recombinant fusion protein consisting of two identical chains, each consisting of a modified form of the extracellular domain (ECD) of human activin receptor type IIB (ActRIIB) linked to the human IgG1 Fc domain.

Physicochemical properties: Luspatercept is produced in Chinese hamster ovary cells by recombinant DNA technology. Reblozyl® (luspatercept for injection) is supplied as a sterile, preservative-free, white to off-white, lyophilized powder in single-dose vials for subcutaneous use after reconstitution.

14 CLINICAL TRIALS

The clinical efficacy and safety of Reblozyl® were evaluated in adult patients with transfusion dependent (TD) β-thalassemia-associated anemia in the BELIEVE trial and in adult patients with transfusion-dependent anemia resulting from very low- to intermediate-risk MDS with ring sideroblasts in the MEDALIST trial.

14.1 Clinical Trials by Indication

β-thalassemia (BELIEVE):

Trial Design and Study Demographics

Table 11 - Summary of patient demographics for clinical trials in β-thalassemia (BELIEVE Trial)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
BELIEVE Trial	Phase III, double-blind, randomized, double-blind, placebo-controlled trial comparing treatment with Reblozyl® + best support care (BSC) to placebo + BSC in patients with β-thalassemia-associated anemia requiring regular red blood cell (RBC) transfusions	Reblozyl® 1 mg/kg SC every 3 weeks + BSC for 48 weeks Placebo SC every 3 weeks + BSC for 48 weeks	N = 336 Reblozyl® arm = 224 Placebo arm = 112	30 (18-66)	58% (F) 42% (M)

In the BELIEVE trial, adult patients with β-thalassemia requiring regular RBC transfusions (6-20 RBC units per 24 weeks) with no transfusion-free period greater than 35 days during that 24-week period were randomized 2:1 to Reblozyl® or placebo. Reblozyl® was administered subcutaneously once every 3 weeks as long as a reduction in transfusion requirement was observed or until unacceptable toxicity. All patients were eligible to receive best supportive care, which included RBC transfusions; iron-chelating agents; use of antibiotic, antiviral, and antifungal therapy; and/or nutritional support, as needed.

The trial excluded patients with hemoglobin S/β-thalassemia or alpha-thalassemia or patients who had major organ damage (liver disease, heart disease, lung disease, renal insufficiency). Patients with recent (within past 24 weeks) deep vein thrombosis or stroke or recent use (within past 24 weeks) of erythropoiesis-stimulating agents, immunosuppressant, or hydroxyurea therapy were also excluded.

The median age was 30 years (range: 18-66). The trial was comprised of patients who were 42% male; 54.2% Caucasian, 34.8% Asian, and 0.3% Black or African American.

Table 12 summarizes the baseline disease-related characteristics.

Table 12 – Baseline Disease Characteristics of β-thalassemia in the BELIEVE Trial

Disease Characteristic	**Reblozyl® (N=224)**	**Placebo (N=112)**
β-thalassemia diagnosis, n (%)		
β-thalassemia	174 (77.7)	83 (74.1)
HbE/β-thalassemia	31 (13.8)	21 (18.8)
β-thalassemia combined with α-thalassemia	18 (8)	8 (7.1)
Missing[a]	1 (0.4)	0
Baseline transfusion burden 12 weeks prior to randomization		
Median units/12 weeks (min, max)	6.12 (3, 14)	6.27 (3,12)
β-thalassemia gene mutation grouping, n (%)		
β0/β0	68 (30.4)	35 (31.3)
Non-β0/β0	155 (69.2)	77 (68.8)
Missing[a]	1 (0.4)	0
Baseline serum ferritin level (µg/L)		
Median (min, max)	1441.25[b] (88, 6400)	1301.50[c] (136, 6400)
Splenectomy, n (%)		
Yes	129 (57.6)	65 (58)
No	95 (42.4)	47 (42)
Age patient started regular transfusions (years)		
Median (min, max)	2[d] (0, 52)	2[e] (0, 51)

HbE=hemoglobin E [a]"Missing" category includes patients in the population who had no result for the parameter listed [b]N=220; [c]N=111; [d]N=169; [e]N=85.

Study Results

The efficacy of Reblozyl ® in adult patients with RBC transfusion dependent β-thalassemia was based on the reduction in RBC transfusion burden defined by the number of patients who achieved a specified rate of transfusion burden reduction (see Table 13).

The trial was unblinded when all patients had received at least 48 weeks of treatment or discontinued treatment.

Table 13 - Results of study in β-thalassemia the BELIEVE Trial (ITT Population)

Endpoints	Reblozyl® N=224 n (%)	Placebo N=112 n (%)	p-value[a]	Risk Difference % (95% CI)
Primary Endpoint				
≥33% reduction from baseline in RBC transfusion burden with a reduction of ≥2 units from Weeks 13-24	48 (21.4)	5 (4.5)	< 0.0001	17.0 (10.4, 23.6)
Key Secondary Endpoints				
≥33% reduction from baseline in RBC transfusion burden with a reduction of ≥2 units from Weeks 37–48	44 (19.6)	4 (3.6)	< 0.0001	16.1 (9.8, 22.4)
≥50% reduction from baseline in RBC transfusion burden with a reduction of ≥2 units at:				
Weeks 13–24	17 (7.6)	2 (1.8)	0.0303	5.8 (1.6, 10.1)
Weeks 37–48	23 (10.3)	1 (0.9)	0.0017	9.4 (5.0, 13.7)

[a] The p-value was from the Cochran-Mantel-Haenszel (CMH) test to compare Reblozyl® treatment group to placebo group.
ITT = intent to treat; RBC = red blood cells

Subgroup analysis based on the primary endpoint hazard ratio were generally consistent across the pre-defined subgroups including patients with the β0/β0 gene mutation, or patients with a high transfusion burden (>6 units/12 weeks) at baseline.

Very Low- to Intermediate Risk MDS with Ring Sideroblasts (MEDALIST):

Trial Design and Study Demographics

Table 14 - Summary of patient demographics for clinical trials in Very Low- to Intermediate Risk MDS with Ring Sideroblasts (MEDALIST Trial)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
MEDALIST Trial	Phase III, double-blind, randomized, double-blind, placebo-controlled trial comparing treatment with Reblozyl® + best support care (BSC) to placebo + BSC in patients with transfusion-dependent anemia resulting from IPSS-R very low- to intermediate-risk MDS with ring sideroblasts	Reblozyl® 1 mg/kg SC every 3 weeks + BSC for 48 weeks Placebo SC every 3 weeks + BSC for 48 weeks	N = 229 Reblozyl® arm = 153 Placebo arm = 76	71 (26-95)	37.1% (F) 62.9% (M)

In the MEDALIST trial, adult patients with very low- to intermediate-risk MDS requiring regular RBC transfusions (≥2 RBC units per 8 weeks) with ring sideroblasts with no transfusion-free period greater than 56 days during the 16-week period prior to randomization were randomized 2:1 to Reblozyl® or placebo. Reblozyl® was administered subcutaneously once every 3 weeks. All patients were eligible to receive best supportive care, which included RBC transfusions; iron-chelating agents; use of antibiotic, antiviral, and antifungal therapy; and/or nutritional support, as needed.

Patients were required to have 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). The MEDALIST trial excluded patients with deletion 5q (del 5q), WBC count ≥ 13 x 109/L, neutrophils < 0.5 x 109/L, platelets < 50 x109/L, or with prior use of a disease modifying agent for treatment of MDS.

The median age was 71 years (range: 26-95); 62.9% were male, and 69% were Caucasian. Race was not reported for 29.7% of patients.

Table 15 summarizes the baseline demographics and disease-related characteristics.

Table 15 – Baseline Demographics and Disease Characteristics of MDS in 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[a] (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[b], 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[c], n (%)		
MDS RARS	7 (4.6)	2 (2.6)
MDS RCMD-RS	145 (94.8)	74 (97.4)
Other[d]	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)

EPO = erythropoietin; ESA = erythropoiesis-stimulating agent; IPSS-R = International Prognostic Scoring System-Revised; MDS = myelodysplastic syndromes; RARS = refractory anemia with ring sideroblasts; RBC = red blood cells; RCMD = refractory cytopenia with multilineage dysplasia; DS = standard deviation; WHO = World Health Organization

[a] Time since original MDS diagnosis was defined as the number of years 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] Per the WHO 2008 criteria. [d] Locally diagnosed MDS-RS and multilineage dysplasia.

Study Results

In the MEDALIST trial, the efficacy of Reblozyl® was established based on the proportion of patients who were RBC transfusion independent (RBC-TI), defined as the absence of any RBC transfusion during any consecutive 8-week period within the first 24 weeks of treatment, see Table 16.

Table 16 - Efficacy Results from the MEDALIST Trial (ITT Population)

Endpoints	Reblozyl® N=153 n (%)	Placebo N=76 n (%)	p-value[a]	Risk Difference % (95% CI)
Primary Endpoint				
RBC-TI ≥8 weeks from Week 1 through Week 24[b]	58 (37.9)	10 (13.2)	< 0.0001	24.6 (14.5, 34.6)
Key Secondary Endpoints				
RBC-TI ≥12 weeks from Week 1 through Week 24[c]	43 (28.1)	6 (7.9)	0.0002	20.0 (10.9, 29.1)
RBC-TI ≥12 weeks from Week 1 through Week 48[d]	51 (33.3)	9 (11.8)	0.0003	21.4 (11.2, 31.5)

[a] 2-sided p-value from Cochran-Mantel-Haenszel (CMH) test stratified for average baseline RBC transfusion requirement (≥6 units versus < 6 units for RBC per 8 weeks), and baseline IPSS-R score

(very low or low versus intermediate).

[b] 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).

[c] 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).

[d] Defined as the absence of any RBC transfusion during any consecutive 84-day (12 week) period during Week 1 to Week 48.

ITT = intent to treat; RBC = red blood cell; RBC-TI = RBC transfusion independence.

Of the patients who achieved the primary endpoint (RBC-TI ≥8 weeks during Weeks 1-24), 62% (36/58) had more than 1 episode of RBC-TI during the treatment period.

14.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to luspatercept in the studies described below with the incidence of antibodies in other studies or other products may be misleading.

Of 284 patients with β-thalassemia who were treated with Reblozyl® and evaluable for the presence of anti-luspatercept antibodies, 4 patients (1.4%) tested positive for treatment-emergent anti-luspatercept antibodies, including 2 patients (0.7%) who had neutralizing antibodies. Of 260 patients with MDS who were treated with Reblozyl® and evaluable for the presence of anti-luspatercept antibodies, 23 patients (8.8%) tested positive for treatment-emergent anti-luspatercept antibodies, including 9 patients (3.5%) who had neutralizing antibodies.

Luspatercept serum concentrations tended to decrease in the presence of neutralizing antibodies. There were no severe acute systemic hypersensitivity reactions reported for patients with anti-luspatercept antibodies in Reblozyl® clinical trials, and there was no association between hypersensitivity type reaction or injection site reaction and presence of anti-luspatercept antibodies.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

No carcinogenicity or mutagenicity studies have been conducted with luspatercept.

Repeat-Dose Toxicity Studies:

In repeat-dose toxicity studies toxicities in rats included: membranoproliferative glomerulonephritis; congestion, necrosis and/or mineralization of the adrenal glands; hepatocellular vacuolation and necrosis; and mineralization of the glandular stomach. In monkeys, toxicities included:

membranoproliferative glomerulonephritis; vascular degeneration and inflammatory infiltrates in the choroid plexus.

Repeat dose studies were conducted in cynomolgus monkeys. In a 6-month study, monkeys received 0, 0.3, 1 or 6 mg/kg luspatercept once every two weeks, followed by a 3-month recovery period. In a 13-week study, monkeys received 0, 1, 6 or 30 mg/kg Reblozyl®, followed by a 10-week recovery period. Increases in blood parameters (increased red blood cell count, hemoglobin, hematocrit and reticulocytes) occurred at ≥ 1 mg/kg in males and ≥ 0.3 mg/kg in females (at least one time point). Creatinine and/or blood urea nitrogen (BUN) were increased at ≥ 1 mg/kg. Ferritin and ALP were increased at ≥ 6 mg/kg. The microalbumin:creatinine ratio was increased in one 1 mg/kg and two 6 mg/kg animals at most time-points. Hematology and clinical chemistry parameters were reversible in the recovery period, urine biomarkers showed a trend to pre-study levels. Histopathological analyses revealed evidence of toxicity in the kidneys, brain and lymph nodes.

Kidney: Membranoproliferative glomerulonephritis was observed at ≥ 1 mg/kg. Immune complex deposition was observed in intramembranous locations and/or mesangia of affected glomeruli. Interstitial or tubular hemorrhage with or without accompanying hemosiderin deposition was identified in the cortex and/or medulla at ≥ 1 mg/kg. Interstitial fibrosis/fibroplasia was identified at 6 mg/kg; however, subtle interstitial changes, including increased extracellular matrix, vacuolization of interstitial cells and/or degeneration/atrophy of tubules, were identified in the medulla, near the corticomedullary junction at ≥ 1 mg/kg. Minimal to mild interstitial mixed inflammatory cell infiltrates were seen in 2 of 6 animals in the 6 mg/kg dose group. Animals that received 1 mg/kg recovered following the 3-month recovery period; whereas, animals that received 6 mg/kg only partially recovered.

Brain: Changes to the choroid plexus occurred in the interstitium and blood vessels at ≥ 1 mg/kg, and included: vascular degeneration (small to medium sized blood vessels), deposition of pigment (hemosiderin), deposition of eosinophilic proteinaceous material, a mixed inflammatory cell infiltrate (small numbers of neutrophils, macrophages, and lymphocytes including plasma cells), and an infiltrate of foamy (vacuolated) macrophages. Immunohistochemistry results revealed increased deposition of immune components. These effects improved during the recovery period.

Lymph nodes: Extramedullary hematopoiesis in the mandibular and axillary lymph nodes occurred at 0.3 and 1 mg/kg, and was reversible during the recovery period.

In a repeat dose study, adult Sprague Dawley rats received 0, 1, 3 or 15 mg/kg luspatercept once every two weeks for 13 weeks, followed by a 10-week recovery period. The effects observed in the rat were similar to those observed in the monkey and occurred at similar doses. Increases in blood parameters occurred at ≥ 3 mg/kg. Membranoproliferative glomerulonephritis was observed at ≥ 1 mg/kg with, with increase in BUN at 15mg/kg. Increased levels of ALP were observed and, in the liver, minimal to mild hepatocellular vacuolation was observed at all doses, and minimal focal or multifocal hepatic necrosis was observed at ≥ 3 mg/kg. In the adrenal glands, minimal to moderate cortical necrosis was observed at ≥ 3 mg/kg. Following the recovery period, treatment-related effects persisted in the kidney, liver and adrenal gland.

In a repeat-dose definitive juvenile toxicity study, hematologic malignancies were observed in 3 out of 44 rats examined in the highest dose group (10mg/kg). The occurrence of these tumors in young

animals is unusual and the relationship to luspatercept treatment cannot be ruled out. Juvenile rats were administered luspatercept subcutaneously at 1, 3 or 10 mg/kg once every 2 weeks from postnatal day 7 to 91. Hematologic malignancies (granulocytic leukemia, lymphocytic leukemia, malignant lymphoma) were observed at 10 mg/kg resulting in exposures (based on area under the curve [AUC]) approximately 8 times the maximum recommended human (β-thalassemia) dose (MRHD) of 1.25 mg/kg. No other proliferative or pre-neoplastic lesions, attributable to luspatercept, have been observed in any species in other nonclinical safety studies conducted with luspatercept, including a 6-month study in monkeys.

Fertility and Early Embryonic Development Studies:

In a combined male and female fertility and early embryonic development study in rats, luspatercept was administered subcutaneously to animals at doses of 0, 1, 3 or 15 mg/kg. There were significant reductions in the average numbers of corpora lutea, implantations, and viable embryos in luspatercept-treated females. Effects on female fertility were observed at the highest dose (15 mg/kg) with exposures (based on AUC) approximately 12 times the MRHD of 1.25 mg/kg. Adverse effects on fertility in female rats were reversible after a 14-week recovery period. No adverse effects were noted in male rats.

Embryo-Fetal Development (EFD) Studies:

Luspatercept is a developmental toxicant. Embryo-fetal developmental toxicity studies (range-finding and definitive studies) were conducted in the pregnant Sprague Dawley rat and New Zealand White rabbit. In definitive studies, rats received 0, 5,15 or 30 mg/kg, and rabbits received 0, 5, 20 or 40 mg/kg administered twice during the period of organogenesis. Embryofetal effects seen in both species included: reductions in numbers of live fetuses, reduction in fetal body weights, increases in resorptions, and increased post-implantation loss.

Maternal toxicity: The number of pregnant rats was significantly reduced at 30 mg/kg, and the number pregnant rabbits was reduced at ≥20 mg/kg. In both species, and the average number of resorptions and percent post-implantation loss were increased (30 mg/kg in rat and ≥ 20 mg/kg in rabbit).

Fetal Toxicity: In rat, skeletal variations occurred at ≥ 5 mg/kg. Gross malformations occurred at 15 mg/kg (n=3 fetuses) that were considered possibly related to luspatercept. Malformations included: agnathia with a small oral opening and absent tongue; depressed eye bulge, cleft palate, cleft snout and no nares; and, thread like tail, no anal opening, as well as skeletal malformations (only one sacral vertebra, no caudal vertebra and an extra ossification point in the sacral vertebra). There was an increase in embryo/fetal death at 30 mg/kg, which may have masked a dose response of these malformations. Other malformations that were observed were considered not treatment related because they had been previously observed in historical controls. In rabbit, skeletal variations occurred at ≥ 5 mg/kg. Skeletal malformations to the ribs and vertebra occurred in fetuses at 20 mg/kg (n=1) and 40 mg/kg (n=5). There was one grossly malformed fetus at 40 mg/kg that had gastroschisis with portions of the liver, intestines, stomach and spleen protruding; this fetus also had a malpositioned cervical vertebral centrum. In both species, the NOAEL for embryo fetal effects of luspatercept was observed in the EFD studies at the lowest dose tested, 5 mg/kg, which corresponds to an estimated exposure in rats and rabbits of 4.9 and 9.9 times greater, respectively, than the estimated clinical exposure.

Pre and Postnatal Development (PPND) Studies:

Parental generation Sprague Dawley rats received 0, 3, 10 or 30 mg/kg luspatercept; F1 generation rats were not dosed directly, but received luspatercept in utero and through breast milk. F1 rats had lower body weights and adverse effects of the kidney, including: minimal to mild membranoproliferative glomerulonephritis, and/or tubular atrophy/hypoplasia, and vessel ectasia occasionally associated with hemorrhage. Kidney effects were considered adverse at ≥ 3 mg/kg.

PATIENT MEDICATION INFORMATION – USE IN BETA-THALASSEMIA

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrREBLOZYL®

luspatercept for injection

Read this carefully before you start taking **Reblozyl®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Reblozyl®**.

What is Reblozyl® used for?

Reblozyl® is used to treat adults who have low red blood cell counts (anemia) and require red blood cell transfusions due to a blood disorder (β-thalassemia) that affects the production of hemoglobin (a protein in the red blood cells that transports oxygen throughout the body).

How does Reblozyl® work?

Reblozyl® may improve red blood cell production and increase hemoglobin levels, reducing the need for red blood cell transfusions.

What are the ingredients in Reblozyl®?

Medicinal ingredients: luspatercept

Non-medicinal ingredients: Non-medicinal ingredients: citric acid monohydrate, hydrochloric acid, polysorbate 80, sodium hydroxide, sucrose, tri-sodium citrate dihydrate

Reblozyl® comes in the following dosage forms:

Reblozyl® is a powder that will be mixed with sterile water before it is injected under the skin (subcutaneous injection). It comes in vials and is available in two strengths 25 mg and 75 mg.

Do not use Reblozyl® if:

- You are allergic to luspatercept or any of the other ingredients in Reblozyl®.

If you are not sure, talk to your doctor or nurse before you are given Reblozyl®.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Reblozyl®. Talk about any health conditions or problems you may have, including if:

- You are a β-thalassemia patient and have had your spleen removed. You may have a higher risk for a blood clot when given Reblozyl®. Discuss with your doctor other potential risk factors that my increase your risk including hormone replacement therapy or a previous blood clot. Your doctor may use preventive measures or medication to reduce the likelihood of a blood clot formation.
- You are a β-thalassaemia patient with medical history of mass producing blood cells outside the bone marrow (extramedullary haematopoiesis masses, EMH masses), or with low hemoglobin, spleen removed, or enlarged liver/spleen. You may have a high risk of EMH

masses. Your doctor will talk to you about other possible risk factors that may increase your risk - these include:

- compression of the spinal cord.

- You have or previously had high blood pressure, since Reblozyl® may increase it. Your blood pressure will be monitored before Reblozyl® administration and throughout treatment.

Other warnings you should know about:

Pregnancy:

- Do not use this medicine during pregnancy. Reblozyl® may cause harm to your unborn baby.
- Your healthcare professional may arrange a pregnancy test before treatment.
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your healthcare professional for advice before taking this medicine.

Breast-feeding:

- Do not breast-feed when using this medicine and for a least 3 months after your last dose. It is not known if Reblozyl® passes into the mother's milk.

Contraception:

- Women of childbearing potential should use an effective method of contraception during treatment with Reblozyl® and for at least 3 months after their last dose.
- You should not become pregnant while you are taking this medicine. Reblozyl® may cause harm to your unborn baby.

Fertility:

- If you are a woman, this medicine may cause fertility problems, which may affect your ability to have a baby. Talk to your healthcare profession for advice before taking Reblozyl®.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How you will be treated with Reblozyl®

Reblozyl® will be given by injections under your skin. The injections will be given to you by a doctor, nurse or other healthcare professional.

You will have a blood test to measure your hemoglobin level before you receive Reblozyl®. If your hemoglobin level is too high, you may not receive Reblozyl® at your visit. Your blood pressure will also be monitored before each administration of this medicine and throughout treatment.

Usual dose:

The dose you are given will be based on your body weight in kilograms.

- The recommended starting dose is 1.0 mg/kg of body weight once every three weeks.
- The highest recommended dose is 1.25 mg/kg of body weight once every three weeks.

- Your doctor will check your progress and may change your dose if needed.

Overdose:

If you think you, or a person you are caring for, have taken too much Reblozyl®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

In case of a missed or delayed injection of Reblozyl®, you will receive a Reblozyl® injection as soon as possible and your dose will continue as prescribed with at least 3 weeks between doses.

What are possible side effects from using Reblozyl®?

These are not all the possible side effects you may feel when taking Reblozyl®. If you experience any side effects not listed here, contact your healthcare professional.

Very common side effects (may affect more than 1 in 10 people):

- dizziness, headache
- bone pain and/or joint pain
- fatigue (tired or feeling weak)
- cough
- abdominal pain
- diarrhea

Common side effects (may affect up to 1 in 10 people):

- flu-like symptoms
- nausea
- upper respiratory tract infections
- increase blood pressure
- high level of uric acid in the blood (hyperuricaemia)
- injection site reactions: redness, burning and pain at the site of the injection

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Anemia (decrease in red blood cells): tiredness, fatigue		√	
Cellulitis (skin infection): red, swollen, hot, tender area of the skin.			√
Cholangitis (inflammation of the bile duct system): abdominal pain, fever, chills, yellowing of skin/eyes, nausea, vomiting, clay-coloured stools, dark urine, tiredness			√
Deep vein thrombosis (blood clots that form in your blood vessels): arm or leg pain with swelling			√
Extramedullary Haematopoiesis (EMH) Masses (mass producing blood cells outside the bone marrow): severe pain in the back that does not go away, numbness or weakness or loss of voluntary movement in legs, hands or arms, loss of bowel and bladder control			√
Fever		√	
Septic shock (overwhelming infection): fever, chills, very low body temperature, decreased urine, rapid heat beat, rapid breathing, nausea, vomiting, diarrhea			√
Stroke: difficulty moving limbs, walking or speaking			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Reblozyl ® will be stored in a refrigerator at 2-8˚C. Do not freeze.

Keep out of reach and sight of children.

If you want more information about Reblozyl®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website https://bms.com/ca/en, or by calling 1-866-463-6267.

This leaflet was prepared by Bristol-Myers Squibb Canada, Montréal, Canada H4S 0A4.

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Last Revised: March 26, 2024

PATIENT MEDICATION INFORMATION – USE IN MYELODYSPLASTIC SYNDROMES

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrREBLOZYL®

luspatercept for injection

Read this carefully before you start taking **Reblozyl®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Reblozyl®**.

What is Reblozyl® used for?

Reblozyl® is used in adults who have low red blood cell counts (anemia) and require red blood cell transfusions due to a blood and bone marrow disorder (myelodysplastic syndromes with ring sideroblasts). It is used in patients who have not responded to or are not able to receive erythropoietin therapies.

How does Reblozyl® work?

Reblozyl® may improve red blood cell production and increases hemoglobin levels, reducing the number of red blood cell transfusions.

What are the ingredients in Reblozyl®?

Medicinal ingredients: luspatercept

Non-medicinal ingredients: citric acid monohydrate, hydrochloric acid, polysorbate 80, sodium hydroxide, sucrose, tri-sodium citrate dihydrate

Reblozyl® comes in the following dosage forms:

Reblozyl® is a powder that will be mixed with sterile water before it is injected under the skin (subcutaneous injection). It comes in vials and is available in two strengths 25 mg and 75 mg.

Do not use Reblozyl® if:

- You are allergic to luspatercept or any of the other ingredients in Reblozyl®.

If you are not sure, talk to your doctor or nurse before you are given Reblozyl®.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Reblozyl®. Talk about any health conditions or problems you may have, including if:

- You have or previously had high blood pressure, since Reblozyl® may increase it. Your blood pressure will be monitored before Reblozyl® administration and throughout treatment.

Other warnings you should know about:

Pregnancy:

- Do not use this medicine during pregnancy. Reblozyl® may cause harm to your unborn baby.
- Your healthcare professional may arrange a pregnancy test before treatment.

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your healthcare professional for advice before taking this medicine.

Breast-feeding:
- Do not breast-feed when using this medicine and for a least 3 months after your last dose. It is not known if Reblozyl® passes into the mother's milk.

Contraception:
- Women of childbearing potential should use an effective method of contraception during treatment with Reblozyl® and for at least 3 months after their last dose.
- You should not become pregnant while you are taking this medicine. Reblozyl® may cause harm to your unborn baby.

Fertility:
- If you are a woman, this medicine may cause fertility problems, which may affect your ability to have a baby. Talk to your healthcare profession for advice before taking Reblozyl®.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How you will be treated with Reblozyl®

Reblozyl® will be given by injections under your skin. The injections will be given to you by a doctor, nurse or other healthcare professional.

You will have a blood test to measure your hemoglobin level before you receive Reblozyl®. If your hemoglobin level is too high, you may not receive Reblozyl® at your visit. Your blood pressure will also be monitored before each administration of this medicine and throughout treatment.

Usual dose:

The dose you are given will be based on your body weight in kilograms.

- The recommended starting dose is 1.0 mg/kg of body weight once every three weeks.
- The highest recommended dose is 1.75 mg/kg of body weight once every three weeks.
- Your doctor will check your progress and may change your dose if needed.

Overdose:

If you think you, or a person you are caring for, have taken too much Reblozyl®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

In case of a missed or delayed injection of Reblozyl®, you will receive a Reblozyl® injection as soon as possible and your dose will continue as prescribed with at least 3 weeks between doses.

What are possible side effects from using Reblozyl®?

These are not all the possible side effects you may have when taking Reblozyl®. If you experience any side effects not listed here, tell your healthcare professional.

Very common side effects (may affect more than 1 in 10 people):

- fatigue (tired or feeling weak, low energy)
- nausea, diarrhea or constipation
- dizziness, headache
- back pain
- cough
- difficulty in breathing or shortness of breath
- infection of the bladder (urinary tract infection)

Common side effects (may affect up to 1 in 10 people):

- muscle pain
- flu-like symptoms
- upper respiratory tract infections
- decreased appetite
- increased blood sugar
- injection site reactions: redness, burning and pain at the site of the injection

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Anemia (decrease in red blood cells): tiredness, fatigue		√	
Basal Cell Carcinoma (certain types of skin cancer): changes in the appearance of your skin or growths on your skin			√
Heart Problems including: Cardiac Failure: shortness of breath, swelling of legs, ankles and feet, rapid heartbeat, cough/wheeze with white/pink phlegm; **Angina:** chest pain/discomfort; **AV block:** chest pain, dizziness/fainting, fatigue, shortness of breath, feeling that heart skips a beat			√

Kidney failure: lack of urine, shortness of breath, confusion, swelling of legs, ankles, feet; drowsiness/fatigue, nausea			√
Pneumonia: fever, chills, fatigue, cough, shortness of breath, coughing up thick yellow or green mucous, fast heartbeat		√	
Progression of MDS to acute myeloid leukemia (AML) (symptoms): fever, bone pain, fatigue, shortness of breath, unusual bleeding, easy bruising.			√
Sepsis (overwhelming infection): fever, chills, very low body temperature, decreased urine, rapid heat beat, rapid breathing, nausea, vomiting, diarrhea			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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product-database.html; the manufacturer's website https://bms.com/ca/en, or by calling 1-866-463-6267.

This leaflet was prepared by Bristol-Myers Squibb Canada, Montreal, Canada H4S 0A4.

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Last Revised: March 26, 2024