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RESEARCH**

APPLICATION NUMBER:

761136Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use REBLOZYL safely and effectively. See full prescribing information for REBLOZYL.

REBLOZYL® (luspatercept-aamt) for injection, for subcutaneous use
Initial U.S. Approval: 2019

INDICATIONS AND USAGE

REBLOZYL is an erythroid maturation agent indicated for the treatment of anemia in:

- Adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions (1.1).

DOSAGE AND ADMINISTRATION

- The recommended starting dose is 1 mg/kg once every 3 weeks by subcutaneous injection (2.1).
- Review hemoglobin (Hgb) results prior to each administration (2.1).
- See full prescribing information for preparation and administration instructions (2.4).

DOSAGE FORMS AND STRENGTHS

- For injection: 25 mg lyophilized powder in a single-dose vial for reconstitution (3).
- For injection: 75 mg lyophilized powder in a single-dose vial for reconstitution (3).

CONTRAINDICATIONS

None (4).

WARNINGS AND PRECAUTIONS

- Thrombosis/Thromboembolism: Increased risk in patients with beta thalassemia. Monitor patients for signs and symptoms of thromboembolic events and institute treatment promptly (5.1).
- Hypertension: Monitor blood pressure (BP) during treatment. Initiate anti-hypertensive treatment if necessary (5.2).
- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception (5.3, 8.1, 8.3).

ADVERSE REACTIONS

The most common adverse reactions (>10%) in patients with beta thalassemia were headache, bone pain, arthralgia, fatigue, cough, abdominal pain, diarrhea, and dizziness (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Beta Thalassemia

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

Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Starting Dosage in Beta Thalassemia

The recommended starting dose of REBLOZYL is 1 mg/kg once every 3 weeks by subcutaneous injection.

If a planned administration of REBLOZYL is delayed or missed, administer REBLOZYL as soon as possible and continue dosing as prescribed, with at least 3 weeks between doses.

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

If the pre-dose Hgb is greater than or equal to 11.5 g/dL and the Hgb level is not influenced by recent transfusion, delay dosing until the Hgb is less than or equal to 11 g/dL.

2.2 Dose Increases during Treatment

Beta Thalassemia

If a 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, increase the REBLOZYL dose to 1.25 mg/kg.

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

2.3 Continuation and Discontinuation Recommendations

If a patient experienced a response followed by a lack of or lost response to REBLOZYL, initiate a search for causative factors (e.g., 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 [*see Dosage and Administration (2.2)*].

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 [see *Dosage and Administration* (2.2)].

2.4 Preparation and Administration

REBLOZYL should be reconstituted and administered by a healthcare professional.

Reconstitute REBLOZYL with Sterile Water for Injection, USP only.

Table 1: Reconstitution Volumes

Vial Size	Amount of Sterile Water for Injection, USP required for reconstitution	Final Concentration	Deliverable Volume
25 mg vial	0.68 mL	25 mg/0.5 mL	0.5 mL
75 mg vial	1.6 mL	75 mg/1.5 mL (50 mg/mL)	1.5 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.

Reconstitution Instructions

1. Reconstitute with Sterile Water for Injection, USP using volumes described in Table 1 (Reconstitution volumes) with the stream directed onto 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 injections.
3. Gently swirl the vial in a circular motion for 30 seconds. Stop swirling and let the vial sit in an 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 times to ensure complete reconstitution of material on the sides of the vial.
7. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.
REBLOZYL is a colorless 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 (68°F to 77°F) in the original vial for up to 8 hours. Discard if not used within 8 hours of reconstitution.
- Alternatively, store refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours in the original vial. Remove from refrigerated condition 15-30 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.

Instructions for Subcutaneous Administration

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

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.

3 DOSAGE FORMS AND STRENGTHS

- For injection: 25 mg white to off-white lyophilized powder in a single-dose vial for reconstitution.
- For injection: 75 mg white to off-white lyophilized powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombosis/Thromboembolism

In adult patients with beta thalassemia, thromboembolic events (TEE) were reported in 8/223 (3.6%) REBLOZYL-treated patients. Reported TEEs included deep vein thromboses, pulmonary embolus, portal vein thrombosis, and ischemic strokes. Patients with known risk factors for thromboembolism, e.g. splenectomy or concomitant use of hormone replacement therapy, may be at further increased risk of thromboembolic conditions. Consider thromboprophylaxis in

patients with beta thalassemia at increased risk of TEE. Monitor patients receiving REBLOZYL for signs and symptoms of thromboembolic events and institute treatment promptly.

5.2 Hypertension

Hypertension was reported in 10.7% (61/571) of REBLOZYL-treated patients. Across clinical studies, the incidence of grade 3-4 hypertension ranged from 1.8% to 8.6%. In adult 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-onset hypertension or exacerbations of preexisting hypertension using anti-hypertensive agents.

5.3 Embryo-Fetal Toxicity

Based on findings from animal reproductive studies, REBLOZYL may cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of luspaterecept-aamt to pregnant rats and rabbits during organogenesis resulted in adverse developmental outcomes including increased embryo-fetal mortality, alterations to growth, and structural abnormalities at exposures (based on area under the curve [AUC]) above those occurring at the maximum recommended human dose (MRHD) of 1.25 mg/kg.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with REBLOZYL and for at least 3 months after the final dose [see *Use in Specific Populations* (8.1, 8.3)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Thrombosis/Thromboembolism [see *Warnings and Precautions* (5.1)]
- Hypertension [see *Warnings and Precautions* (5.2)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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 to 1.75 mg/kg) in 571 patients in 4 trials.

Beta Thalassemia

The safety of REBLOZYL in patients with beta thalassemia was evaluated in the BELIEVE trial [see *Clinical Studies* (14.1)]. Key eligibility criteria included adult patients with beta thalassemia (with exception of S/β-thalassemia) without major organ damage or recent DVT stroke and platelet counts less than or equal to $1000 \times 10^9/L$.

Patients received a starting dose of REBLOZYL 1 mg/kg subcutaneous injection every 3 weeks. Overall, 53% of patients had their dose increased to 1.25 mg/kg (46% REBLOZYL, n = 223) or

placebo (66%, 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 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 one year.

The median age of patients who received REBLOZYL was 30 years (range: 18, 66); 59% female; 54% White and 36% Asian.

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 one patient treated with REBLOZYL who died due to an unconfirmed case of AML (M6).

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.

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%).

Table 2 summarizes the adverse reactions in BELIEVE.

Table 2: Adverse Drug Reactions (>5%) in Patients Receiving REBLOZYL with a Difference Between Arms of 1% in BELIEVE Trial

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)

Body System Adverse Reaction	REBLOZYL (N=223)		Placebo (N=109)	
	All Grades n (%)	Grades ≥3 ^a n (%)	All Grades n (%)	Grades ≥3 n (%)
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)

^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.

Clinically relevant adverse reactions in <5% of patients include vertigo/vertigo positional, syncope/presyncope, injection site reactions and hypersensitivity.

Liver function abnormalities in the BELIEVE trial are shown in Table 3.

Table 3: Liver Function Laboratory Abnormalities in the BELIEVE Trial

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

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

6.2 Immunogenicity

As with all therapeutic proteins, there is 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 to other products may be misleading.

Of 284 patients with beta thalassemia who were treated with REBLOZYL and evaluable for the presence of anti-luspatercept-aamt antibodies, 4 patients (1.4%) tested positive for treatment-emergent anti-luspatercept-aamt antibodies, including 2 patients (0.7%) who had neutralizing antibodies.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal reproduction studies, REBLOZYL may cause fetal harm when administered to a pregnant woman. There are no available data on REBLOZYL use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal

or fetal outcomes. In animal reproduction studies, administration of luspatercept-aamt to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes including embryo-fetal mortality, alterations to growth, and structural abnormalities at exposures (based on area under the curve [AUC]) above those occurring at the maximum recommended human dose (MRHD) (*see Data*). Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In embryo-fetal development studies, luspatercept-aamt was administered subcutaneously at 5, 15, or 30 mg/kg on gestation days 3 and 10 (rats) or 5, 20, or 40 mg/kg on gestation days 4 and 11 (rabbits). Effects in both species included reductions in numbers of live fetuses and fetal body weights, and increases in resorptions, post-implantation losses, and skeletal variations (such as asymmetric sternal centra in rats and angulated hyoid in rabbits). Effects were observed at exposures (based on AUC) approximately 13-times (rats) and 18-times (rabbits) the MRHD of 1.25 mg/kg.

In a pre- and postnatal development study, pregnant rats were administered luspatercept-aamt subcutaneously at 3, 10, or 30 mg/kg once every 2 weeks during organogenesis and through weaning, gestation day 6 through postnatal day 20. At all dose levels lower F₁ pup body weights and adverse kidney findings (such as membranoproliferative glomerulonephritis, tubular atrophy/hypoplasia, and vessel ectasia occasionally associated with hemorrhage) were observed. These effects were observed at exposures (based on AUC) approximately 1.6-times the MRHD of 1.25 mg/kg.

8.2 Lactation

Risk Summary

Luspatercept-aamt 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. There are no data on the presence of REBLOZYL in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with REBLOZYL, and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential before starting REBLOZYL treatment.

Contraception

Females

REBLOZYL may cause embryo-fetal harm when administered to pregnant women [see *Use in Specific Populations (8.1)*]. Advise female patients of reproductive potential to use effective contraception during treatment with REBLOZYL and for at least 3 months after the last dose.

Infertility

Females

Based on findings in animals, REBLOZYL may impair female fertility [see *Nonclinical Toxicology (13.1)*]. Adverse effects on fertility in female rats were reversible after a 14-week recovery period.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Based on findings in juvenile animals, REBLOZYL is not recommended for use in pediatric patients [see *Non-Clinical Toxicology (13.1)*].

8.5 Geriatric Use

Clinical studies of REBLOZYL in beta thalassemia did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Luspatercept-aamt is an erythroid maturation agent. Luspatercept-aamt is a receptor fusion protein consisting of a modified extracellular domain of the human activin receptor type IIB linked to a human IgG1 Fc domain with a calculated molecular mass of approximately 76 kD. Luspatercept is produced in Chinese hamster ovary cells by recombinant DNA technology.

REBLOZYL (luspatercept-aamt) for injection is a sterile, preservative-free, white to off-white, lyophilized powder in single-dose vials for subcutaneous use after reconstitution.

Each 25 mg single-dose vial provides nominal 25 mg of luspatercept-aamt and citric acid monohydrate (0.085 mg), polysorbate 80 (0.10 mg), sucrose (45.0 mg), and tri-sodium citrate dihydrate (1.35 mg) at pH 6.5. After reconstitution with 0.68 mL Sterile Water for Injection USP, the resulting concentration is 25 mg/0.5 mL of luspatercept-aamt and the deliverable volume is 0.5 mL.

Each 75 mg single-dose vial provides nominal 75 mg of luspatercept-aamt and citric acid monohydrate (0.254 mg), polysorbate 80 (0.30 mg), sucrose (135 mg), and tri-sodium citrate dihydrate (4.06 mg) at pH 6.5. After reconstitution with 1.6 mL Sterile Water for Injection USP, the resulting concentration is 75 mg/1.5 mL (50 mg/mL) of luspatercept-aamt and the deliverable volume is 1.5 mL.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Increases in Hemoglobin in Patients with Low RBC Transfusion Burden

In patients having received < 4 units of RBC transfusion within 8 weeks prior to study, hemoglobin increased within 7 days of initiating REBLOZYL and correlated with the time to luspatercept-aamt maximum serum concentration ($C_{\max}$). The greatest Hgb increase occurred after the first dose (0.75 g/dL on average at a dose of 0.6 to 1.25 times the recommended starting dose), with additional smaller increases observed after subsequent doses. Hemoglobin levels returned to baseline approximately 8 weeks from the last dose following administration of luspatercept-aamt at a dose of 0.6 to 1.25 times the recommended starting dosage.

Increasing luspatercept-aamt serum exposure (AUC) was associated with greater Hgb increase in patients with beta thalassemia (a mean increase of 0.7 g/dL in Hgb for 100-unit increase in AUC after the first dose).

12.3 Pharmacokinetics

Luspatercept-aamt exhibited linear pharmacokinetics (PK) over the dose range of 0.2 to 1.25 mg/kg (0.2 to 1.25 times the recommended starting dosage) in patients with beta thalassemia. The mean (% coefficient of variation [%CV]) steady-state AUC was 126 (35.9%) day $\cdot\mu$ g/mL at 1 mg/kg and 157 (35.9%) day $\cdot\mu$ g/mL at 1.25 mg/kg in patients with beta thalassemia. The mean (%CV) steady-state $C_{\max}$ was 8.17 (29.9%) μ g/mL at 1 mg/kg and 10.2 (29.9%) μ g/mL at 1.25 mg/kg in patients with beta thalassemia. Luspatercept-aamt serum concentration reached steady state after 3 doses when administered every 3 weeks. The accumulation ratio of luspatercept-aamt was approximately 1.5.

Absorption

The median (range) time to maximum concentration ($T_{\max}$) of luspatercept-aamt was observed at approximately 7 [6 to 8] days post-dose in adult healthy volunteers and patients with beta thalassemia. The absorption of luspatercept-aamt was not significantly affected by the subcutaneous injection sites (upper arm, thigh, or abdomen).

Distribution

The mean (%CV) apparent volume of distribution (V_d/F) of luspatercept-aamt was 7.1 (26.7%) L for patients with beta thalassemia.

Elimination

The mean (%CV) half-life ($t_{1/2}$) of luspatercept-aamt was approximately 11 (25.7%) days and the mean (%CV) apparent total clearance (CL/F) was 0.44 (38.5%) L/day in patients with beta thalassemia.

Metabolism

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

Specific Populations

No clinically significant differences in the luspatercept-aamt PK was observed based on age (18 to 66 years), sex, race/ethnicity (Asian, White), mild to severe hepatic impairment (total bilirubin $\leq$ upper limit of normal [ULN] and aspartate aminotransaminase [AST] or alanine transaminase [ALT] $>$ ULN, or total bilirubin $>$ ULN and any AST or ALT), mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73 m²), baseline albumin (30 to 56 g/L), baseline serum erythropoietin (2.4 to 972 U/L), red blood cell (RBC) transfusion burden (0 to 34 units/24 weeks), beta thalassemia genotype (β^0/β^0 vs. non- β^0/β^0) and splenectomy. The effect of AST or ALT $>3 \times$ ULN and the effect of severe renal impairment (eGFR <29 mL/min/1.73 m²) on luspatercept-aamt PK is unknown.

Body Weight

The apparent CL/F and V_d/F of luspatercept-aamt increased with increasing body weight (34 to 97 kg).

Drug Interaction Studies

Effect of Iron-chelating Agents on Luspatercept-aamt

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity studies have been conducted with luspatercept-aamt.

In a repeat-dose toxicity study, juvenile rats were administered luspatercept-aamt 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 dose (MRHD) of 1.25 mg/kg.

In a combined male and female fertility and early embryonic development study in rats, luspatercept-aamt was administered subcutaneously to animals at doses of 1 to 15 mg/kg. There were significant reductions in the average numbers of corpora lutea, implantations, and viable embryos in luspatercept-aamt-treated females. Effects on female fertility were observed at the highest dose with exposures (based on AUC) approximately 7 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.

14 CLINICAL STUDIES

14.1 Beta Thalassemia

The efficacy of REBLOZYL was evaluated in adult patients with beta thalassemia in the BELIEVE trial (NCT02604433).

BELIEVE is a multicenter, randomized, double-blind, placebo-controlled trial in which (n=336) patients with beta thalassemia requiring regular red blood cell transfusions (6-20 RBC units per 24 weeks) with no transfusion-free period greater than 35 days during that period 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. 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 BELIEVE trial excluded patients with hemoglobin S/ β -thalassemia or alpha-thalassemia or who had major organ damage (liver disease, heart disease, lung disease, renal insufficiency). Patients with recent deep vein thrombosis or stroke or recent use of ESA, 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% white, 34.8% Asian, and 0.3% Black or African American. The percent of patients reporting their race as “other” was 7.7%, and race was not collected or reported for 3% of patients.

Table 4 summarizes the baseline disease-related characteristics in the BELIEVE study.

Table 4: Baseline Disease Characteristics of Beta Thalassemia in BELIEVE

Disease Characteristic	REBLOZYL (N=224)	Placebo (N=112)
Beta thalassemia diagnosis, n (%)		
Beta-thalassemia	174 (77.7)	83 (74.1)
HbE/beta thalassemia	31 (13.8)	21 (18.8)
Beta thalassemia combined with alpha-thalassemia	18 (8)	8 (7.1)
Missing ^a	1 (0.4)	0
Baseline transfusion burden 12 weeks prior to randomization		
Median (min, max) (Units/12 weeks)	6.12 (3, 14)	6.27 (3, 12)

Disease Characteristic	REBLOZYL (N=224)	Placebo (N=112)
Beta 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)

BSC=best supportive care; ECOG=Eastern Cooperative Oncology Group; Hb=hemoglobin; HbE=hemoglobin E; ITT=intent to treat; SD=standard deviation.

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

The efficacy of REBLOZYL in adult patients with beta thalassemia was established based upon the proportion of patients achieving RBC transfusion burden reduction ($\geq 33\%$ reduction from baseline) with a reduction of at least 2 units from Week 13 to Week 24.

Efficacy results are shown in Table 5.

Table 5: Efficacy Results in Beta Thalassemia - BELIEVE

Endpoint	REBLOZYL (N=224)	Placebo (N=112)	Risk Difference (95% CI)	p-value
$\geq 33\%$ Reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks				
Primary endpoint – Week 13 to Week 24	48 (21.4)	5 (4.5)	17.0 (10.4, 23.6)	<0.0001

Endpoint	REBLOZYL (N=224)	Placebo (N=112)	Risk Difference (95% CI)	p-value
Week 37 to Week 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				
Week 13 to Week 24	17 (7.6)	2 (1.8)	5.8 (1.6, 10.1)	0.0303
Week 37 to Week 48	23 (10.3)	1 (0.9)	9.4 (5, 13.7)	0.0017

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

REBLOZYL (luspatercept-aamt) for injection is a white to off-white lyophilized powder supplied in a single-dose vial. Each carton contains one vial.

REBLOZYL 25 mg/vial (NDC 59572-711-01)

REBLOZYL 75 mg/vial (NDC 59572-775-01)

16.2 Storage

Store vials refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze.

17 PATIENT COUNSELING INFORMATION

Discuss the following with patients prior to and during treatment with REBLOZYL.

Thromboembolic Events

Advise beta thalassemia patients of the potential risk of thromboembolic events. Review known risk factors for developing thromboembolic events and advise patients to reduce modifiable risk factors (e.g., smoking, use of oral contraceptives) [see *Warnings and Precautions* (5.1)].

Effects on Blood Pressure

Caution patients that REBLOZYL may cause an increase in blood pressure [see *Warnings and Precautions* (5.2)].

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving REBLOZYL and for at least 3 months after the final dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with REBLOZYL [*see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)*].

Lactation

Advise females not to breastfeed during treatment with REBLOZYL and for 3 months after the final dose [*see Use in Specific Populations (8.2)*].

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U.S. License No. 2114

Jointly Marketed by:
Acceleron Pharma, Inc.
Cambridge, MA 02139

REBLOZYL[®] is a registered trademark of Celgene Corporation.

Patent: www.celgene.com/therapies

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/s/

RICHARD PAZDUR
11/08/2019 12:00:00 AM