

# REBLOZYL® (LUSPATERCEPT-AAMT) AND ITS MECHANISM OF ACTION

## WHAT IS REBLOZYL?

REBLOZYL is a treatment for adults with anemia which aims to promote late-stage erythropoiesis and, in turn, promote red blood cell (RBC) production.<sup>1</sup>

**Erythropoiesis refers to the natural production of RBCs in the body.<sup>2</sup>**

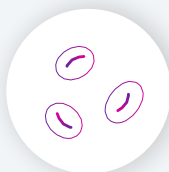
**When erythropoiesis becomes defective in patients with myelodysplastic syndromes (MDS) and beta thalassemia, a common sign can be anemia.<sup>3</sup> Anemia can cause fatigue and weakness due to the lack of healthy RBCs to carry adequate oxygen to the body's tissues.<sup>4</sup> One of the treatments for anemia can be RBC transfusions.<sup>5</sup>**

## HOW DOES REBLOZYL WORK?



### **Red Blood Cells in Individuals with Healthy Erythropoiesis**

Erythropoiesis occurs mostly in the bone marrow and ends in the blood stream as erythroblasts become mature RBCs – the primary function of which is to carry oxygen from the lungs to the rest of the body.<sup>2</sup>

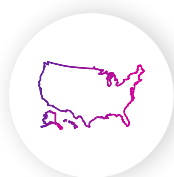


### **Red Blood Cells in Individuals with Impaired Erythropoiesis**

In the bone marrow of patients with MDS and beta thalassemia, intracellular signaling by means of the Smad2/3 pathway is increased.<sup>3</sup> This increased presence is known to inhibit the process of RBC maturation. Anemia results in a decreased oxygen-carrying capacity of the blood. In the short term, the body can compensate with an increase in heart rate and respiratory rate.<sup>6</sup>

**REBLOZYL**, an erythroid maturation agent, is a recombinant fusion protein that binds several endogenous TGF- $\beta$  superfamily ligands, thereby diminishing Smad2/3 signaling.<sup>1</sup> REBLOZYL promotes erythroid maturation through differentiation and increases the percentage of late-stage erythroid precursors (normoblasts) in the bone marrow of mice and humans, thereby increasing erythropoiesis.<sup>1</sup>

## WHAT DOES REBLOZYL TREAT?



REBLOZYL is indicated for the treatment of:<sup>1</sup>

- ☑ Anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions.
- ☑ Anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk MDS who may require regular red blood cell (RBC) transfusions.
- ☑ Anemia failing an ESA 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).

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

## HOW IS REBLOZYL ADMINISTERED?

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

REBLOZYL should be reconstituted and administered by a healthcare professional.<sup>1</sup>



## IMPORTANT SAFETY INFORMATION

### WARNINGS AND PRECAUTIONS

#### Thrombosis/Thromboembolism

In adult patients with beta thalassemia, thromboembolic events (TEE) were reported in 8/223 (3.6%) of 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 11.4% (63/554) of REBLOZYL-treated patients. Across clinical studies, the incidence of Grade 3 to 4 hypertension ranged from 2% to 9.6%. In patients with beta thalassemia with normal baseline blood pressure, 13 (6.2%) patients developed systolic blood pressure (SBP)  $\geq$ 130 mm Hg and 33 (16.6%) patients developed diastolic blood pressure (DBP)  $\geq$ 80 mm Hg. In ESA-refractory or -intolerant adult patients with MDS with normal baseline blood pressure, 26 (30%) patients developed SBP  $\geq$ 130 mm Hg and 23 (16%) patients developed DBP  $\geq$ 80 mm Hg. In ESA-naïve adult patients with MDS with normal baseline blood pressure, 23 (36%) patients developed SBP  $\geq$ 140 mm Hg and 11 (6%) patients developed DBP  $\geq$ 80 mm Hg. Monitor blood pressure prior to each administration. Manage new or exacerbations of preexisting hypertension using anti-hypertensive agents.

#### Extramedullary Hematopoietic (EMH) 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.

#### Embryo-Fetal Toxicity

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

## ADVERSE REACTIONS

### Beta-Thalassemia

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

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

### ESA-naïve adult patients with Myelodysplastic Syndromes

Grade  $\geq 3$  ( $\geq 2\%$ ) adverse reactions included hypertension and dyspnea.

The most common ( $\geq 10\%$ ) all-grade adverse reactions included diarrhea, fatigue, hypertension, peripheral edema, nausea, and dyspnea.

### ESA-refractory or -intolerant adult patients with Myelodysplastic Syndromes

Grade  $\geq 3$  ( $\geq 2\%$ ) adverse reactions included fatigue, hypertension, syncope and musculoskeletal pain. A fatal adverse reaction occurred in 5 (2.1%) patients.

The most common ( $\geq 10\%$ ) adverse reactions included fatigue, musculoskeletal pain, dizziness, diarrhea, nausea, hypersensitivity reactions, hypertension, headache, upper respiratory tract infection, bronchitis, and urinary tract infection.

## 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.

## DRUG ABUSE POTENTIAL

Abuse: Abuse of REBLOZYL may be seen in athletes for the effects on erythropoiesis. Misuse of drugs that increase erythropoiesis, such as REBLOZYL, by healthy persons may lead to polycythemia, which may be associated with life-threatening cardiovascular complications.

Please click [here](#) for full Prescribing Information for REBLOZYL.

<sup>1</sup> Reblozyl U.S. Prescribing Information. Available at: [https://packageinserts.bms.com/pi/pi\\_reblozyl.pdf](https://packageinserts.bms.com/pi/pi_reblozyl.pdf). Accessed August 2023.

<sup>2</sup> Liang, R. and Ghaffari, S. Advances in understanding the mechanisms of erythropoiesis in homeostasis and disease. Br J Haematol. 2016 Sep;174(5):661-73. Available at: <https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.14194>. Accessed August 2023.

<sup>3</sup> Parisi S, Finelli C, Fazio A, De Stefano A, Mongiorgi S, Ratti S, Cappellini A, Billi AM, Cocco L, Follo MY, Manzoli L. Clinical and Molecular Insights in Erythropoiesis Regulation of Signal Transduction Pathways in Myelodysplastic Syndromes and  $\beta$ -Thalassemia. Int J Mol Sci. 2021 Jan 15;22(2):827. Available at: <https://www.mdpi.com/1422-0067/22/2/827>. Accessed August 2023.

<sup>4</sup> Mayo Clinic. Anemia. Available at: <https://www.mayoclinic.org/diseases-conditions/anemia/symptoms-causes/syc-20351360>. Accessed August 2023.

<sup>5</sup> Mayo Clinic. Anemia. Available at: <https://www.mayoclinic.org/diseases-conditions/anemia/diagnosis-treatment/drc-20351366>. Accessed August 2023.

<sup>6</sup> Badireddy M, Baradhi KM. Chronic Anemia. PubMed. 2023. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK534803/>. Accessed August 2023.