Discover the first and only erythroid maturation agent

FDA APPROVED FOR ANEMIA

IN β-THAL

Reblozyl®

(luspatercept-aamt)

for injection 25mg • 75mg

for adults with β-thalassemia requiring regular RBC transfusions[1]

REBLOZYL is indicated for the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions.

REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Thrombosis/Thromboembolism

Thromboembolic events (TEE) were reported in 8/223 (3.6%) REBLOZYL-treated patients. TEEs included deep vein thrombosis, pulmonary embolus, portal vein thrombosis, and ischemic stroke. Patients with known risk factors for thromboembolism (splenectomy or concomitant use of hormone replacement therapy) may be at further increased risk of thromboembolic conditions. Consider thromboprophylaxis in patients at increased risk of TEE. Monitor patients for signs and symptoms of thromboembolic events and institute treatment promptly.

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

REBLOZYL was studied in the pivotal phase 3 BELIEVE trial of 336 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 period who were randomized 2:1 to REBLOZYL (n = 224) or placebo (n = 112). In BELIEVE, REBLOZYL was administered subcutaneously once every 3 weeks as long as a reduction in transfusion requirement was observed or until unacceptable toxicity. Patients were able to receive best supportive care (BSC) as needed, including: RBC transfusions; iron-chelating agents; use of antibiotic, antiviral, and antifungal therapy; and nutritional support. The exclusion criteria for this trial included HbS/β-thalassemia or α-thalassemia; major organ damage (liver, heart, or lung disease, or renal insufficiency); recent deep vein thrombosis or stroke; or recent use of ESA, immunosuppressant, or hydroxyurea therapy. At 48 weeks, patients could cross over to REBLOZYL as part of the long-term follow-up.[1,2]

α-thalassemia, alpha thalassemia; ESA, erythropoiesis-stimulating agent; HbS, hemoglobin S.

SELECT BASELINE CHARACTERISTICS IN THE TOTAL POPULATION OF THE PIVOTAL PHASE 3 BELIEVE TRIAL[1,2]

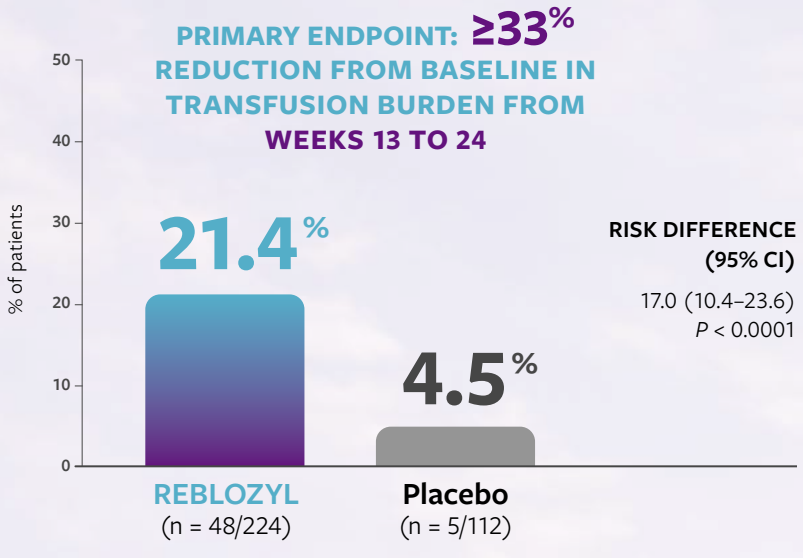
6 units (N = 336) — was the median transfusion burden every 12 weeks[2]

58% (194/336) — of patients previously had a splenectomy[1]

31% (103/336) — of patients had β0/β0 genotype[1]

1441 µg/L REBLOZYL + BSC (n = 220) — was the median serum ferritin level at baseline vs 1301 µg/L for placebo + BSC (n = 111)[1]

REBLOZYL provided substantial clinical benefit by reducing RBC transfusion burden[1]



CI, confidence interval.

4X greater percentage of patients receiving REBLOZYL achieved the primary endpoint vs placebo

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Hypertension

Hypertension was reported in 10.7% (61/571) of REBLOZYL-treated patients. Across clinical studies, the incidence of Grade 3 to 4 hypertension ranged from 1.8% to 8.6%. In patients with beta thalassemia with normal baseline blood pressure, 13 (6.2%) patients developed systolic blood pressure (SBP) ≥130 mm Hg and 33 (16.6%) patients developed diastolic blood pressure (DBP) ≥80 mm Hg. Monitor blood pressure prior to each administration. Manage new or exacerbations of preexisting hypertension using anti-hypertensive agents.

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Key secondary endpoints: Clinically meaningful reductions in transfusion burden[1]

≥50% REDUCTION IN TRANSFUSION BURDEN FROM BASELINE OF AT LEAST 2 UNITS FROM WEEKS 13 TO 24

REBLOZYL (n = 17/224) – VS – Placebo (n = 2/112)

RISK DIFFERENCE (95% CI)
5.8 (1.6–10.1)
P = 0.0303

≥33% REDUCTION IN TRANSFUSION BURDEN FROM BASELINE OF AT LEAST 2 UNITS FROM WEEKS 37 TO 48

REBLOZYL (n = 44/224) – VS – Placebo (n = 4/112)

RISK DIFFERENCE (95% CI)
16.1 (9.8–22.4)
P < 0.0001

≥50% REDUCTION IN TRANSFUSION BURDEN FROM BASELINE OF AT LEAST 2 UNITS FROM WEEKS 37 TO 48

REBLOZYL (n = 23/224) – VS – Placebo (n = 1/112)

RISK DIFFERENCE (95% CI)
9.4 (5.0–13.7)
P = 0.0017

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Embryo-Fetal Toxicity

REBLOZYL may cause fetal harm when administered to a pregnant woman. REBLOZYL caused increased post-implantation loss, decreased litter size, and an increased incidence of skeletal variations in pregnant rat and rabbit studies. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 3 months after the final dose.

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Adverse reactions with REBLOZYL

The majority of adverse reactions with REBLOZYL were Grade 1 or 2 (mild to moderate)[1,3]

ADVERSE DRUG REACTIONS (>5%) IN PATIENTS WITH β-THALASSEMIA RECEIVING REBLOZYL WITH A DIFFERENCE BETWEEN ARMS OF 1% IN BELIEVE TRIAL[1]

Body system/ adverse reaction	REBLOZYL (n = 223)		Placebo (n = 109)	
	All Grades n (%)	Grades ≥3[a] n (%)	All Grades n (%)	Grades ≥3 n (%)
Musculoskeletal and connective tissue disorders				
Bone pain	44 (20)	3 (1)	9 (8)	0 (0)
Arthralgia	43 (19)	0 (0)	13 (12)	0 (0)
Infections and infestation				
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				
Headache	58 (26)	1 (<1)	26 (24)	1 (1)
Dizziness	25 (11)	0 (0)	5 (5)	0 (0)
General disorders and administration site conditions				
Fatigue	30 (14)	0 (0)	14 (13)	0 (0)
Gastrointestinal disorders				
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)
Vascular disorders				
Hypertension[c]	18 (8)	4 (2)	3 (3)	0 (0)
Metabolism and nutrition disorders				
Hyperuricemia	16 (7)	6 (3)	0 (0)	0 (0)
Respiratory, thoracic, and mediastinal disorders				
Cough	32 (14)	0 (0)	12 (11)	0 (0)

- Serious adverse reactions occurred in 3.6% of patients on REBLOZYL[1]
- Serious adverse reactions reported in 1% of patients were cerebrovascular accident and deep vein thrombosis[1]
- A fatal adverse reaction occurred in 1 patient treated with REBLOZYL who died due to an unconfirmed case of acute myeloid leukemia (AML)[1]

[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: Essential hypertension, hypertension, and hypertensive crisis.

REBLOZYL discontinuations and dose modifications due to adverse reactions[1,2]

5.4%
(12/223)

PERMANENT DISCONTINUATIONS DUE TO AN ADVERSE REACTION (GRADE 1–4)

Most frequent adverse reactions requiring permanent discontinuation in patients who received REBLOZYL included arthralgia (1%), back pain (1%), bone pain (<1%), and headache (<1%).

2.7 %
(6/223)

DOSAGE REDUCTIONS DUE TO AN ADVERSE REACTION

Most frequent adverse reactions requiring dosage reduction in >0.5% of patients who received REBLOZYL included hypertension and headache.

15.2%
(34/223)

DOSAGE INTERRUPTIONS DUE TO AN ADVERSE REACTION

Most frequent adverse reactions requiring dosage interruption in >1% of patients who received REBLOZYL included upper respiratory tract infection, ALT increase, and cough.

ALT, alanine aminotransferase.

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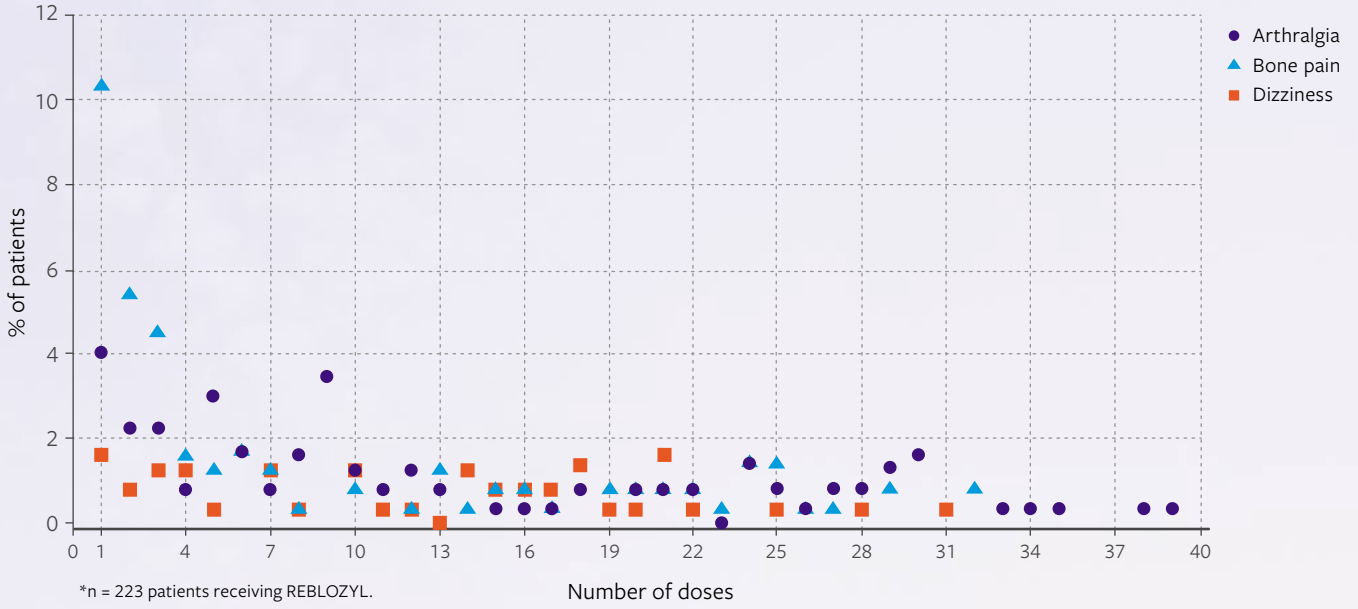
Additional analyses of adverse events (AEs) by REBLOZYL treatment cycle

ANALYSIS 1: PROPORTION OF PATIENTS WITH NEWLY EXPERIENCED AEs

PROPORTION OF PATIENTS WITH NEWLY EXPERIENCED AEs THAT OCCURRED IN ≥10% OF PATIENTS AND HAD A ≥5% HIGHER INCIDENCE IN THE REBLOZYL ARM VS PLACEBO BY TREATMENT CYCLE[2,4*]



*n = 223 patients receiving REBLOZYL.

- This additional analysis examined the AEs that occurred in ≥10% of patients and had a ≥5% higher incidence in the REBLOZYL arm vs placebo. The AEs that met these requirements included bone pain, arthralgia, and dizziness.[2,4] The incidence of adverse reactions in the REBLOZYL and placebo arms can be seen on page 4

ANALYSIS LIMITATIONS

- All patients in both arms were eligible to receive BSC as needed: RBC transfusions; iron-chelating agents; use of antibiotic, antiviral, and antifungal therapy; and nutritional support[1]
- AEs were analyzed in terms of treatment-emergent adverse events (TEAEs), which were defined as any AEs that occurred or worsened on or after the start of study drug through 63 days after the last dose of the study drug. In addition, any AE with an onset date beyond this time frame and that was assessed by the investigator as related to the study drug was considered a TEAE. If a subject experienced multiple TEAEs under the same system organ class (SOC) or preferred term (PT), then the subject was counted only once for that SOC or PT[2]

ADDITIONAL ANALYSIS INFORMATION

- The BELIEVE trial captured all TEAEs, including all AEs independent of attribution of treatment or disease[1,2]
- Patients who crossed over from the placebo arm to the REBLOZYL arm had similar rates of incidence and discontinuation due to these AEs, compared with patients who were initially randomized to the REBLOZYL arm[2]
- "Newly experienced" is defined as first occurrence of indicated TEAE at the given treatment cycle

ANALYSIS 2: OVERALL INCIDENCE AND MEDIAN DURATION OF BONE PAIN, ARTHRALGIA, AND DIZZINESS

The incidence of all-grade adverse reactions occurring in ≥10% of patients and ≥5% higher in REBLOZYL vs placebo were bone pain (20% vs 8%, respectively), arthralgia (19% vs 12%), and dizziness (11% vs 5%)[1]

- **BONE PAIN:** In patients receiving REBLOZYL, Grade 1/2 bone pain occurred in 18% (41/223) of patients and Grade ≥3 bone pain occurred in 1% (3/223) of patients. The median duration of the TEAE bone pain was 22.0 days (min, max: 1, 413; n = 45/223)[1,2]
- **ARTHRALGIA:** In patients receiving REBLOZYL, Grade 1/2 arthralgia occurred in 19% (43/223) of patients; there were no Grade ≥3 events. The median duration of the TEAE arthralgia was 15.0 days (min, max: 1, 524; n = 47/223)[1,2]
- **DIZZINESS:** In patients receiving REBLOZYL, Grade 1/2 dizziness occurred in 11% (25/223) of patients; there were no Grade ≥3 events. The median duration of the TEAE dizziness was 6.0 days (min, max: 1, 387; n = 27/223)[1,2]

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Treatment with REBLOZYL should continue as long as patients experience clinical benefit[1]

ASSESS AND REVIEW PATIENTS' Hgb AND TRANSFUSION RECORD PRIOR TO EACH ADMINISTRATION[1]

- If an RBC transfusion occurred prior to dosing, use the pretransfusion Hgb for dose evaluation[1]
- If a patient experiences a dose delay due to Hgb increase, measure Hgb every week[2]

REBLOZYL DOSE TITRATION FOR RESPONSE[1]

	REBLOZYL Dosing recommendation*
Starting dose	**1 mg/kg every 3 weeks**
Dose increases for insufficient response at initiation of treatment	
No reduction in RBC transfusion burden after at least 2 consecutive doses (6 weeks) at the **1 mg/kg** starting dose	• Increase the 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 treatment
Dose modifications for predose Hgb levels or rapid Hgb rise	
Predose Hgb is **≥11.5 g/dL** in the absence of transfusions	• Interrupt treatment • Restart when the Hgb is no more than **11 g/dL**
Increase in Hgb **>2 g/dL** within 3 weeks in the absence of transfusions and	
• current dose is **1.25 mg/kg**	• Reduce dose to **1 mg/kg**
• current dose is **1 mg/kg**	• Reduce dose to **0.8 mg/kg**
• current dose is **0.8 mg/kg**	• Reduce dose to **0.6 mg/kg**
• current dose is **0.6 mg/kg**	• Discontinue treatment

***Do not increase the dose if the patient is experiencing an adverse reaction as described in the Dosing Modifications for Adverse Reactions table.**

At least 5 doses (15 weeks of treatment) unless unacceptable toxicity occurs at any time

DOSE INCREASES IN THE EVENT OF LOSS OF RESPONSE[1]

- A dose increase to 1.25 mg/kg may occur at any time during treatment after patients have received at least 2 consecutive doses of 1 mg/kg
- **Do not increase the dose beyond the maximum dose of 1.25 mg/kg**

DISCONTINUE TREATMENT IF NO REDUCTION IN TRANSFUSION BURDEN IS OBSERVED[1]

- Discontinue REBLOZYL if a patient does not experience a decrease in transfusion burden after 3 doses (9 weeks of treatment) at the maximum dose level or if unacceptable toxicity occurs at any time

IF A PLANNED ADMINISTRATION OF REBLOZYL IS DELAYED OR MISSED[1]

- Administer REBLOZYL as soon as possible and continue dosing as prescribed, with at least 3 weeks between doses

IMPORTANT SAFETY INFORMATION (CONT'D)

ADVERSE REACTIONS

Serious adverse reactions occurred in 3.6% of patients on REBLOZYL. Serious adverse reactions occurring in 1% of patients included cerebrovascular accident and deep vein thrombosis. A fatal adverse reaction occurred in 1 patient treated with REBLOZYL who died due to an unconfirmed case of acute myeloid leukemia (AML).

Most common adverse reactions (at least 10% for REBLOZYL and 1% more than placebo) were headache (26% vs 24%), bone pain (20% vs 8%), arthralgia (19% vs 12%), fatigue (14% vs 13%), cough (14% vs 11%), abdominal pain (14% vs 12%), diarrhea (12% vs 10%) and dizziness (11% vs 5%).

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Dose modifications with REBLOZYL

REBLOZYL DOSING MODIFICATIONS FOR ADVERSE REACTIONS[1]

	REBLOZYL Dosing recommendation*
Grade 3 or 4 hypersensitivity reactions	• Discontinue treatment
Other Grade 3 or 4 adverse reactions	• Interrupt treatment • Restart when the adverse reaction resolves to no more than Grade 1

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, and Grade 4 is life-threatening.

DOSING EXPERIENCE IN THE BELIEVE TRIAL[1,2]

54%
(n = 120/223)
of patients in the REBLOZYL arm received the **maximum dose of 1 mg/kg**[1,2]

46%
(n = 103/223)
of patients in the REBLOZYL arm had their **dose increased to 1.25 mg/kg**[1,2]

147 DAYS
was the **median time to first titration** in the REBLOZYL arm (min, max: 57, 575 days)[2]

94%
of patients receiving REBLOZYL were **exposed for 6 months or longer**[1]

72%
of patients receiving REBLOZYL were **exposed for greater than 1 year**[1]

63.3 WEEKS
was the **median duration of treatment** with REBLOZYL (similar to placebo group, 62.1 weeks)[1]

IMPORTANT SAFETY INFORMATION (CONT'D)

LACTATION

It is not known whether REBLOZYL is excreted into human milk or absorbed systemically after ingestion by a nursing infant. REBLOZYL was detected in milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because many drugs are excreted in human milk, and because of the unknown effects of REBLOZYL in infants, a decision should be made whether to discontinue nursing or to discontinue treatment. Because of the potential for serious adverse reactions in the breastfed child, breastfeeding is not recommended during treatment and for 3 months after the last dose.

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References: 1. REBLOZYL [Prescribing Information]. Summit, NJ: Celgene Corporation; 2020. **2.** Data on file, Celgene Corporation. Summit, New Jersey. **3.** National Cancer Institute; US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) v4.03. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Revised June 14, 2010. Accessed December 9, 2019. **4.** Viprakasit V, Taher AT, Hermine O, et al. Evaluating luspatercept responders in the phase 3, randomized, double-blind, placebo-controlled BELIEVE trial of luspatercept in adult β-thalassemia patients who require regular red blood cell transfusions. Poster presented at: 61st Annual Meeting of the American Society of Hematology (ASH); December 7-10, 2019; Orlando, FL.

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01/21 2007-US-2100003