REBLOZYL® (luspatercept-aamt) for injection, for subcutaneous use

DOSAGE AND ADMINISTRATION

• The recommended starting dose is 1 mg/kg once every 3 weeks by subcutaneous injection (2.1, 2.2).
• Review hemoglobin (Hgb) results prior to each administration (2.1, 2.2).
• See full prescribing information for preparation and administration instructions (2.3).

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).
- Anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions (1.2).
- Anemia failing an erythropoiesis stimulating agent and requiring 2 or more RBC units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) (1.3).

Limitations of Use: REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia (1.4).

ADVERSE REACTIONS

The most common (>10%) adverse reactions were fatigue, headache, musculoskeletal pain, arthralgia, dizziness/vertigo, nausea, diarrhea, cough, abdominal pain, dyspnea, COVID-19, edema peripheral, hypertension, and hypersensitivity (6.1).

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

ADVERSE REACTIONS

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).
- Extramedullary Hematopoietic (EMH) Masses: Increased risk in patients with beta thalassemia. Monitor patients for symptoms and signs or complications resulting from the EMH masses. Treat according to clinical guidelines and discontinue treatment in case of serious complications due to EMH masses (5.3).
- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception (5.4, 8.1, 8.3).

PATIENT COUNSELING INFORMATION

Lactation: Advise not to breastfeed (8.2).
**1 INDICATIONS AND USAGE**

**1.1 Beta Thalassemia**

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

**1.2 Myelodysplastic Syndromes Associated Anemia**

REBLOZYL® is indicated for the treatment of anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions.

**1.3 Myelodysplastic Syndromes with Ring Sideroblasts or Myelodysplastic/Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis Associated Anemia**

REBLOZYL® is indicated for the treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).

**1.4 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 Dosage for Beta Thalassemia**

The recommended starting dose of REBLOZYL® is 1 mg/kg once every 3 weeks by subcutaneous injection for patients with beta thalassemia. Prior to each REBLOZYL® dose, review the patient’s hemoglobin and transfusion record. Titrate the dose based on responses according to Table 1.

**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

**Table 1: Beta Thalassemia - REBLOZYL Dose Titration for Response**

<table>
<thead>
<tr>
<th>Starting Dose</th>
<th>REBLOZYL Dosing Recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg/kg every 3 weeks</td>
<td>• Increase the dose to 1.25 mg/kg every 3 weeks</td>
</tr>
</tbody>
</table>

**Table 2: Beta Thalassemia - REBLOZYL Dosing Modifications for Adverse Reactions**

* Do not increase the dose if the patient is experiencing an adverse reaction as described in Table 2.

**2.2 Recommended Dosage for Myelodysplastic Syndromes Associated Anemia**

The recommended starting dosage of REBLOZYL® is 1 mg/kg once every 3 weeks by subcutaneous injection for the treatment of anemia of MDS. Prior to each REBLOZYL® dose, review the patient’s hemoglobin and transfusion record. Titrate the dose based on responses according to Table 2.

**Dose Increases for Insufficient Response at Initiation of Treatment**

- No increase from baseline hemoglobin after at least 9 weeks of treatment
  - Increase the dose to 1.25 mg/kg

- No increase from baseline hemoglobin after 9 weeks of treatment (administration of 3 doses) at the maximum dose level (1.75 mg/kg)
  - Discontinue treatment

**Dose Modifications for Toxicity**

- Extramedullary hematopoietic (EMH) masses causing serious complications
  - Discontinue treatment

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

**Table 3: MDS Associated Anemia - REBLOZYL Dose Titration for Response**

<table>
<thead>
<tr>
<th>Starting Dose</th>
<th>REBLOZYL Dosing Recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg/kg every 3 weeks</td>
<td>• Increase the dose to 1.33 mg/kg</td>
</tr>
</tbody>
</table>

**Table 4.**

- Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose, increase the REBLOZYL® dose to 1.33 mg/kg (Table 3).

**Dose Modifications for Response**

Assess and review hemoglobin results prior to each administration of REBLOZYL®. If an RBC transfusion occurred prior to dosing, use the pretransfusion hemoglobin for dose evaluation.

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. In the absence of transfusions, if hemoglobin increase is greater than 2 g/dL within 3 weeks or the predose hemoglobin is greater than or equal to 11.5 g/dL, reduce the dose or interrupt treatment with REBLOZYL® as described in Table 1.

**Dose Level modifications for response are provided in Table 1.**

**Table 5: MDS Associated Anemia - REBLOZYL Dose Titration for Response**

<table>
<thead>
<tr>
<th>Starting Dose</th>
<th>REBLOZYL Dosing Recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose</td>
<td>• Increase the dose to 1.33 mg/kg every 3 weeks</td>
</tr>
</tbody>
</table>

**Dose Modifications for Insufficient Response at Initiation of Treatment**

- Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1.33 mg/kg dose level, 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.

In the absence of transfusions, if hemoglobin increase is greater than 2 g/dL within 3 weeks or if the predose hemoglobin is greater than or equal to 11.5 g/dL, reduce the dose or interrupt treatment with REBLOZYL® as described in Table 3. If, upon dose reduction, the patient loses response (i.e., requires a transfusion) or hemoglobin concentration drops by 1 g/dL or more in 3 weeks, the dose is no more than 11.5 g/dL.

**Dose Modifications for Toxicity**

- Extramedullary hematopoietic (EMH) masses causing serious complications
  - Discontinue treatment

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

**Table 6.**

- Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1.75 mg/kg dose level, increase the REBLOZYL® dose to 2.5 mg/kg. Do not increase the dose more frequently than every 6 weeks (2 doses) or beyond the maximum dose of 2.5 mg/kg.

In the absence of transfusions, if hemoglobin increase is greater than 2 g/dL within 3 weeks or if the predose hemoglobin is greater than or equal to 11.5 g/dL, reduce the dose or interrupt treatment with REBLOZYL® as described in Table 3. If, upon dose reduction, the patient loses response (i.e., requires a transfusion) or hemoglobin concentration drops by 1 g/dL or more in 3 weeks, the dose is no more than 11.5 g/dL.

**Dose Modifications for Toxicity**

- Extramedullary hematopoietic (EMH) masses causing serious complications
  - Discontinue treatment

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

**Table 7.**

- Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 2.5 mg/kg dose level, increase the REBLOZYL® dose to 3.75 mg/kg. Do not increase the dose more frequently than every 6 weeks (2 doses) or beyond the maximum dose of 3.75 mg/kg.

In the absence of transfusions, if hemoglobin increase is greater than 2 g/dL within 3 weeks or if the predose hemoglobin is greater than or equal to 11.5 g/dL, reduce the dose or interrupt treatment with REBLOZYL® as described in Table 3. If, upon dose reduction, the patient loses response (i.e., requires a transfusion) or hemoglobin concentration drops by 1 g/dL or more in 3 weeks, the dose is no more than 11.5 g/dL.

**Dose Modifications for Toxicity**

- Extramedullary hematopoietic (EMH) masses causing serious complications
  - Discontinue treatment

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

**Table 8.**

- Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 3.75 mg/kg dose level, increase the REBLOZYL® dose to 5 mg/kg. Do not increase the dose more frequently than every 6 weeks (2 doses) or beyond the maximum dose of 5 mg/kg.

In the absence of transfusions, if hemoglobin increase is greater than 2 g/dL within 3 weeks or if the predose hemoglobin is greater than or equal to 11.5 g/dL, reduce the dose or interrupt treatment with REBLOZYL® as described in Table 3. If, upon dose reduction, the patient loses response (i.e., requires a transfusion) or hemoglobin concentration drops by 1 g/dL or more in 3 weeks, the dose is no more than 11.5 g/dL.

**Dose Modifications for Toxicity**

- Extramedullary hematopoietic (EMH) masses causing serious complications
  - Discontinue treatment

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

**Table 9.**

- Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 5 mg/kg dose level, increase the REBLOZYL® dose to 7.5 mg/kg. Do not increase the dose more frequently than every 6 weeks (2 doses) or beyond the maximum dose of 7.5 mg/kg.

In the absence of transfusions, if hemoglobin increase is greater than 2 g/dL within 3 weeks or if the predose hemoglobin is greater than or equal to 11.5 g/dL, reduce the dose or interrupt treatment with REBLOZYL® as described in Table 3. If, upon dose reduction, the patient loses response (i.e., requires a transfusion) or hemoglobin concentration drops by 1 g/dL or more in 3 weeks, the dose is no more than 11.5 g/dL.

**Dose Modifications for Toxicity**

- Extramedullary hematopoietic (EMH) masses causing serious complications
  - Discontinue treatment

- Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, and Grade 4 is life-threatening.
Dose Modifications for Toxicity

For patients experiencing Grade 3 or higher adverse reactions, modify treatment as described in Table 4.

Table 4: MDS Associated Anemia - REBLOZYL Dosing Modifications for Adverse Reactions

<table>
<thead>
<tr>
<th>Grade 3 or 4 hypersensitivity reactions</th>
<th>REBLOZYL Dosing Recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Discontinue treatment **</td>
<td></td>
</tr>
<tr>
<td>Other Grade 3 or 4 adverse reactions</td>
<td>• Interrupt treatment</td>
</tr>
<tr>
<td>• When the adverse reaction resolves to no more than Grade 1, restart treatment at the next lower dose level**</td>
<td></td>
</tr>
<tr>
<td>• If the dose delay is ≥12 consecutive weeks, discontinue treatment</td>
<td></td>
</tr>
</tbody>
</table>

* Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, and Grade 4 is life-threatening.
** Per Table 3 dose reductions above.

2.3 Preparation and Administration

REBLOZYL should be reconstituted and administered by a healthcare professional.

Reconstitute REBLOZYL with Sterile Water for Injection, USP only.

Table 5: Reconstitution Volumes

<table>
<thead>
<tr>
<th>Vial Size</th>
<th>Amount of Sterile Water for injection, USP required for reconstitution</th>
<th>Final Concentration</th>
<th>Deliverable Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg vial</td>
<td>0.68 mL</td>
<td>25 mg/0.5 mL (50 mg/mL)</td>
<td>0.5 mL</td>
</tr>
<tr>
<td>75 mg vial</td>
<td>1.6 mL</td>
<td>75 mg/1.5 mL (50 mg/mL)</td>
<td>1.5 mL</td>
</tr>
</tbody>
</table>

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 5.
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. Set the vial in the refrigerator for up to 8 hours. Discard if not used within 8 hours of reconstitution.
7. Store at room temperature at 20°C to 25°C (68°F to 77°F) in the original vial for up to 6 hours. Discard if not used within 6 hours of reconstitution.
8. Alternatively, store reconstituted 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.
9. 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 63/554 (11.4%) of REBLOZYL-treated patients. Across clinical studies, the incidence of Grade 3–4 hypertension ranged from 2% to 9.6%. 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.

In ESA-refractory or -intolerant adult patients with MDS with normal baseline blood pressure, 26 (30%) patients developed SBP ≥130 mm Hg and 23 (16%) patients developed DBP ≥80 mm Hg. In ESA-naive adult patients with MDS with normal baseline blood pressure, 23 (36%) patients developed SBP ≥140 mm Hg and 11 (6%) patients developed 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 Extramedullary Hematopoietic Masses

In adult patients with transfusion dependent beta thalassemia, EMH masses were observed in 3.2% of REBLOZYL-treated patients, with spinal cord compression symptoms due to EMH masses occurring in 1.9% of patients (BELIEVE and REBLOZYL long-term follow-up study).

In a study of adult patients with non-transfusion dependent beta thalassemia, a higher incidence of EMH masses was observed in 6.3% of REBLOZYL-treated patients vs. 2% of placebo-treated patients in the double-blind phase of the study, with spinal cord compression due to EMH masses occurring in 1 patient with a prior history of EMH. REBLOZYL is not indicated for use in patients with non-transfusion dependent beta-thalassemia.

Possible risk factors for the development of EMH masses in patients with beta thalassemia include history of EMH masses, splenectomy, splenomegaly, hepatomegaly, or low baseline hemoglobin (<8.5 g/dL). Signs and symptoms may vary depending on the anatomical location. Monitor patients with beta thalassemia 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. Avoid use of REBLOZYL in patients requiring treatment to control the growth of EMH masses.

5.4 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 luspatercept-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 1.75 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)]
- Extramedullary Hematopoietic Masses [see Warnings and Precautions (5.3)]
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 the exception of patients with hemoglobin S or alpha-thalassemia disease) without major organ damage or recent DVT stroke and platelet counts less than or equal to 1000 x 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 >0.5% 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 6 summarizes the adverse reactions in BELIEVE.

Table 6: Adverse Drug Reactions (>5%) in Patients with Beta Thalassemia Receiving REBLOZYL with a Difference Between Arms of 1% in BELIEVE Trial

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>REBLOZYL (N = 223)</th>
<th>Placebo (N = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades n (%)</td>
<td>Grades ≥3 n (%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Pain</td>
<td>44 (20)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>43 (19)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Infections and infestation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>19 (9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Viral Upper Respiratory Infection</td>
<td>14 (6)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>58 (26)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>25 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>30 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>31 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>27 (12)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (8)</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>

(Continued)
**Table 10:** Adverse Reactions (≥5%) in Patients Receiving REBLOZYL with a Difference Between Arms of >2% in MEDALIST Trial Through Cycle 8

**Body System/Adverse Reaction** | **REBLOZYL (N=153)** | **Placebo (N=76)**
---|---|---
**All Grades n (%)** | **Grade ≥3 n (%)** | **All Grades n (%)** | **Grade ≥3 n (%)**

**General disorders and administration site conditions**
- Fatigue
  - REBLOZYL: 83 (41)
  - Placebo: 11 (7)
  - Difference: 72 (4)
- Musculoskeletal and connective tissue disorders
  - Musculoskeletal pain
    - REBLOZYL: 30 (20)
    - Placebo: 3 (2)
    - Difference: 27 (18)

**Nervous system disorders**
- Dizziness/vertigo
  - REBLOZYL: 28 (18)
  - Placebo: 1 (< 1)
  - Difference: 27 (17)
- Headache
  - REBLOZYL: 21 (14)
  - Placebo: 0 (0)
  - Difference: 21 (14)
- Syncope/presyncope
  - REBLOZYL: 8 (5)
  - Placebo: 5 (3)
  - Difference: 3 (2)

**Respiratory, thoracic and mediastinal disorders**
- Dyspnea (exertional)
  - REBLOZYL: 9 (5)
  - Placebo: 0 (0)
  - Difference: 9 (5)

**Infections and infestations**
- Influenza / influenza like illness
  - REBLOZYL: 9 (6)
  - Placebo: 0 (0)
  - Difference: 9 (6)
- Upper respiratory tract infection
  - REBLOZYL: 2 (3)
  - Placebo: 0 (0)
  - Difference: 2 (3)

**Cardiac disorders**
- Tachycardia
  - REBLOZYL: 9 (6)
  - Placebo: 0 (0)
  - Difference: 9 (6)

**Gastrointestinal disorders**
- Nausea
  - REBLOZYL: 25 (16)
  - Placebo: 1 (< 1)
  - Difference: 24 (15)
- Diarrhea
  - REBLOZYL: 25 (16)
  - Placebo: 7 (9)
  - Difference: 18 (7)

**Other clinically relevant adverse reactions reported in <5% of patients include bronchitis, urinary tract infection, and hypertension.**

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.
10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action
Luspatercept-aamt is a recombinant fusion protein that binds several endogenous TGF-β superfamily ligands, thereby diminishing Smad2/3 signaling. In models of β-thalassemia and MDS, luspatercept-aamt decreased abnormally elevated Smad2/3 signaling and improved hematologic parameters associated with ineffective erythropoiesis in mice. Luspatercept-aamt promoted erythroid maturation through differentiation and increasing the percentage of late-stage erythroid precursors (normoblasts) in the bone marrow of mice and increased erythroid precursors in humans, thereby increasing erythropoiesis.

10.2 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 (Cmax). The greatest hemoglobin (Hgb) increase occurred after the first dose; approximately 0.75 g/dL at a dose of 0.6 to 1.25 times the recommended starting dose for beta thalassemia, or approximately 1 g/dL at a dose of 0.75 to 1.75 times the recommended starting dose for MDS. Additional smaller increases were observed after subsequent doses. Hemoglobin levels returned to baseline approximately 6 to 8 weeks from the last dose following administration of luspatercept-aamt (0.6 to 1.75 mg/kg).

Starting luspatercept-aamt serum exposure (AUC) was associated with greater Hgb increase in patients with beta thalassemia or MDS who had a baseline transfusion burden <4 units/8 weeks. Increasing luspatercept-aamt serum exposure (time-averaged AUC) was associated with greater probability of achieving transfusion independence for at least 8 consecutive weeks in ESA-refractory or -intolerant patients with MDS requiring transfusions (>2 units of RBC transfusion within 8 weeks).

10.3 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, and from 0.125 mg/kg to 1.75 mg/kg (0.125 to 1.75 times the recommended starting dosage) in patients with MDS. The geometric mean (% coefficient of variation (%CV)) for luspatercept-aamt serum exposure (time-averaged AUC) at the starting dose of 1 mg/kg was 126 (55.9%) day•µg/mL in patients with beta thalassemia and 154 (37.4%) day•µg/mL for patients with MDS. 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.

Abnormal
The median range time to maximum concentration (tmax) of luspatercept-aamt was observed at approximately 5 [3 to 8] days post-dose in adult patients with beta thalassemia or 6 [3 to 7] days post-dose in adult patients with MDS. The absorption of luspatercept-aamt was not significantly affected by the subcutaneous injection sites (upper arm, thigh, or abdomen).

Elimination
The geometric mean (%CV) half-lives (t1/2) of luspatercept-aamt were approximately 11 (25.7%) days in patients with beta thalassemia and 9.6 (26.7%) days in patients with MDS.

Metabolism
Luspatercept-aamt is expected to be catabolized into small peptides and amino acids by general catabolic degradation processes in multiple tissues.
Specific Populations
No clinically significant differences in the luspatercept-aamt PK were observed based on age (18 to 95 years), sex, race/ethnicity (Asian, White), mild to severe hepatic impairment (total bilirubin ≤ 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), baseline albumin (30 to 56 g/L), baseline serum erythropoietin (2.4 to 2920 U/L), red blood cell (RBC) transfusion burden (0 to 43 units/24 weeks), beta thalassemia genotype (β0/β0 vs. non-β0/β0), splenectomy, and ring sideroblast status in MDS (negative vs. positive). The effect of ALT or AST >3 x ULN and the effect of severe renal impairment (eGFR <30 mL/min) on luspatercept-aamt PK is unknown.

Body Weight
The apparent CL/F and Vd/F of luspatercept-aamt increased with increasing body weight in patients with beta thalassemia (34 to 97 kg) and in patients with MDS (33 to 124 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.

12.6 Immunogenicity
The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of REBLOZYL or of other luspatercept products.

In the BELIEVE trial, the median duration of exposure was 64 weeks, with a median ADA sampling period of 50 weeks. Of the 220 patients in the BELIEVE trial with beta thalassemia who require regular RBC transfusions treated with REBLOZYL and evaluable for the presence of anti-luspatercept-aamt antibodies, 4 patients (1.81%) tested positive for treatment-emergent anti-luspatercept-aamt antibodies, including 2 patients (0.9%) who had neutralizing antibodies detected. The majority of anti-luspatercept-aamt antibodies were of low titers.

In the COMMANDS trial, the median duration of exposure was 42 weeks, with the median ADA sampling period of 27 weeks. In the MEDALIST trial, the median duration of exposure was 49 weeks, with the median ADA sampling period of 46 weeks. Of the 331 ESA-naïve (COMMANDS trial) and ESA-refractory or -intolerant (MEDALIST trial) patients with MDS who were treated with REBLOZY, 21 patients (6.3%) tested positive for treatment-emergent anti-luspatercept-aamt antibodies, including 14 patients (4.2%) who had neutralizing antibodies. The majority of anti-luspatercept-aamt antibodies were of low titers.

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, red cell transfusion burden (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 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. Efficacy results are shown in Table 13.
14.2 Treatment of Myelodysplastic Syndromes with Associated Anemia in ESA-naïve Patients

The efficacy of REBLOZYL was evaluated in the COMMANDS trial (NCT02631070), a multi-center, open-label, randomized active-controlled trial comparing REBLOZYL versus epoetin alfa in patients with anemia due to IPSS-R very low, low, or intermediate-risk myelodysplastic syndromes or with myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) in ESA-naïve patients (with endogenous sEPO levels of <500 U/L) who require regular red blood cell transfusions. For eligibility, patients were required to have had 2 to 6 RBC units in 8 weeks confirmed for a minimum of 8 weeks immediately preceding randomization. The COMMANDS trial included 356 patients randomized 1:1 to REBLOZYL (N=178) or epoetin alfa (N=178). Randomization was stratified by RBC transfusion burden, RS status, and endogenous serum erythropoietin (sEPO) level at baseline. Treatment was started at 1 mg/kg subcutaneously every 3 weeks. Two dose level increases were allowed (to 1.33 mg/kg and to 1.75 mg/kg). Doses were held and subsequently reduced for adverse reactions, reduced if the hemoglobin increased by ≥2 g/dL from the prior cycle, and held if the predose hemoglobin was ≥12 g/dL.

All patients received best supportive care, which included RBC transfusions as needed. Patients were treated for 24 weeks and were assessed for efficacy at that time point. Treatment beyond 24 weeks was optional based upon response to treatment and absence of disease progression.

The median age of the 356 study participants was 74 years (range: 33, 93 years). The trial population was 56% male and 44% female; 79.5% were White, 0.6% Black or African American, 12.1% Asian, and race was not reported in 7.9% of patients. Ethnicities were reported as 85.4% for Not Hispanic or Latino patients, 6.5% for Hispanic or Latino patients, 7.6% for patients with no ethnicity reported, and 0.6% were unknown. IPSS-R risk classification at baseline was 93.9% very low, 72.2% low, 17.4% intermediate, 0.3% high, and 0.8% missing. Table 14 summarizes the baseline disease-related characteristics in the COMMANDS study.

<table>
<thead>
<tr>
<th>Disease Characteristic</th>
<th>REBLOZYL (N=178)</th>
<th>Epotin Alfa (N=178)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL) – n (%)</td>
<td>7.80 (4.7, 9.2)</td>
<td>7.80 (4.5, 10.2)</td>
</tr>
<tr>
<td>Serum EPO (U/L) – n (%)</td>
<td>78.7 (7.8, 495.8)</td>
<td>85.9 (4.6, 462.5)</td>
</tr>
<tr>
<td>IPSS-R risk classification at baseline – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very low</td>
<td>16 (9.0)</td>
<td>17 (9.6)</td>
</tr>
<tr>
<td>Low</td>
<td>126 (70.8)</td>
<td>131 (73.6)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>34 (19.1)</td>
<td>28 (15.7)</td>
</tr>
<tr>
<td>High</td>
<td>1 (0.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.6)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Ring sideroblast status (per WHO criteria) – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RS+</td>
<td>130 (73.0)</td>
<td>128 (71.9)</td>
</tr>
<tr>
<td>RS-</td>
<td>46 (27.0)</td>
<td>49 (27.5)</td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>SF3B1 mutation status – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutated</td>
<td>111 (62.4)</td>
<td>99 (55.6)</td>
</tr>
<tr>
<td>Non-mutated</td>
<td>65 (36.5)</td>
<td>72 (40.4)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (1.1)</td>
<td>7 (3.9)</td>
</tr>
</tbody>
</table>

The efficacy of REBLOZYL in the treatment of anemia in ESA-naïve adult patients with MDS was established at the time of the interim efficacy analysis based upon the proportion of patients who experienced both red blood cell transfusion independence (RBC-TI) [defined as the absence of any RBC transfusion during any consecutive 12-week period] and an associated concurrent mean improvement in hemoglobin by at least 1.5 g/dL for any consecutive 12-week period during Weeks 1-24. At the time of the interim efficacy analysis, 301 subjects were included in the efficacy analysis, of which 147 were in the luspatercept arm and 154 were in the epoetin alfa arm, which is about 85% of the total information. The key efficacy results are shown in Table 15.

Table 15: Key Efficacy Results in COMMANDS

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>REBLOZYL (N=147)</th>
<th>Epoetin Alfa* (N=154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC-TI for ≥12 weeks with associated concurrent mean Hgb increase of ≥1.5 g/dL (Weeks 1-24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response rate, n (%)</td>
<td>86 (58.5)</td>
<td>48 (31.2)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(50.1, 66.6)</td>
<td>(24.0, 39.1)</td>
</tr>
<tr>
<td>Common Rate Difference (95% CI)</td>
<td>26.6 (15.8, 37.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean Hgb increase ≥1.5 g/dL (Weeks 1-24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response rate, n (%)</td>
<td>106 (72.1)</td>
<td>75 (48.7)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(64.1, 79.2)</td>
<td>(40.6, 56.9)</td>
</tr>
<tr>
<td>Common Rate Difference (95% CI)</td>
<td>23.2 (12.2, 34.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RBC-TI for 24 weeks (Weeks 1-24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response rate, n (%)</td>
<td>70 (47.6)</td>
<td>45 (29.2)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(39.3, 56.0)</td>
<td>(22.2, 37.1)</td>
</tr>
<tr>
<td>Common Rate Difference (95% CI)</td>
<td>22.3 (11.8, 32.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RBC-TI for ≥12 weeks (Weeks 1-24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response rate, n (%)</td>
<td>98 (66.7)</td>
<td>71 (46.1)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(58.4, 74.2)</td>
<td>(38.1, 54.3)</td>
</tr>
<tr>
<td>Common Rate Difference (95% CI)</td>
<td>19.1 (8.6, 29.6)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

No major outliers were observed in clinically relevant baseline demographic and disease characteristic subgroups.

14.3 Myelodysplastic Syndromes with Ring Sideroblasts or Myelodysplastic/ Myeloproliferative Neoplasms with Ring Sideroblasts and Thrombocytosis Associated Anemia in ESA-refractory or -intolerant Patients

The efficacy of REBLOZYL was evaluated in the MEDALIST trial (NCT02631070), a multi-center, randomized, double-blind, placebo-controlled trial in patients with IPSS-R very low, low, or intermediate-risk myelodysplastic syndromes or MDS/MPN-RS-T who require red blood cell transfusions and have received at least one RBC transfusion in the prior 6 weeks. For eligibility, patients were required to have had an inadequate response to prior treatment with an erythropoiesis-stimulating agent (ESA), be intolerant of ESAs, or have a serum erythropoietin level ≥200 U/L. The MEDALIST trial excluded patients with deletion 5q, with a serum ferritin level ≥1000 μg/L, or with a history of a hemolytic anemia. The efficacy of REBLOZYL was evaluated in the MEDALIST trial (NCT02631070), a multi-center, randomized, double-blind, placebo-controlled trial in patients with IPSS-R very low, low, or intermediate-risk myelodysplastic syndromes who have ring sideroblasts and require regular red blood cell transfusions. For eligibility, patients were required to have had an inadequate response to prior treatment with an erythropoiesis-stimulating agent (ESA), be intolerant of ESAs, or have a serum erythropoietin level ≥200 U/L. The MEDALIST trial excluded patients with deletion 5q, with a serum ferritin level ≥1000 μg/L, or with a history of a hemolytic anemia. The efficacy of REBLOZYL in the treatment of anemia in ESA-naive adult patients with MDS was established at the time of the interim efficacy analysis based upon the proportion of patients who experienced both red blood cell transfusion independence (RBC-TI) [defined as the absence of any RBC transfusion during any consecutive 12-week period] and an associated concurrent mean improvement in hemoglobin by at least 1.5 g/dL for any consecutive 12-week period during Weeks 1-24. At the time of the interim efficacy analysis, 301 subjects were included in the efficacy analysis, of which 147 were in the luspatercept arm and 154 were in the epoetin alfa arm, which is about 85% of the total information. The key efficacy results are shown in Table 15.
All patients received best supportive care, which included RBC transfusions as needed. The primary efficacy assessment was conducted after completion of 24 weeks on study drug. Patients with a decrease in transfusion requirement or increase in hemoglobin could continue on blinded study drug thereafter until unacceptable toxicity, loss of efficacy, or disease progression.

The median age of the 229 study participants was 71 years (range: 26, 95 years). The trial population was 63% male and 69% White. Table 16 summarizes the baseline disease-related characteristics in the MEDALIST study.

### Table 16: Baseline Disease Characteristics of Patients in MEDALIST

<table>
<thead>
<tr>
<th>Disease Characteristic</th>
<th>REBLOZYL (N=153)</th>
<th>Placebo (N=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Since Original MDS Diagnosis* (months)</td>
<td>44.0 (3, 421)</td>
<td>36.1 (4, 193)</td>
</tr>
<tr>
<td>Serum EPO (U/L) Categories*, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>88 (57.5)</td>
<td>50 (65.8)</td>
</tr>
<tr>
<td>200 to 500</td>
<td>43 (28.1)</td>
<td>15 (19.7)</td>
</tr>
<tr>
<td>&gt;500</td>
<td>21 (13.7)</td>
<td>11 (14.5)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Diagnosis per WHO Criteria, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS-RS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>135 (88.2)</td>
<td>65 (85.5)</td>
</tr>
<tr>
<td>MDS/MPN-RS-T</td>
<td>14 (9.2)</td>
<td>9 (11.8)</td>
</tr>
<tr>
<td>Other&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4 (2.6)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>IPSS-R Classification Risk Category, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very low</td>
<td>18 (11.8)</td>
<td>6 (7.9)</td>
</tr>
<tr>
<td>Low</td>
<td>109 (71.2)</td>
<td>57 (75)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>25 (16.3)</td>
<td>13 (17.1)</td>
</tr>
<tr>
<td>High</td>
<td>1 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>RBC Transfusions/8 Weeks Over 16 Weeks Categories, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4 units</td>
<td>46 (30.1)</td>
<td>20 (26.3)</td>
</tr>
<tr>
<td>4 - 6 units</td>
<td>41 (26.8)</td>
<td>23 (30.3)</td>
</tr>
<tr>
<td>≥6 units</td>
<td>66 (43.1)</td>
<td>33 (43.4)</td>
</tr>
</tbody>
</table>

The efficacy of REBLOZYL in adult patients with MDS-RS and MDS-RS-T was established based upon the proportion of patients who were red blood cell transfusion independent (RBC-TI), defined as the absence of any RBC transfusion during any consecutive 8-week period occurring entirely within Weeks 1 through 24.

### Table 17: Efficacy Results in MEDALIST

#### Endpoint

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>REBLOZYL (N=153)</th>
<th>Placebo (N=76)</th>
<th>Common Risk Difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC-TI ≥8 weeks during Weeks 1-24</td>
<td>58 (37.9)</td>
<td>10 (13.2)</td>
<td>26.7 (14.5, 38.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RBC-TI ≥12 weeks during Weeks 1-24</td>
<td>43 (28.1)</td>
<td>6 (7.9)</td>
<td>26.0 (10.9, 38.9)</td>
<td>0.0002</td>
</tr>
<tr>
<td>RBC-TI ≥12 weeks during Weeks 1-8*</td>
<td>51 (33.3)</td>
<td>9 (11.8)</td>
<td>21.4 (11.2, 31.5)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

* The median (range) duration of treatment was 49 weeks (6 to 114 weeks) on the REBLOZYL arm and 24 weeks (7 to 89 weeks) on the placebo arm.

Table 18 shows the proportion of patients who achieved RBC-TI ≥8 weeks during Weeks 1-24 by diagnosis and baseline transfusion requirement.

### Table 18: RBC-TI ≥8 Weeks during Weeks 1-24 By Diagnosis and Baseline Transfusion Burden in MEDALIST

<table>
<thead>
<tr>
<th>Group</th>
<th>Responders/N</th>
<th>% Response (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS-RS</td>
<td>46/135</td>
<td>34.1 (26.1, 42.7)</td>
</tr>
<tr>
<td>MDS/MPN-RS-T</td>
<td>9/14</td>
<td>64.3 (35.1, 87.2)</td>
</tr>
<tr>
<td>Other&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3/4</td>
<td>75.0 (19.4, 99.4)</td>
</tr>
<tr>
<td>2 - 3 units/8 weeks&lt;sup&gt;b&lt;/sup&gt;</td>
<td>37/46</td>
<td>80.4 (66.1, 90.6)</td>
</tr>
<tr>
<td>4 - 5 units/8 weeks&lt;sup&gt;b&lt;/sup&gt;</td>
<td>15/41</td>
<td>36.6 (22.1, 53.1)</td>
</tr>
<tr>
<td>≥6 units/8 weeks</td>
<td>6/66</td>
<td>9.1 (3.4, 18.7)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes MDS-RS-MLD and MDS-RS-SLD.

<sup>b</sup> Includes patients who received 3.5 units.

**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.

**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)].

**Extraordinary Hematopoietic Masses**

Advise patients with beta-thalassemia of the potential risk of extraordinary hematopoietic masses. Review possible risk factors for developing extraordinary hematopoietic masses. Instruct patients to report possible signs and symptoms of EMM masses [see Warnings and Precautions (5.3)].

**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 (5.4) 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)].

Manufactured by:

Celgene Corporation, a Bristol-Myers Squibb Company

86 Morris Avenue

Summit, NJ 07901

U.S. License No. 2252

REBLOZYL® is a registered trademark of Celgene Corporation, a Bristol-Myers Squibb Company.

REB1.006
What is REBLOZYL?
REBLOZYL is a prescription medicine used to treat anemia (low red blood cells) in adults with:
- beta thalassemia who need regular red blood cell (RBC) transfusions.
- myelodysplastic syndromes who may need regular RBC transfusions and have never received an erythropoiesis stimulating agent (ESA).
- myelodysplastic syndromes with ring sideroblasts (MDS-RS) or myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) who need 2 or more RBC units over 8 weeks and have not responded well to an ESA.

REBLOZYL is not for use as a substitute for RBC transfusions in people who need immediate treatment for anemia. It is not known if REBLOZYL is safe and effective in children.

Before receiving REBLOZYL, tell your healthcare provider about all of your medical conditions, including if you:
- have or have had blood clots
- take hormone replacement therapy or birth control pills (oral contraceptives)
- have had your spleen removed (splenectomy)
- smoke
- have or have had high blood pressure (hypertension)
- have a history of extramedullary hematopoietic (EMH) masses
- have or have had enlarged spleen or liver
- are pregnant or plan to become pregnant. REBLOZYL may harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with REBLOZYL.

Females who are able to become pregnant:
- Your healthcare provider should do a pregnancy test before you start treatment with REBLOZYL.
- You should use effective birth control (contraception) during treatment with REBLOZYL and for at least 3 months after the last dose.

- are breastfeeding or plan to breastfeed. It is not known if REBLOZYL passes into your breast milk.
- Do not breastfeed during treatment with REBLOZYL and for 3 months after the last dose. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive REBLOZYL?
- Your healthcare provider will prescribe REBLOZYL in a dose that is right for you. Depending on how you respond to REBLOZYL, your healthcare provider may adjust your dose or stop treatment.
- REBLOZYL is given as an injection under your skin (subcutaneous) in the upper arm, thigh, or stomach (abdomen) by your healthcare provider.
- Your healthcare provider will do regular blood tests to check your hemoglobin to monitor if your anemia is getting better before each injection and during your treatment with REBLOZYL.

If your scheduled REBLOZYL dose is delayed or missed, your healthcare provider will give your dose of REBLOZYL as soon as possible and continue your treatment as prescribed with at least 3 weeks between doses.

What are the possible side effects of REBLOZYL?
REBLOZYL may cause serious side effects, including:
- Blood clots. Blood clots in the arteries, veins, brain, and lungs have happened in people with beta thalassemia during treatment with REBLOZYL. The risk of blood clots may be higher in people who have had their spleen removed or who take hormone replacement therapy or birth control (oral contraceptives). Call your healthcare provider or get medical help right away if you get any of these symptoms:
  - chest pain
  - trouble breathing or shortness of breath
  - pain in your leg, with or without swelling
  - a cold or pale arm or leg
REBLOZYL® (luspatercept-aamt)

- sudden numbness or weakness that are both short-term or continue to happen over a long period of time, especially on one side of the body
- severe headache or confusion
- sudden problems with vision, speech, or balance (such as trouble speaking, difficulty walking, or dizziness)

- **High blood pressure.** REBLOZYL may cause an increase in your blood pressure. Your healthcare provider will check your blood pressure before you receive your REBLOZYL dose. Your healthcare provider may prescribe you medicine to treat high blood pressure or increase the dose of medicine you already take to treat high blood pressure if you develop high blood pressure during treatment with REBLOZYL.

- **Extramedullary Hematopoietic (EMH) Masses.** EMH masses have happened in people with beta thalassemia during treatment with REBLOZYL. You may have a higher risk for developing EMH masses if you have a history of EMH masses, have had your spleen removed, have or have had an enlarged spleen or liver, or have low hemoglobin levels. Your healthcare provider will monitor you before you start and during treatment with REBLOZYL. Call your healthcare provider or get medical help right away if you get any of these symptoms:
  - severe pain in the back
  - numbness, weakness, or loss of voluntary movement in feet, legs, hands, or arms
  - loss of bowel and bladder control

The most common side effects of REBLOZYL include:

- tiredness
- headache
- back, joint, muscle, or bone pain
- joint pain
- dizziness
- nausea
- diarrhea

- cough
- stomach (abdominal) pain
- trouble breathing
- swelling of your hands, legs, or feet
- high blood pressure
- allergic reactions

REBLOZYL may cause fertility problems in females. This could affect your ability to become pregnant. Talk to your healthcare provider if this is a concern for you.

These are not all of the possible side effects of REBLOZYL.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about the safe and effective use of REBLOZYL.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your healthcare provider or pharmacist for information about REBLOZYL that is written for health professionals.

**What are the ingredients in REBLOZYL?**

**Active ingredient:** luspatercept-aamt

**Inactive ingredients:** citric acid monohydrate, polysorbate 80, sucrose, and tri-sodium citrate dihydrate.

For more information, go to www.REBLOZYL.com or call 1-888-423-5436.

Manufactured by: Celgene Corporation, a Bristol-Myers Squibb Company, 86 Morris Avenue, Summit, NJ 07901

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This Patient Information has been approved by the U.S. Food and Drug Administration.