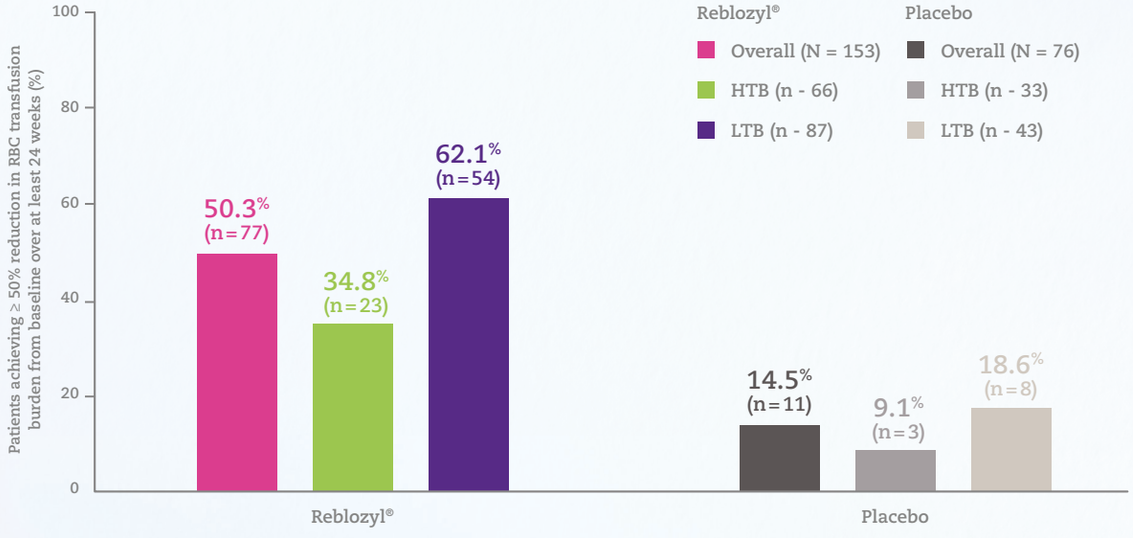
Reblozyl® in **myelodysplastic syndrome (MDS)**: Proven efficacy also in patients with high transfusion burden (HTB).

- The recommended initial dose is **1 mg/kg** every 3 weeks, independently of the transfusion burden at the start of the treatment [1].
- The dose can be increased up to **1.75 mg/kg** every 3 weeks in MDS [1].

PATIENTS ACHIEVING ≥ 50% REDUCTION IN RBC TRANSFUSION BURDEN FROM BASELINE OVER AT LEAST 24 WEEKS [2]



- Mean time to first achievement of a ≥ 50% reduction in RBC transfusion burden over at least 24 weeks was 2.7 months for the Reblozyl®-treated HTB responders
- 18.2% HTB patients receiving Reblozyl® achieved ≥ 75% reduction in RBC transfusion burden from baseline over at least 24 weeks

1. Reblozyl SmPC
2. Zeidan et al., EHA 2020, poster EP798
RBC: red blood cell

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Bristol Myers Squibb™

Reblozyl®	Belgium
25 mg	*[1,566.68 €]*
75 mg	*[4,698.98 €]*

ESSENTIAL INFORMATION ▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions. **NAME OF THE MEDICINAL PRODUCT** Reblozyl 25 mg powder for solution for injection Reblozyl 75 mg powder for solution for injection **QUALITATIVE AND QUANTITATIVE COMPOSITION** Reblozyl 25 mg powder for solution for injection Each vial contains 25 mg of luspatercept. After reconstitution, each mL of solution contains 50 mg luspatercept. Reblozyl 75 mg powder for solution for injection Each vial contains 75 mg of luspatercept. After reconstitution, each mL of solution contains 50 mg luspatercept. Luspatercept is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology. For the full list of excipients, see section 6.1. **PHARMACEUTICAL FORM**Powder for solution for injection (powder for injection). White to off-white lyophilised powder. **CLINICAL PARTICULARS Therapeutic indications** Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy (see section 5.1). Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia associated with betathalassaemia (see section 5.1). **Posology and method of administration** Reblozyl treatment should be initiated by a physician experienced in treatment of haematological diseases Posology Prior to each Reblozyl administration, the haemoglobin (Hb) level of patients should be assessed. In case of a red blood cell (RBC) transfusion occurring prior to dosing, the pretransfusion Hb level must be considered for dosing purposes. *Myelodysplastic syndromes* The recommended starting dose of Reblozyl is 1.0 mg/kg administered once every 3 weeks. In patients who are not RBC transfusion-free after at least 2 consecutive doses at the 1.0 mg/kg starting dose, the dose should be increased to 1.33 mg/kg. If patients are not RBC transfusion-free after at least 2 consecutive doses at the 1.33 mg/kg dose level, the dose should be increased to 1.75 mg/kg. The dose increase should not occur more frequently than every 6 weeks (2 administrations) and should not exceed the maximum dose of 1.75 mg/kg every 3 weeks. The dose should not be increased immediately after a dose delay. For patients with a pre-dose Hb level of > 9 g/dL and who have not yet achieved transfusion independence, a dose increase may be required at the physician's discretion; the risk of Hb increasing above the target threshold with concomitant transfusion cannot be excluded. If a patient loses response (i.e., transfusion independence), the dose should be increased by one dose level. β-*thalassaemi* The recommended starting dose of Reblozyl is 1.0 mg/kg administered once every 3 weeks. In patients who do not achieve a response, defined as a reduction in RBC transfusion burden of at least a third after ≥ 2 consecutive doses (6 weeks), at the 1.0 mg/kg starting dose, the dose should be increased to 1.25 mg/kg. The dose should not be increased beyond the maximum dose of 1.25 mg/kg every 3 weeks. If a patient loses response (if the RBC transfusion burden increases again after an initial response) the dose should be increased by one dose level. *MDS and* β-*thalassaemia Dose reduction and dose delay* In case of Hb increase > 2 g/dL within 3 weeks of luspatercept treatment in absence of transfusion, the Reblozyl dose should be reduced by one dose level. If the Hb is ≥ 11.5 g/dL in the absence of transfusion for at least 3 weeks, the dose should be delayed until the Hb is ≤ 11.0 g/dL. If there is also a concomitant rapid increase in Hb (> 2 g/dL within 3 weeks in absence of transfusion), a dose reduction to one step down (minimum 0.8 mg/kg) should be considered after the dose delay. Dose should not be reduced below 0.8 mg/kg. Dose reductions during treatment with luspatercept are provided below. **Table 1: Dose reductions for MDS Current dose - Dose reduction** 1.75 mg/kg, 1.33 mg/kg; 1.33 mg/kg, 1 mg/kg, 0.8 mg/kg. **Table 2: Dose reductions for β-thalassaemia. Current dose - Dose reduction** 1.25 mg/kg, 1 mg/kg; 1 mg/kg, 0.8 mg/kg. If patients experience persistent treatment-related Grade 3 or higher adverse reactions (see section 4.8), the treatment should be delayed until toxicity has improved or returned to baseline. After a dose delay, patients should be re-started at their previous dose or at reduced dose as per dose reduction guidance. *Missed doses* In case of a missed or delayed scheduled treatment administration, the patient should be administered Reblozyl as soon as possible and dosing continued as prescribed with at least 3 weeks between doses. *Patients experiencing a loss of response* If patients experience a loss of response to Reblozyl, causative factors (e.g. a bleeding event) should be assessed. If typical causes for a loss of haematological response are excluded, dose increase should be considered as described above for the respective indication being treated. *Discontinuation* Reblozyl should be discontinued if patients do not experience a reduction in transfusion burden after 9 weeks of treatment (3 doses) at the maximum dose level if no alternative explanations for response failure are found (e.g. bleeding, surgery, other concomitant illnesses) or if unacceptable toxicity occurs at any time. Special populations *Elderly* No starting dose adjustment is required for Reblozyl (see section 5.2). *Hepatic impairment* No starting dose adjustment is required for patients with total bilirubin (BIL) > upper limit of normal (ULN) and/or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) < 3 x ULN (see section 5.2). No specific dose recommendation can be made for patients with ALT or AST ≥ 3 x ULN or liver injury CTCAE Grade ≥ 3 due to lack of data (see section 5.2). *Renal impairment* No starting dose adjustment is required for patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] < 90 and ≥ 30 mL/min/1.73 m^2). No specific dose recommendation can be made for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) due to lack of clinical data (see section 5.2). Patients with renal impairment at baseline should be closely monitored for renal function as per standard of care. *Paediatric population* There is no relevant use of Reblozyl in the paediatric population for the indication of myelodysplastic syndromes, or in paediatric patients less than 6 months of age in β-thalassaemia. For non-clinical data, see section 5.3. The safety and efficacy of Reblozyl in the paediatric patients aged from 6 months to less than 18 years have not yet been established in β-thalassaemia. For nonclinical data, see section 5.3. Method of administration For subcutaneous use. After reconstitution, Reblozyl solution should be injected subcutaneously into the upper arm, thigh or abdomen. The exact total dosing volume of the reconstituted solution required for the patient should be calculated and slowly withdrawn from the singledose vial(s) into a syringe. The recommended maximum volume of medicinal product per injection site is 1.2 mL. If more than 1.2 mL is required, the total volume should be divided into separate similar volume injections and administered across separate sites. If multiple injections are required, a new syringe and needle must be used for each subcutaneous injection. No more than one dose from a vial should be administered. If the Reblozyl solution has been refrigerated after reconstitution, it should be removed from the refrigerator 15-30 minutes prior to injection to allow it to reach room temperature. This will allow for a more comfortable injection. For instructions on reconstitution of the medicinal product before administration, see section 6.6. **Contraindications** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Pregnancy (see section 4.6). **Undesirable effects** Summary of the safety profile *Myelodysplastic syndromes* The most frequently reported adverse drug reactions in patients receiving Reblozyl (at least 15% of patients) were fatigue, diarrhoea, asthenia, nausea, dizziness, back pain and headache. The most commonly reported Grade 3 or higher adverse drug reactions (at least 2% of patients) included syncope/presyncope, fatigue, hypertension and asthenia. The most commonly reported serious adverse drug reactions (at least 2% of patients) were urinary tract infection, back pain and syncope. Asthenia, fatigue, dizziness and headache occurred more frequently during the first 3 months of treatment. Treatment discontinuation due to an adverse reaction occurred in 2.0% of patients treated with luspatercept. The adverse reactions leading to treatment discontinuation in the luspatercept treatment arm were fatigue and headache. β-*thalassaemia* The most frequently reported adverse drug reactions in patients receiving Reblozyl (at least 15% of patients) were headache, bone pain and arthralgia. The most commonly reported Grade 3 or higher adverse drug reaction was hyperuricaemia. The most serious adverse reactions reported included thromboembolic events of deep vein thrombosis, ischaemic stroke portal vein thrombosis and pulmonary embolism (see section 4.4). Bone pain, asthenia, fatigue, dizziness and headache occurred more frequently during the first 3 months of treatment. Treatment discontinuation due to an adverse reaction occurred in 2.6% of patients treated with luspatercept. The adverse reactions leading to treatment discontinuation in the luspatercept treatment arm were arthralgia, back pain, bone pain and headache. Tabulated list of adverse reactions The highest frequency for each adverse reaction that was observed and reported in the two pivotal studies in MDS and βthalassaemia is shown in Table 3 below. The adverse reactions are listed below by body system organ class and preferred term. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000). **Table 3. Adverse drug reactions (ADRs) in patients treated with Reblozyl for MDS and β-thalassaemia Infections and infestations** bronchitis Very common**,** Common; urinary tract infection Very common**,** Common; upper respiratory tract infection Common, Very common; influenza Common, Common; **Immune system disorders** hypersensitivity* Common, Common; **Metabolism and nutrition disorders** hyperuricaemia Common, Common; **Nervous system disorders** dizziness Very common, Very common; headache Very common, Very common; syncope/presyncope Common, Common; **Ear and labyrinth disorders** vertigo/vertigo positional Common, Common **Vascular disorders** hypertension¨ Common, Common; thromboembolic events§ Common, Common; **Respiratory, thoracic and mediastinal disorders** dyspnoea Very common, Common **Gastrointestinal disorders** diarrhoea Very common, Very common; nausea Very common, Common **Musculoskeletal and connective tissue disorders** back pain Very common, Very common; arthralgia Common, Very common; bone pain Common, Very common; **General disorders and administration site conditions** fatigue Very common, Very common; asthenia Very common Common; injection site reactions# Common Common; * Hypersensitivity includes eyelid oedema, drug hypersensitivity, swelling face, periorbital oedema, face oedema, angioedema, lip swelling, drug eruption. ¨ Hypertension reaction includes essential hypertension, hypertension and hypertensive crisis. # Injection site reactions include injection site erythema, injection site pruritus, injection site swelling and injection site rash.§ Thromboembolic events include deep vein thrombosis, portal vein thrombosis, ischaemic stroke and pulmonary embolism. Description of selected adverse reactions *Bone pain* Bone pain was reported in 19.7% of β-thalassaemia patients treated with luspatercept (placebo 8.3%) and in 2.6% of MDS patients treated with luspatercept (placebo 3.9%). In β-thalassaemia patients treated with luspatercept, bone pain was most common in the first 3 months (16.6%) compared to months 4-6 (3.7%). Most events (41/44 events) were Grade 1-2, with 3 events Grade 3. One of the 44 events was serious, and 1 event led to treatment discontinuation. *Arthralgia* Arthralgia was reported in 19.3% of β-thalassaemia patients treated with luspatercept (placebo 11.9%) and in 5.2% of MDS patients treated with luspatercept (placebo 11.8%). In the β-thalassaemia patients treated with luspatercept, arthralgia led to treatment discontinuation in 2 patients (0.9%). *Hypertension* Patients treated with luspatercept had an average increase in systolic and diastolic blood pressure of 5 mmHg from baseline not observed in patients receiving placebo. Hypertension was reported in 8.5% of MDS patients treated with luspatercept (placebo 9.2%) and in 8.1% of β-thalassaemia patients treated with luspatercept (placebo 2.8%). See section 4.4. In MDS patients, Grade 3 events were reported for 5 patients (3.3%) treated with luspatercept and in 3 patients (3.9%) receiving placebo. No patient discontinued due to hypertension. In β-thalassaemia patients, Grade 3 events were reported in 4 patients (1.8%) treated with luspatercept (0.0% placebo). No patient discontinued due to hypertension. See section 4.4. *Hypersensitivity* Hypersensitivity-type reactions (including eyelid oedema, drug hypersensitivity, swelling face, periorbital oedema, face oedema, angioedema, lip swelling, drug eruption) were reported in 4.6% of MDS (2.6% placebo) and 4.5% of β-thalassaemia patients treated with luspatercept (1.8% placebo). In clinical studies, all events were Grade 1/2. In β-thalassaemia patients treated with luspatercept, hypersensitivity led to treatment discontinuation in 1 patient (0.4%). *Injection site reactions* Injection site reactions (including injection site erythema, injection site pruritus, injection site swelling and injection site rash) were reported in 3.9% of MDS (placebo 0.0%) and in 2.2% of β-thalassaemia patients receiving luspatercept (placebo 1.8%). In clinical studies, all events were Grade 1 and none led to discontinuation. *Thromboembolic events* Thromboembolic events (including deep vein thrombosis, portal vein thrombosis, ischaemic stroke and pulmonary embolism) occurred in 3.6% of β-thalassaemia patients receiving luspatercept (placebo 0.9%). All events were reported in patients who had undergone splenectomy and had at least one other risk factor. No difference in TEEs was observed between luspatercept and placebo arms in MDS patients. See section 4.4. *Immunogenicity* In clinical studies in MDS, an analysis of 260 MDS patients who were treated with luspatercept and who were evaluable for the presence of anti-luspatercept antibodies showed that 23 (8.8%) MDS patients tested positive for treatmentemergent anti-luspatercept antibodies, including 9 (3.5%) MDS patients who had neutralising antibodies against luspatercept. In clinical studies in β-thalassaemia, an analysis of 284 β-thalassaemia patients who were treated with luspatercept and who were evaluable for the presence of anti-luspatercept antibodies showed that 4 (1.4%) β-thalassaemia patients tested positive for treatmentemergent anti-luspatercept antibodies, including 2 (0.7%) β-thalassaemia patients who had neutralising antibodies against luspatercept. Luspatercept serum concentration tended to decrease in the presence of neutralising antibodies. There were no severe systemic hypersensitivity reactions reported for patients with anti-luspatercept antibodies. There was no association between hypersensitivity type reactions or injection site reactions and presence of anti-luspatercept antibodies. Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V. **MARKETING AUTHORISATION HOLDER** Bristol Myers Squibb Pharma EEIG Plaza 254 Blanchardstown Corporate Park 2 Dublin 15, D15 T867 Ireland **MARKETING AUTHORISATION NUMBER(S)b**EU/1/20/1452/001 EU/1/20/1452/002 **CLASSIFICATION** Medicinal product subject to medical prescription. **DATE OF REVISION OF THE TEXT** 04/02/2021 Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Reblozyl®
(luspatercept)