NOW APPROVED

Reblozyl®

(luspatercept-aamt)

for injection 25mg • 75mg

The first and only erythroid maturation agent (EMA) for anemia in adults with β-thalassemia requiring regular red blood cell 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.

November 8, 2019

Celgene Corporation and Acceleron Pharma Inc. are pleased to announce that REBLOZYL has received **FDA approval** for anemia in adult patients with β-thalassemia requiring regular RBC transfusions. REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

REBLOZYL access and reimbursement

AUTHORIZED DISTRIBUTORS

REBLOZYL can only be purchased through authorized distributors for administration in physician offices, hospital outpatient facilities, institutions, Veterans Affairs, and the Department of Defense. The following distributors are authorized to sell REBLOZYL and are able to service qualified accounts.

Authorized distributor network		
Community practices	**Phone**	**Fax**
Cardinal Specialty	1-877-453-3972	
McKesson Specialty Health	1-800-482-6700	1-800-289-9285
Oncology Supply	1-800-633-7555	1-800-248-8205
Institutions/hospital outpatient facilities		
AmerisourceBergen	1-844-222-2273	1-888-292-9774
ASD Healthcare	1-800-746-6273	1-800-547-9413
Cardinal Specialty	1-866-677-4844	
McKesson Pharma	1-855-625-6285	1-800-599-9893
Puerto Rico hospitals and clinics		
Cardinal Health P. R.	1-787-625-4200	
Cesar Castillo, Inc.	1-787-641-5242 (Hospitals) 1-787-641-5082 (Specialty pharmacy)	1-787-999-1614

NDC AND HOW SUPPLIED

NATIONAL DRUG CODES (NDC) AND PACKAGING INFORMATION		
11-Digit NDC	**Product/Strength**	**Package/Description**
59572-0711-01	**REBLOZYL injection 25 mg**	25 mg lyophilized powder for solution for injection in a single-dose vial for reconstitution
59572-0775-01	**REBLOZYL injection 75 mg**	75 mg lyophilized powder for solution for injection in a single-dose vial for reconstitution

The red zero converts the 10-digit NDC to the 11-digit NDC. Payer requirements regarding the use of NDCs may vary. Electronic data exchange generally requires use of the 11-digit NDC.

BILLING CODES FOR REBLOZYL

HCPCS Codes	
J3490	Not otherwise classified drugs
J3590	Not otherwise classified biologics
J9999	Not otherwise classified anti-neoplastic drugs
C9399	Unclassified or biologicals (hospital outpatient use only)
CPT® Code	
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
ICD-10-CM Diagnosis Code	
D56.1	• Beta thalassemia major • Cooley's anemia • Homozygous beta thalassemia • Severe beta thalassemia • Thalassemia intermedia • Thalassemia major
D56.5	• Hemoglobin E-beta thalassemia

CPT, Current Procedural Terminology; HCPCS, Healthcare Common Procedure Coding System; ICD-10 CM, *International Classification of Diseases*, Tenth Revision, Clinical Modification.

Depending on payer preferences for billing and coding, the required miscellaneous J code for claim submission may vary. Therefore, the provider will want to confirm preference with payer prior to submitting.

Note the use of a miscellaneous C code (C9399) for when REBLOZYL is used in a hospital infusion center.

The information contained herein is not intended to provide specific coding and reimbursement advice for any specific patient or situation. You should check with your coding specialist to ensure appropriate submissions.

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Please see Important Safety Information on page 9 and full Prescribing Information for REBLOZYL.

Study design[1]

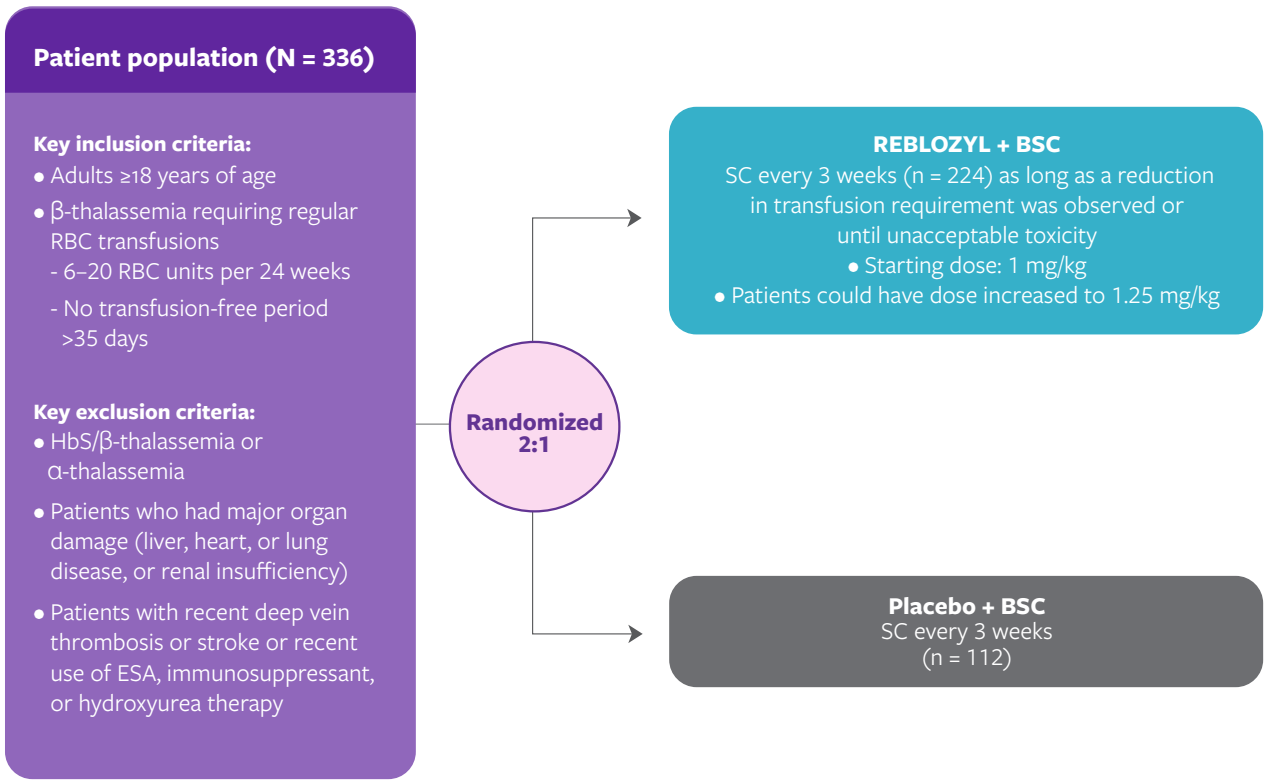
PIVOTAL PHASE 3 BELIEVE TRIAL DESIGN

The efficacy and safety of REBLOZYL were evaluated in the BELIEVE trial, a phase 3, multicenter, randomized, double-blind, placebo-controlled trial in adult patients with β-thalassemia who require regular RBC transfusions.

A total of 336 patients with β-thalassemia who require RBC transfusions (6–20 RBC units per 24 weeks) with no transfusion-free period >35 days received REBLOZYL (n = 224) or placebo (n = 112) subcutaneously once every 3 weeks as long as a reduction in transfusion requirement was observed or until unacceptable toxicity occurred. All patients were eligible to receive best supportive care (BSC).

The efficacy of REBLOZYL was established based upon the proportion of patients achieving RBC transfusion burden reduction (≥33% reduction from baseline) with a reduction of at least 2 units from week 13 to week 24.

TRIAL DESIGN



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

All patients in both arms of the trial were eligible to receive BSC as needed, including:

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

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Baseline characteristics[1]

BASELINE DISEASE CHARACTERISTICS OF β-THALASSEMIA IN BELIEVE

Disease characteristics	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, units/12 weeks		
Median (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		
N	220	111
Median (min, max)	1441.25 (88, 6400)	1301.50 (136, 6400)
Splenectomy, n (%)		
Yes	129 (57.6)	65 (58)
No	95 (42.4)	47 (42)
Age patient started regular transfusions, years		
N	169	85
Median (min, max)	2 (0, 52)	2 (0, 51)

[a]Missing category includes patients in the population who had no result for the parameter listed.

HbE, hemoglobin E.

PATIENT POPULATION CHARACTERISTICS

- The median age was 30 years (range, 18–66)
- 42% of patients were male
- 54.2% of patients were white, 34.8% were Asian, 0.3% were black or African American, 7.7% reported their race as "other," and 3% were not collected

Efficacy in β-thalassemia[1]

EFFICACY RESULTS IN β-THALASSEMIA—BELIEVE

Endpoint	REBLOZYL (n = 224)	Placebo (n = 112)	Risk difference (95% CI)	*P* value
≥33% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks				
Primary endpoint: Weeks 13–24	48 (21.4)	5 (4.5)	17.0 (10.4–23.6)	<0.0001
Weeks 37–48	44 (19.6)	4 (3.6)	16.1 (9.8–22.4)	<0.0001
≥50% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks				
Weeks 13–24	17 (7.6)	2 (1.8)	5.8 (1.6–10.1)	0.0303
Weeks 37–48	23 (10.3)	1 (0.9)	9.4 (5–13.7)	0.0017

Warnings and precautions[1]

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.

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.

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 last dose.

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Adverse reactions in the phase 3 BELIEVE trial[1]

- The data in the Warnings and Precautions reflect exposure to REBLOZYL as a single agent administered across a range of doses (0.125 mg/kg–1.75 mg/kg) in 571 patients in 4 trials
- Overall, 53% of patients in the BELIEVE trial had their dose increased to 1.25 mg/kg (46% REBLOZYL, n = 223; 66% placebo, n = 109)
- The median duration of treatment was similar between the REBLOZYL and placebo arms (63.3 weeks vs 62.1 weeks, respectively)
- Per protocol, patients in both the REBLOZYL and placebo arms were to remain on therapy for at least 48 weeks in the double-blind phase of the trial
- Among patients receiving REBLOZYL, 94% were exposed for 6 months or longer and 72% were exposed for greater than 1 year
- Serious adverse reactions occurred in 3.6% of patients on REBLOZYL. Serious adverse reactions reported in 1% of patients were 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)
- The most common adverse reactions (at least 10% for REBLOZYL and 1% more than placebo) were headache (26%), bone pain (20%), arthralgia (19%), fatigue (14%), cough (14%), abdominal pain (14%), diarrhea (12%), and dizziness (11%)
- Permanent discontinuation due to an adverse reaction (Grades 1–4) occurred in 5.4% of patients who received REBLOZYL
  - Most frequent adverse reactions requiring permanent discontinuation in patients who received REBLOZYL included arthralgia (1%), back pain (1%), bone pain (<1%), and headache (<1%)
- Dosage reductions due to an adverse reaction occurred in 2.7% of patients who received REBLOZYL
  - Most frequent adverse reactions requiring dosage reduction in >0.5% of patients who received REBLOZYL included hypertension and headache
- Dosage interruptions due to an adverse reaction occurred in 15.2% of patients who received REBLOZYL
  - Most frequent adverse reactions requiring dosage interruption in >1% of patients who received REBLOZYL included upper respiratory tract infection, ALT increase, and cough

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

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)

[a]Limited to Grade 3 reactions with the exception of 4 events of Grade 4 hyperuricemia.

ALT, alanine aminotransferase.

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ADVERSE DRUG REACTIONS (>5%) IN PATIENTS RECEIVING REBLOZYL WITH A DIFFERENCE BETWEEN ARMS OF 1% IN THE BELIEVE TRIAL (CONT'D)[1]

Adverse reaction	REBLOZYL (n = 223)		Placebo (n = 109)	
	All Grades n (%)	Grades ≥3[a] n (%)	All Grades n (%)	Grades ≥3 n (%)
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)

[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.

LIVER FUNCTION LABORATORY ABNORMALITIES IN THE BELIEVE TRIAL[1]

	REBLOZYL (n = 223) n (%)	Placebo (n = 109) n (%)
ALT ≥3 × ULN	26 (12)	13 (12)
AST ≥3 × ULN	25 (11)	5 (5)
ALP ≥2 × ULN	17 (8)	1 (<1)
Total bilirubin ≥2 × ULN	143 (64)	51 (47)
Direct bilirubin ≥2 × ULN	13 (6)	4 (4)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

REBLOZYL dosage and administration[1]

RECOMMENDED STARTING DOSAGE

- The recommended starting dose of REBLOZYL is 1 mg/kg once every 3 weeks by SC injection
- Assess and review Hgb results prior to each administration. If an RBC transfusion occurred prior to dosing, the pretransfusion Hgb level must be considered for dosing purposes
- If the pre-dose Hgb is ≥11.5 g/dL and the Hgb level is not influenced by recent transfusion, delay dosing until Hgb is ≤11 g/dL
- If a planned administration is delayed or missed, administer REBLOZYL as soon as possible and continue dosing as prescribed, with at least 3 weeks between doses

DOSE INCREASES DURING TREATMENT

- **Increase REBLOZYL dose to 1.25 mg/kg** if patient does not achieve a reduction in RBC transfusion burden after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose

- **Do not increase the dose beyond the maximum dose of 1.25 mg/kg**

CONTINUATION AND DISCONTINUATION RECOMMENDATIONS[1]

- If a patient experienced a response followed by a lack of or lost response to REBLOZYL, initiate a search for causative factors (eg, a bleeding event)
- If typical causes for a lack or loss of hematologic response are excluded, follow dosing recommendations for management of patients with an insufficient response to REBLOZYL therapy
- Discontinue REBLOZYL if a patient does not experience a decrease in transfusion burden after 9 weeks of treatment (administration of 3 doses) at the maximum dose level or if unacceptable toxicity occurs at any time

Hgb, hemoglobin; RBC, red blood cell; SC, subcutaneous.

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Thrombosis/Thromboembolism

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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.

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 last dose.

ADVERSE REACTIONS

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%).

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.

Please see full Prescribing Information for REBLOZYL.

Reference: 1. REBLOZYL [Prescribing Information]. Summit, NJ: Celgene Corporation; 2019.

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