swissmedic

Date: 16 July 2026
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Reblozyl

International non-proprietary name:	luspatercept
Pharmaceutical form:	powder for solution for injection
Dosage strength(s):	75 mg, 25 mg
Route(s) of administration:	subcutaneous injection
Marketing authorisation holder:	Bristol-Myers Squibb SA
Marketing authorisation no.:	69592
Decision and decision date:	approved on 21 May 2026

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BSC	Best supportive care
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
EMH	Extramedullary haematopoiesis
ERA	Environmental risk assessment
ESA	Erythropoiesis-stimulating agents
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
Hb	Haemoglobin
Hbg	Haemoglobin
HI-E	Haematologic improvement-erythroid
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IPSS-R	Revised International Prognostic Scoring System
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MDS	Myelodysplastic syndromes
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RBC	Red blood cells
RMP	Risk management plan
RS	Ring sideroblast
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event

TEE	Thromboembolic event
TD	Transfusion-dependent
TI	Transfusion independence
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for luspatercept in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 13 June 2029 and 11 July 2019.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Reblozyl is indicated in adults for the treatment of transfusion-dependent anaemia due to very low-, low-, and intermediate-risk myelodysplastic syndromes (MDS).
Reblozyl is indicated in adults for the treatment of anaemia associated with transfusion-dependent and non-transfusion-dependent beta thalassaemia.

2.2.2 Approved indication

Reblozyl is indicated as monotherapy in adults for the treatment of
- Transfusion-dependent anaemia due to very low-risk to intermediate-risk myelodysplastic syndromes (MDS) that has not previously been treated with erythropoiesis-stimulating agents (ESA-naïve) (see "Properties and Effects")
- Anaemia that has not responded to an erythropoiesis-stimulating agent and requires transfusions of 2 or more units of packed red blood cells (RC) units over an 8-week period in patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) and ring sideroblasts (see "Properties and Effects").

Reblozyl is indicated as monotherapy for the treatment of anaemia in adult patients with β-thalassaemia who require regular red blood cell transfusions (see "Properties/Effects").

2.2.3 Requested dosage

Summary of the requested standard dosage:

Therapy introduction
The recommended starting dose of luspatercept is 1.0 mg/kg once every 3 weeks.

Myelodysplastic syndromes
If a patient is not RBC transfusion-free or does not reach Hb concentration of ≥ 10 g/dL and an Hb increase < 1 g/dL after at least 2 consecutive doses at the 1.0 mg/kg starting dose level, the luspatercept dose level should be increased to 1.33 mg/kg. If a patient is not RBC transfusion-free or does not reach Hb concentration of ≥ 10 g/dL and an Hb increase < 1 g/dL after at least 2 consecutive doses at the 1.33 mg/kg dose level, the luspatercept dose level should be increased to 1.75 mg/kg.

The dose should not be increased more frequently than every 6 weeks (2 doses) or beyond the maximum dose level of 1.75 mg/kg every 3 weeks. If a patient loses response (i.e. transfusion independence), the dose should be increased by one dose level

Transfusion-dependent beta thalassaemia
If a patient does not achieve a response, defined as a reduction in RBC transfusion burden of at least a third after at least 2 consecutive doses (6 weeks) at the 1.0 mg/kg starting dose, increase the dose 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.

Non-transfusion-dependent beta thalassaemia
If a patient does not achieve or maintain a response, defined as an increase from baseline in pre-dose Hb of ≥1 g/dL, after ≥ 2 consecutive doses (6 weeks) at the same dose level (in absence of transfusions, i.e. at least 3 weeks after the last transfusion), increase the dose by one dose level. The dose should not exceed the maximum dose of 1.25 mg/kg every 3 weeks.

Increase to next level dose:

Increase to next dose level for MDS

Current dose	Increased dose
0.8 mg/kg	1 mg/kg
1 mg/kg	1.33 mg/kg
1.33 mg/kg	1.75 mg/kg

Increase to next dose level for β-thalassaemia

Current dose	Increased dose
0.6 mg/kg*	0.8 mg/kg
0.8 mg/kg	1 mg/kg
1 mg/kg	1.25 mg/kg

* Applicable only to non-transfusion-dependent β-thalassaemia.

Dose reduction and dose delay
In case of Hb increase > 2 g/dL within 3 weeks in absence of transfusion compared with the Hb value at previous dose, the dose should be reduced by one dose level.
If the Hb is ≥ 12 g/dL in absence of transfusion for at least 3 weeks, the dose should be delayed until Hb ≤ 11.0 g/dL.
If there is also a concomitant rapid increase in Hb from the Hb value at previous dose (> 2 g/dL within 3 weeks in absence of transfusion), a dose reduction to one step down should be considered after the dose delay. Dose should not be reduced below 0.8 mg/kg (for MDS or transfusion-dependent β-thalassaemia) and below 0.6 mg/kg (for non-transfusion-dependent β-thalassaemia).

Reduced dose for MDS

Current dose	Reduced dose
1.75 mg/kg	1.33 mg/kg
1.33 mg/kg	1 mg/kg
1 mg/kg	0.8 mg/kg

Reduced dose for β-thalassaemia

Current dose	Reduced dose
1.25 mg/kg	1 mg/kg
1 mg/kg	0.8 mg/kg
0.8 mg/kg	0.6 mg/kg*

* Applicable only to non-transfusion-dependent β-thalassaemia.

In case of a missed or delayed scheduled treatment administration, administer Reblozyl as soon as possible and continue dosing as prescribed with at least 3 weeks between doses. If a loss of response is experienced, 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.

Reblozyl should be discontinued if patients do not experience a reduction in transfusion burden (for transfusion-dependent β-thalassaemia patients) or an increase from baseline Hb in the absence of transfusions (for non-transfusion-dependent β-thalassaemia patients), or a decrease in transfusion burden including no increase from baseline Hb (for MDS patients) 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.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	16 April 2024
Formal objection	15 May 2024
Response to formal objection	26 May 2024
Formal control completed	29 May 2024
List of Questions (LoQ)	6 August 2024
Response to LoQ	4 December 2024
2nd LoQ	20 March 2025
Response to 2nd LoQ	20 July 2025
Preliminary decision	17 October 2025
Response to preliminary decision	6 January 2026
Labelling corrections and/or other aspects	12 March 2026
Response to labelling corrections and/or other aspects	26 April 2026
Final decision	21 May 2026
Decision	approval

Based on Art. 13 TPA Swissmedic has only assessed parts of the primary data submitted with this application. As regards the remaining data, Swissmedic relies for its decision on the assessment of the foreign reference authority, the EMA. This SwissPAR relates to the assessment reports for Reblozyl (Procedure No. EMEA/H/C/004444/0000, published 30 April 2020; Procedure No. EMEA/H/C/004444/II/0009, published 26 January 2023; and Procedure No. EMEA/H/C/00444/II/0021, published 22 February 2024) issued by the EMA.

3 Medical context

Myelodysplastic syndromes (MDS) are chronic clonal stem cell disorders, observed mainly in older adults, causing ineffective blood cell production, cytopenias, and a risk of progressing to acute myeloid leukaemia. In lower-risk cases, treatment focuses on managing symptoms like anaemia and improving quality of life through therapies such as erythropoiesis-stimulating agents (ESAs), transfusions, or lenalidomide. In these patients, transfusion dependence is a common complication and can lead to lower quality of life and to iron overload. Therefore, there is an urgent need for new therapeutic options for patients with MDS, including both treatment for the underlying disease and for amelioration of symptoms.

Beta-thalassaemia is an inherited blood disorder caused by reduced or absent production of globin chains. This disease results in ineffective erythropoiesis leading to anaemia and to several subsequent pathophysiologic complications such as haemolysis, hypercoagulability, transfusional iron overload secondary to frequent RBC transfusions, heart disease, and hepatic cirrhosis. The transfusion-dependent form requires periodic and lifelong transfusions, iron chelation, and sometimes stem cell transplantation or gene therapy. In this disease, there is also an unmet medical need for effective treatment options in patients with beta thalassaemia who require regular transfusions.

4 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA (see section 2.3 “Regulatory history (milestones)”).

5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA (see section 2.3 “Regulatory history (milestones)”).

6 Clinical aspects

6.1 Clinical pharmacology

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the EMA and FDA. The available assessment reports and respective product information from these authorities were used as a basis for the clinical pharmacology evaluation.

For details regarding clinical pharmacology, please refer to the attached Information for healthcare professionals.

6.2 Dose finding and dose recommendation

There was no dedicated dose-finding study submitted for this application; instead, the recommended doses, which were up to 1.75 mg/kg for MDS and up to 1.25 mg/kg for beta thalassaemia, were supported by Phase 2 studies (A536-03 and A536-04). These open-label studies demonstrated that luspatercept was well tolerated in patients with MDS and both transfusion-dependent and non-transfusion-dependent β-thalassaemia.

6.3 Efficacy

To support the proposed indication in MDS, the applicant has submitted 2 pivotal Phase 3 studies (Final analysis of MEDALIST and Primary analysis of COMMANDS).

MEDALIST is a double-blind, randomised, placebo-controlled study, enrolling patients with anaemia due to very low-, low-, or intermediate-risk MDS with ring sideroblasts (RS). Patients required RBC transfusions and were refractory to, intolerant of, or ineligible for ESA treatment. For details regarding the included patient population, please refer to the attached Information for healthcare professionals.

The primary endpoint of this study was transfusion independence (TI) for any 56-day (8-week) period during the first 24 weeks of treatment. The key secondary endpoint was red blood cell (RBC)-TI ≥ 12 weeks (from Week 1 to 24 and from Week 1 to 48).

A total of 229 patients were enrolled in the MEDIALIST trial; of these, 153 patients were treated with luspatercept for a median duration of 51 weeks and 76 patients with placebo for a median duration of 24 weeks. The median age of these patients was 71.0 years (range: 26 to 95 years) and their baseline disease characteristics were reflective of a population that is refractory to, intolerant of, or ineligible for ESA treatment. Please refer to the attached Information for healthcare professionals for details regarding demographics and baseline characteristics.

As per a data cutoff date of 2018 (date of the primary endpoint analysis), a total of 38% of patients with TD anaemia in the context of low-risk to intermediate-risk MDS were independent of RBC transfusion for an 8-week interval compared to 13% in the placebo arm. This difference was statistically significant and clinically meaningful. The key secondary endpoint of transfusion independence for more than 12 weeks also demonstrated statistically significant results. For detailed information on efficacy results, please refer to the attached Information for healthcare professionals

COMMANDS is an ongoing open-label randomised study to compare luspatercept and epoetin alfa. Patients enrolled in the study have anaemia due to IPSS-R very low-, low-, or intermediate-risk MDS, are ESA naïve, and require transfusions. For details regarding the included patient population, please refer to the attached Information for healthcare professionals.

The primary endpoint of this study is RBC-TI for 12 weeks (84 days) with a concurrent mean haemoglobin (Hgb) increase of ≥ 1.5 g/dL compared with epoetin alfa. Key secondary endpoints included in the statistical testing hierarchy are the rate of patients who achieved haematologic improvement-erythroid response (HI-E), and RBC-TI for 24 weeks and for ≥ 12 weeks (84 days) during Week 1 to Week 24.

As per the DCO of March 2023, a total of 361 patients (including 182 in the luspatercept arm and 179 in the epoetin alfa arm) had been treated in this study. The median age of these patients was 74 years and their baseline characteristics were balanced overall between the 2 treatment arms and reflective of a population that is ESA naïve. Please refer to the attached Information for healthcare professionals for details regarding demographics and baseline characteristics.

This study met its primary efficacy endpoint of RBC transfusion-free for any 12-week period associated with a concurrent mean Hb increase of ≥ 1.5 g/dL compared to baseline during Week 1 to 24 (58.5% vs. 31.2%). All the key secondary endpoints hierarchically tested have shown a statistically significant improvement in favour of the luspatercept arm. For detailed information on efficacy results, please refer to the attached Information for healthcare professionals

To support the proposed indication in transfusion dependent beta thalassaemia, the applicant has submitted the final analysis of pivotal Phase 3 study BELIEVE.

This study was a double-blind, randomised, placebo-controlled study to compare the efficacy and safety of luspatercept in addition to best supportive care (BSC) versus placebo in addition to BSC for the treatment of patients with β-thalassaemia who require regular RBC transfusions. For details regarding the included patient population, please refer to the attached Information for healthcare professionals

The primary endpoint of this study was the percentage of “responders”, defined as subjects achieving an RBC transfusion reduction of ≥ 33% from baseline to Week 13-24 compared to the 3 months (12 weeks) preceding the randomisation. The key secondary endpoints included in the hierarchy testing were the proportion of subjects with haematologic improvement, defined as a ≥ 33% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units from Week 37 to Week 48; the proportion of subjects with haematologic improvement, defined as ≥ 50% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units from Week 13 to Week 24; the proportion of subjects with haematologic improvement, defined as ≥ 50% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units from Week 37 to Week 48; and the mean change in transfusion burden (RBC units/12 weeks) from Week 13 to Week 24.

As per the DCO of 2021, a total of 224 patients were randomised to the luspatercept + BSC treatment group and 112 patients to the placebo + BSC treatment group. The median age of these patients was 30.0 years. The demographic and baseline disease characteristics were generally well balanced between the 2 treatment groups and reflective of a population with transfusion-dependent beta thalassaemia. Please refer to the attached Information for healthcare professionals for details regarding demographics and baseline characteristics.

Luspatercept significantly reduced RBC transfusion burden by ≥33% in 21.4% of patients with transfusion-dependent β-thalassaemia compared to 4.5% in the placebo arm. All key secondary endpoints were reached as well, and a continued reduction RBC transfusion burden was observed beyond Week 96. For detailed information on efficacy results, please refer to the attached Information for healthcare professionals.

6.4 Safety

The pooled safety data comprised data from 784 patients, including 335 MDS patients and 449 β-thalassaemia patients. These safety data are presented as per a DCO of May 2024.

In the overall pool of MDS, a total of 96.4% of patients present at least 1 TEAE. The most frequently reported adverse reactions in MDS patients treated with luspatercept (in at least 15% of patients) were diarrhoea, fatigue, asthenia, peripheral oedema, nausea, back pain, dizziness, dyspnoea, cough, hypertension, and headache.

Grade 3-4 (G3-4) TEAEs were reported in 61.5% of patients. The most frequently reported Grade 3-4 adverse reactions (in at least 2% of patients) included hypertension (8%), syncope (4.8%), dyspnoea (2.7%), fatigue (2.7%), thrombocytopenia (2.4%), and urinary tract infection (2.1%).

A total of 45.8% of patients presented SAEs. The most frequently reported serious adverse drug reactions (in at least 1% of patients) were urinary tract infection 2.4%, dyspnoea 1.8%, and back pain 1.2%.

Treatment discontinuation due to an adverse event occurred in 15.2% of patients treated with luspatercept. The most common reason for discontinuation in the luspatercept treatment arm was progression of the underlying MDS.

In the overall pool of beta thalassaemia, a total of 99.2% of the patients presented at least 1 TEAE. The most frequently reported adverse reactions (in at least 15% of patients) treated with luspatercept were upper respiratory tract infections, back pain, headache, arthralgia, bone pain, cough, diarrhoea, hypertension, fatigue, dizziness, and influenza.

Grade 3-4 (G3-4) TEAEs were reported in 44.2% of patients. The most frequently reported Grade 3-4 adverse reactions (in at least 2% of patients) were bone pain (2.4%), hypertension (2.2%), and back pain (2.0%).

The most frequently reported serious adverse reactions included thromboembolic events such as deep vein thrombosis 1.1%, thrombotic stroke 0.2%, portal vein thrombosis 0.2%, stroke 0.2%, superficial vein thrombosis 0.7%, and pulmonary embolism 0.9%.

Treatment discontinuation due to an adverse reaction occurred in 11.4% of patients treated with luspatercept. The adverse reactions leading to discontinuation in the luspatercept treatment arm included thromboembolic events (TEE), arthralgia, cardiac disorders, and extramedullary haematopoiesis (EMH). The cases of EMH were observed in non-transfusion dependent β-thalassaemia patients.

The risk of malignancy is particularly concerning given that animal toxicity studies have demonstrated increased haematologic malignancies and that TGFβ signalling along with GDF11, which are ligands trapped by luspatercept, play a well-established role in cancer. Malignancies have been reported in 4.2% of patients treated with luspatercept, with 9.3% of the MDS and 0.4% of the β-thalassaemia patients reporting a malignancy. While the incidence of secondary malignancies was low in patients with β-thalassaemia treated with luspatercept, the risk cannot be excluded given the drug's mechanism of action and the long-term exposure required for this treatment; the risk of malignancies therefore requires close monitoring.

Cardiac disorder is an additional risk of concern that was observed in 22.2% of patients treated with luspatercept, with 26.9% of the MDS and 18.7% of the β-thalassaemia patients reporting a cardiac adverse event.

For a detailed overview of the safety profile, please refer to the attached Information for healthcare professionals.

6.5 Final clinical benefit-risk assessment

Myelodysplastic syndromes represent a significant unmet medical need, requiring new therapeutic options that address both disease progression and symptom control. In this setting, luspatercept has demonstrated a significant and sustained reduction in red blood cell transfusion burden in both refractory and ESA-naïve MDS patients, with primary endpoint results supported by key secondary endpoints and maintenance of quality of life over time. Although its safety profile is generally manageable, several important adverse events have been identified, including secondary primary malignancies. The observed relevant risk of secondary primary malignancies is described in the Information for healthcare professionals.

Transfusion-dependent β-thalassemia is associated with a high unmet need, and only limited treatment options are available. Luspatercept has shown a clinically meaningful reduction in transfusion burden, supported by statistically significant improvements across all key secondary endpoints. While the safety profile remains manageable, several important adverse events have been identified, including secondary primary malignancies. Given the drug’s mechanism of action and the need for long-term treatment, the potential malignancy risk remains a concern requiring careful long-term monitoring which is described in the Information for healthcare professionals.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Reblozyl was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Reblozyl®

Composition

Active substances

Luspatercept (produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology).

Excipients

Citric acid monohydrate, sodium citrate dihydrate, polysorbate 80, sucrose, hydrochloric acid, sodium hydroxide.
Each vial contains maximum 0.5 mg (25 mg luspatercept per vial) or 1.1 mg (75 mg luspatercept per vial) sodium.

Pharmaceutical form and active substance quantity per unit

Powder for solution for injection containing 25 mg or 75 mg luspatercept per vial. After reconstitution, each mL of solution contains 50 mg luspatercept for subcutaneous (s.c.) injection.

Indications/Uses

Reblozyl is indicated as monotherapy in adults for the treatment of

- Transfusion-dependent anemia due to very low-risk to intermediate-risk myelodysplastic syndromes (MDS) that has not previously been treated with erythropoiesis-stimulating agents (ESA-naive) (see “Properties and Effects”)
- Anemia that has not responded to an erythropoiesis-stimulating agent and requires transfusions of 2 or more units of packed red blood cells (RC) units over an 8-week period in patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) and ring sideroblasts (see “Properties and Effects”).

Reblozyl is indicated as monotherapy for the treatment of anemia in adult patients with β- thalassemia who require regular red blood cell transfusions (see “Properties/Effects”).

Dosage/Administration

Treatment should be initiated by a physician experienced in treatment of haematological diseases. Reblozyl is not indicated for patients who require immediate correction of anemia with a red blood cell transfusion.
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

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 pre-transfusion Hb level must be considered for dosing purposes.

The recommended starting dose of Reblozyl is 1 mg/kg administered once every 3 weeks.

Myelodysplastic syndromes
The recommended desired Hb concentration range is between 10 g/dL and 12 g/dL. Dose increase for insufficient response is provided below.

Table 1: Dose increase for insufficient response

Dose at 1 mg/kg	**Dose increase**
If after at least 2 consecutive doses at 1 mg/kg, a patient: • is not RBC transfusion-free, or • does not reach Hb concentration of ≥ 10 g/dL and the Hb increase is < 1 g/dL	• Dose should be increased to 1.33 mg/kg
Dose at 1.33 mg/kg	**Dose increase**
If after at least 2 consecutive doses at 1.33 mg/kg, a patient: • is not RBC transfusion-free, or • does not reach Hb concentration of ≥ 10 g/dL and the Hb increase is < 1 g/dL	• 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 (see Table 2).

Transfusion-dependent β-thalassaemia (TDT)

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 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 (see Table 3).

Increase to next dose level

Increase to next dose level based on current dose is provided below.

Table 2: Increase to next dose level for MDS

Current dose	Increased dose
0.8 mg/kg	1 mg/kg
1 mg/kg	1.33 mg/kg
1.33 mg/kg	1.75 mg/kg

Table 3: Increase to next dose level for β-thalassaemia

Current dose	Increased dose
0.6 mg/kg	0.8 mg/kg
0.8 mg/kg	1 mg/kg
1 mg/kg	1.25 mg/kg

Dose reduction and dose delay

In case of Hb increase ≥ 2 g/dL within 3 weeks in absence of transfusion compared with the Hb value at previous dose, Reblozyl dose should be reduced by one dose level.

If the Hb is 11.5 g/dL (12 g/dL for ESA naïve MDS patients) in the absence of transfusion for at least 3 weeks, the dose should be delayed until the Hb is ≤ 11 g/dL. If there is also a concomitant rapid increase in Hb from the Hb value at previous dose (> 2 g/dL within 3 weeks in absence of transfusion), a dose reduction to one step down should be considered after the dose delay.

Dose should not be reduced below 0.8 mg/kg (for MDS or transfusion-dependent β-thalassaemia).

Reduced dose during treatment with luspatercept are provided below.

Table 4: Reduced dose for MDS

Current dose	Reduced dose
1.75 mg/kg	1.33 mg/kg
1.33 mg/kg	1 mg/kg
1 mg/kg	0.8 mg/kg

Table 5: Reduced dose for β-thalassaemia

Current dose	Reduced dose
1.25 mg/kg	1 mg/kg
1 mg/kg	0.8 mg/kg
0.8 mg/kg	0.6 mg/kg

Dose modification due to adverse reactions

Instructions on dose interruptions or reductions for luspatercept treatment-related adverse reactions are outlined in Table 6.

Table 6: Dose modification instructions

Treatment-related adverse reactions*	Dose instructions
Grade 2 adverse reactions (see ”Undesirable effects”), including Grade 2 hypertension (see ”Warnings and precautions” and “Undesirable effects”)	• Interrupt treatment • Restart at previous dose when adverse reaction has improved or returned to baseline
Grade ≥ 3 hypertension (see ”Warnings and precautions” and “Undesirable effects”)	• Interrupt treatment • Restart at reduced dose once the blood pressure is controlled as per dose reduction guidance
Other persistent Grade ≥ 3 adverse reactions (see ”Undesirable effects”)	• Interrupt treatment • Restart at previous dose or at reduced dose when adverse reaction has improved or returned to baseline as per dose reduction guidance
Extramedullary haemopoiesis (EMH) masses causing serious complications (see ”Warnings and precautions” and “Undesirable effects”)	• Discontinue treatment

* Grade 1: mild; Grade 2: moderate; Grade 3: severe; and Grade 4: life-threatening.

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 (see Table 2 and Table 3).

Discontinuation

Reblozyl should be discontinued if patients do not experience a reduction of more than 33% in transfusion burden after 9 weeks at maximum tolerated dose (for transfusion-dependent β-thalassaemia patients), or a decrease in transfusion burden including no increase from baseline Hb (for MDS patients) 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 “Pharmacokinetics”). Limited data are available in β-thalassaemia patients ≥ 60 years of age.

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 “Pharmacokinetics”).

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 “Pharmacokinetics”).

Renal impairment

No starting dose adjustment is required for patients with mild or moderate renal impairment (individual estimated glomerular filtration rate [eGFR] 30 to 89 mL/min).

No specific dose recommendation can be made for patients with severe renal impairment (individual eGFR < 30 mL/min) due to lack of clinical data (see “Pharmacokinetics”). Patients with renal impairment at baseline have been observed to have higher exposure (see “Pharmacokinetics”). Consequently, these patients should be closely monitored for adverse reactions and dose adjustment should be managed accordingly (see Table 6).

Paediatric population
The safety and effectiveness of Reblozyl in children and adolescents under 18 years of age have not been established. There are no clinical data available. For non-clinical data, see the section entitled “Preclinical data”.

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 single-dose 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 using the same anatomical location but on opposite sides of the body.

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 “Composition”.
- Pregnancy (see “Pregnancy, lactation”).

- Patients requiring treatment to control the growth of EMH masses (see “Warnings and precautions”).

Warnings and precautions

Thromboembolic events

Thromboembolic events (TEEs) were reported in 6.0% (47/784) of patients treated with luspatercept. In β–thalassaemia patients treated with luspatercept, TEEs were reported in 6.0% (27/449). Reported TEEs included deep vein thrombosis (DVT), portal vein thrombosis, pulmonary emboli, thrombotic stroke and superficial vein thrombosis (see “Undesirable effects”). All patients with TEEs were splenectomised and had at least one other risk factor for developing TEE (e.g. history of thrombocytosis or concomitant use of hormone replacement therapy). The occurrence of TEE was not correlated with elevated Hb levels. The potential benefit of treatment with luspatercept should be weighed against the potential risk of TEEs in β–thalassaemia patients with a splenectomy and other risk factors for developing TEE. Thromboprophylaxis according to current clinical guidelines should be considered in patients with β–thalassaemia at higher risk.

In MDS patients, TEEs were reported in 6.0% (20/335) of patients treated with luspatercept. Reported TEEs included cerebral ischemia in 0.6% (2/335) and cerebrovascular accident in 0.9% (3/335) of patients.

Extramedullary haemopoiesis masses

In β–thalassaemia patients, extramedullary haemopoiesis (EMH) masses were observed in 7.8% (35/449), with 1.6% (7/449) reporting symptoms of spinal cord compression. Confirmatory diagnosis of spinal cord compression due to EMH was reported in 0.9% (4/449) of patients treated with luspatercept. EMH was more commonly observed in patients with non-transfusion dependent β-thalassemia (14.2% (19/134) compared to patients with transfusion dependent β-thalassemia (5.1% (16/315)).

Patients with EMH masses may experience worsening of these masses and complications during treatment. Signs and symptoms may vary depending on anatomical location. Patients should be monitored at initiation and during treatment for symptoms and signs or complications resulting from the EMH masses and be treated according to clinical guidelines. Treatment with luspatercept must be discontinued in case of serious complications due to EMH masses.

Increased blood pressure

In MDS and β–thalassaemia pivotal studies, patients treated with luspatercept had an average increase in systolic and diastolic blood pressure of up to 5 mmHg from baseline (see “Undesirable effects”). Hypertension of any grade was reported in 18.2% (143/784) of the patients treated with luspatercept. Grade 3/4 hypertension has been reported in 4.7% (37/784) of patients treated with luspatercept.
An increased incidence of hypertension was observed in the first 12 months of treatment in non-transfusion-dependent- β–-thalassaemia patients treated with luspatercept (see “Undesirable effects”).

The treatment must be started only if the blood pressure is adequately controlled. Blood pressure should be monitored prior to each luspatercept administration. Luspatercept dose may require adjustment or may be delayed, and patients should be treated for hypertension as per current clinical guidelines (see Table 6 in “Dosage/Administration”). The potential benefit of treatment with Reblozyl should be re-evaluated in case of persistent hypertension or exacerbations of pre-existing hypertension.

Traumatic fracture

In β–thalassaemia patients treated with luspatercept, traumatic fractures were observed in 1.3% (6/449).
In transfusion-dependent β-thalassaemia patients, traumatic fractures were observed in 0.3% (1/315) of patients treated with luspatercept.

In non-transfusion-dependent β-thalassaemia patients, traumatic fractures were observed in 3.7% (5/134) of patients treated with luspatercept. Patients should be informed of the risk of traumatic fracture.

Malignancies

Malignancies have been reported in 4.2% (33/784) of patients treated with luspatercept, with 9.3% (31/335) of the MDS and 0.4% (2/449) of the β-thalassemia patients reporting a malignancy. Malignancies reported in more than 1 MDS patient included progression to AML 1.8% (6/335), basal cell carcinoma 1.8% (6/335), squamous cell carcinoma 0.9% (3/335) and prostate cancer 0.6% (2/335). Malignancies were diagnosed at different time points, ranging from shortly after luspatercept initiation to after treatment had ended.

Cardiac risks

Cardiac disorders have been reported in 22.2% (174/784) of patients treated with luspatercept, with 26.9% (90/335) of the MDS and 18.7% (84/449) of the β–thalassaemia patients reporting a cardiac adverse event. Cardiac disorders reported in MDS and β-thalassaemia pivotal studies included atrial fibrillation 2.7% (21/784), cardiac failure 1.0% (8/784) and tachycardia 4.6% (36/784).
In luspatercept treated MDS-patients atrial fibrillation was observed in 4.8% (16/335) of the patients, cardiac failure in 2.4% (8/335) of the patients and tachycardia in 4.5% (15/335) of the patients.
In luspatercept treated β-thalassaemia-patients atrial fibrillation was observed in 1.1% (5/449) of the patients and tachycardia in 4.7% (21/449) of the patients.
Patients with a cardiac disorder history should be monitored for worsening of cardiac symptoms and dose modifications considered (See section “dosage/administration”).

Excipients

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

Polysorbate 80 content

This medicinal product contains 0.1 mg of polysorbate 80 in each 25 mg vial or 0.3 mg of polysorbate 80 in each 75 mg vial which is equivalent to 0.2 mg/mL. Polysorbates may cause allergic reactions.

Interactions

No formal clinical interaction studies have been performed. Concurrent use of iron-chelating agents had no effect on luspatercept pharmacokinetics.

Pregnancy, lactation

Women of childbearing potential / Contraception in females

Women of childbearing potential have to use effective contraception during treatment with Reblozyl and for at least 3 months after the last dose. Prior to starting treatment with Reblozyl, a pregnancy test has to be performed for women of childbearing potential and the patient card has to be provided.

Pregnancy

Treatment with Reblozyl should not be started if the woman is pregnant (see “Contraindications”). There are no data from the use of Reblozyl in pregnant women. Studies in animals have shown reproductive toxicity (see “Preclinical data”). Reblozyl is contraindicated during pregnancy (see “Contraindications”). If a patient becomes pregnant, Reblozyl should be discontinued.

Breast-feeding

It is unknown whether luspatercept or its metabolites are excreted in human milk. Luspatercept was detected in the milk of lactating rats (see “Preclinical data”). Because of the unknown adverse effects of luspatercept in newborns/infants, a decision must be made whether to discontinue breast-feeding during therapy with Reblozyl and for 3 months after the last dose or to discontinue Reblozyl therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of luspatercept on fertility in humans is unknown. Based on findings in animals, luspatercept may compromise female fertility (see “Preclinical data”).

Effects on ability to drive and use machines

Reblozyl has a minor influence on the ability to drive and use machines. The ability to react when performing these tasks may be impaired due to risks of fatigue, vertigo, dizziness or syncope (see “Undesirable effects”). Therefore, patients should be advised to exercise caution until they know of any impact on their ability to drive and use machines.

Undesirable effects

Summary of the safety profile

Description patient pool

The data presented in this section was collected from 784 patients (335 MDS and 449 β–thalassaemia patients, including 134 patients with non-transfusion-dependent β-thalassaemia and 315 patients with transfusion-dependent β-thalassaemia) treated with luspatercept in the phase 3 clinical studies as well as in the open-label, long-term study with an estimated follow-up of up to 5 years.

Myelodysplastic syndromes

The most frequently reported adverse drug reactions in MDS patients receiving Reblozyl (at least 15% of patients) were diarrhoea, fatigue, asthenia, oedema peripheral, nausea, back pain, dizziness, dyspnoea, cough, hypertension and headache. The most commonly reported Grade 3/4 adverse drug reactions (at least 2% of patients) included hypertension events (8%), syncope (4.8%), dyspnoea (2.7%), fatigue (2.7%), thrombocytopenia (2.4%), and urinary tract infection (2.1%). The most commonly reported serious adverse drug reactions (at least 1% of patients) were urinary tract infection 2.4% (8/335), dyspnoea 1.8% (6/335) and back pain 1.2% (4/335).
Treatment discontinuation due to an adverse event occurred in 15.2% (51/335) of patients treated with luspatercept. The most common reason for discontinuation in the luspatercept treatment arm was progression of underlying MDS.

Dose delays due to predose Hb ≥12 g/dL occurred in 25.3% of luspatercept treated ESA-naïve MDS patients.

β-thalassaemia
The most frequently reported adverse drug reactions in β-thalassaemia patients receiving Reblozyl (at least 15% of patients) were upper respiratory tract infections, back pain, headache, arthralgia, bone pain, cough, diarrhoea hypertension, fatigue, dizziness and influenza. The most commonly reported Grade 3/4 adverse drug reaction (at least 2% of patients) included bone pain (2.4%), hypertension (2.2%) and back pain (2.0%). The most relevant serious adverse reactions reported included thromboembolic events of deep vein thrombosis 1.1% (5/449), thrombotic stroke 0.2% (1/449) portal vein thrombosis 0.2% (1/449) cerebrovascular accident 0.2% (1/449), superficial vein thrombosis 0.7% (3/449) and pulmonary embolism 0.9% (4/449) (see “Warnings and precautions”).
The most commonly reported Grade 3/4 adverse reactions (at least 2% of patients) in patients with transfusion-dependent β-thalassaemia was bone pain 2.5% (8/315), back pain 2.5% (8/315) and syncope 2.2% (7/315). The most relevant serious adverse reactions included thromboembolic events of deep vein thrombosis in 1.6% (5/315) and pulmonary embolism in 1.3% (4/315) of the patients and spinal cord compression due to EMH in 1.0 % (3/315) of the patients.
The most commonly reported Grade 3/4 adverse reactions (at least 2% of patients) in patients with non-transfusion-dependent β-thalassaemia was hypertension 3.7% (5/134) and bone pain 2.2% (3/134). The most relevant serious adverse reactions included traumatic fractures in 1.5% (2/134) and spinal cord compression due to EMH in 0.7% (1/134) of the patients.

Treatment discontinuation due to an adverse reaction occurred in 11.4% (51/449) of patients treated with luspatercept. The adverse reactions leading to treatment discontinuation in the luspatercept treatment arm were TEE, arthralgia, cardiac disorders and EMH including spinal cord compression due to EMH in 2 β-thalassemia patients.

Tabulated list of adverse reactions

The frequency for each adverse reaction that was reported in a pool of MDS and β–thalassaemia patients in the four pivotal studies as well as in the long-term follow up study (N=784) is shown in Table 7 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), very rare (< 1/10,000) and not known (frequency cannot be estimated from the available data).

Table 7. Adverse drug reactions (ADRs) in patients treated with Reblozyl for MDS and β–thalassaemia

System organ class	Preferred term	Frequency (all grades) in Pivotal MDS (N=335) + β-Thalassaemia (N=449) N=784
Infections and infestations	Bronchitis	Common
	Urinary tract infection	Very Common (10.5%)
	Respiratory tract infection	Common
	Upper respiratory tract infection	Very Common (27.4%)
	Influenza	Very Common (11.5%)
Blood and lymphatic system disorders	Extramedullary haemopoiesis [a, VI VII]	Common
	Thrombocytopenia	Common
Immune system disorders	Hypersensitivity [I, VI]	Common
Metabolism and nutrition disorders	Hyperuricaemia	Common
	Dehydration	Common
	Decreased appetite	Common
	Electrolyte imbalance [IX]	Very common (11.5%)
Psychiatric disorders	Insomnia	Common
	Anxiety	Common
	Irritability	Uncommon
	Confusional state[b]	Common

System organ class	Preferred term	Frequency (all grades) in Pivotal MDS (N=335) + β-Thalassaemia (N=449) N=784
Nervous system disorders	Dizziness	Very common (17.5%)
	Headache	Very common (28.1%)
	Migraine	Common
	Spinal cord compression[c, VI]	Uncommon
	Syncope/presyncope	Common
Ear and labyrinth disorders	Vertigo/vertigo positional	Common
Cardiac disorders	Atrial fibrillation	Common
	Cardiac failure[b]	Common
Vascular disorders	Prehypertension[a]	Common
	Hypertension[II, VI]	Very common (18.2%)
	Tachycardia	Common
	Thromboembolic events[IV, VI]	Common
Respiratory, thoracic and mediastinal disorders	Cough	Very common (21.0%)
	Epistaxis	Common
	Dyspnoea[VIII]	Very common (10.8%)
Gastrointestinal disorders	Abdominal pain	Very common (11.9%)
	Abdominal discomfort	Common
	Diarrhoea	Very common (23.3%)
	Nausea	Very common (16.6%)
Skin and subcutaneous tissue disorders	Hyperhidrosis	Common
Musculoskeletal and connective tissue disorders	Back pain	Very common (31.5%)
	Arthralgia[VI]	Very common (23.6%)
	Bone pain[VI]	Very common (18.2%)
	Myalgia	Very common 11.0%
	Muscular weakness	Common
Renal and urinary disorders	Proteinuria	Common
	Albuminuria [a]	Uncommon
	Kidney inury[x]	Very common (10.3%)

System organ class	Preferred term	Frequency (all grades) in Pivotal MDS (N=335) + β-Thalassaemia (N=449) N=784
General disorders and administration site conditions	Non-cardiac chest pain	Common
	Influenza-like illness	Common
	Fatigue	Very Common (21.9%)
	Asthenia	Very common (16.6%)
	Injection site reactions[III, VI]	Common
	Oedema peripheral	Very common (13.0%)
Liver and gallbladder disorders	Alanine aminotransferase increased	Common
	Aspartate aminotransferase increased	Common
	Blood bilirubin increased	Common
	Gamma-glutamyltransferase increased	Common
Injury, poisoning and procedural complications	Traumatic fracture[a, VI]	Common

[I] Hypersensitivity includes eyelid oedema, drug hypersensitivity, swelling face, periorbital oedema, face oedema, angioedema, lip swelling, drug eruption.

[II] Hypertension includes essential hypertension, hypertension and hypertensive crisis.

[III] Injection site reactions include injection site erythema, injection site pruritus, injection site swelling and injection site rash.

[IV] TEEs include deep vein thrombosis, portal vein thrombosis, ischaemic stroke and pulmonary embolism.

[V] Frequency is based on laboratory values of any grade.

[VI] See “Undesirable effects” Description of selected adverse reactions.

[VII] Reported only in post-marketing in MDS indication.

[VIII] Dyspnoea includes dyspnoea exertional for ACE-536-MDS-002.

[IX] Electrolyte imbalance includes calcium deficiency, hypercalcaemia, hyperkalaemia, hypernatraemia, hypocalcaemia, hypokalaemia, hypomagnesaemia, hyponatraemia, hypophosphataemia and magnesium deficiency .

[X] ADR includes similar/grouped terms.

[a] ADRs only observed in β-thalassaemia studies.

[b] ADRs only observed in MDS studies.

[c] Spinal cord compression due to EMH only observed in β-thalassaemia

Description of selected adverse reactions

Bone pain

Bone pain was reported in 18.2% (143/784) of patients treated with luspatercept, occurring in 3.3% (11/335) of MDS and in 29.4% (132/449) of β-thalassaemia patients. In β-thalassaemia patients treated with luspatercept most events (121/132) were Grade 1/2, and Grade 3/4 events were reported in 2.4% (11/449) patients. Serious bone pain was reported in 0.4% (2/449) of patients.
In the β-thalassaemia studies were 0.4% (2/449) patients with bone pain that led to treatment discontinuation.

Arthralgia

Arthralgia was reported in 23.6% (185/784) of patients treated with luspatercept, occurring in 10.7% (36/335) of MDS and in 33.2% (149/449) of β-thalassaemia patients.
Arthralgia was reported mostly as Grade 1-2 in both indications, with Grade 3/4 events being reported in 0.9% (3/335) of MDS patients and 0.9% (4/449) of β-thalassaemia patients.
During the clinical studies arthralgia led to treatment discontinuation in 0.7% (3/449) patients with β-thalassaemia.

Hypertension

MDS and β-thalassaemia patients treated with luspatercept had an average increase in systolic and diastolic blood pressure of up to 5 mmHg from baseline not observed in patients receiving placebo.
Hypertension events were reported in 18.2% (143/784) of patients treated with luspatercept, occurring in 15.8% (53/335) of MDS and in 20% (90/449) of β-thalassemia patients.
Most hypertension events were Grade 1/2, with Grade 3/4 hypertension events being reported in 8.0% (27/335) of MDS and in 2.2% (10/449) of β-thalassaemia patients treated with luspatercept.
During the clinical studies, hypertension did not lead to treatment discontinuation.

Hypersensitivity

Hypersensitivity-type reactions included eyelid oedema, drug hypersensitivity, swelling face, periorbital oedema, face oedema, angioedema, lip swelling, drug eruption.

Hypersensitivity-type reactions were reported in 5.2% (41/784) of patients treated with luspatercept, occurring in 4.5% (15/335) of MDS and in 5.8% (26/449) of β-thalassaemia patients, with all events being Grade 1/2 in severity.
Face oedema occurred in 0.9% (7/784) of luspatercept treated patients in both indications.

During the clinical study, hypersensitivity led to treatment discontinuation in 0.2 % (1/449) of the patients with β-thalassaemia.

Injection site reactions
Injection site reactions included injection site erythema, injection site pruritus, injection site swelling and injection site rash.
Injection site reactions were reported in 4.3% (34/784) of patients treated with luspatercept, occurring in 3.6% (12/335) of MDS and in 4.9% (22/449) of β-thalassaemia patients, with all events being Grade 1/2.
During the clinical studies, injection site reactions did not lead to discontinuation.

Thromboembolic events
TEEs were reported in 6.0% (47/784) of patients treated with luspatercept. TEEs included deep vein Response to HA: The entire section was updated to reflect the entire treatment duration., portal vein thrombosis, ischaemic stroke and pulmonary embolism.
TEEs were reported in 6.0% (20/335) of MDS patients. TEEs reported in MDS patients included cerebral ischemia in 0.6% (2/335) and cerebrovascular accident in 0.9% (3/335) of patients. TEEs did not lead to treatment discontinuations in MDS patients. All TEEs occurred in patients with significant risk factors (atrial fibrillation, stroke or heart failure and peripheral vascular disease) and were not correlated with elevated Hb, platelet levels or hypertension. See “Warnings and precautions”.
TEEs occurred in 6.0% (27/449) of β-thalassaemia patients receiving luspatercept. TEEs led to treatment discontinuations in 2.2% (10/449) β-thalassaemia patients. All TEEs events were reported in patients who had undergone splenectomy and had at least one other risk factor. See “Warnings and precautions”.

Extramedullary haemopoiesis masses
EMH were reported in 7.8% (35/449) of β-thalassaemia patients treated with luspatercept.
The majority of the events (27/35) were Grade 1/2. Grade 3/4 EMH were reported in 1.0% (8/784) of patients.
During the β-thalassaemia studies, 1.6% (7/449) patients discontinued due to EMH masses.
EMH events were manageable with standard clinical practice.

EMH masses may also occur after extended treatment with luspatercept (i.e. after 96 weeks). See “Warnings and precautions”

Spinal cord compression

Spinal cord compression or symptoms due to EMH masses occurred in 1.6% (7/449) of β-thalassaemia patients treated with luspatercept with a confirmed spinal cord compression diagnosis reported in 0.9% (4/449) of patients. Five patients discontinued treatment due to Grade 3/4 symptoms of spinal cord compression, including 2 patients with a history of EMH who discontinued treatment due to Grade 4 spinal cord compression. See “Warnings and precautions”.

Traumatic fracture

Traumatic fractures were reported in 1.3% (6/449) of β-thalassaemia patients treated with luspatercept, with the majority of events (5/6) being reported in non-transfusion-dependent β-thalassaemia patients receiving luspatercept.

Grade 3/4 events were reported in 0.7% (3/449) of β-thalassaemia patients treated with luspatercept. During the clinical studies, traumatic fractures did not lead to treatment discontinuations.

Cardiac disorders

In the clinical studies for MDS and β-thalassaemia atrial fibrillation was reported in 2.7% (21/784), cardiac failure in 1.0% (8/784), and tachycardia in 4.6% (36/784) of the patients. In the MDS studies, atrial fibrillation was observed in 4.8% (16/335), cardiac failure in 2.4% (8/335), tachycardia in 4.5% (15/335) of the patients treated with luspatercept. Cardiac disorders led to treatment discontinuations in 0.6% (2/335) MDS patients. In the clinical studies for β-thalassaemia, atrial fibrillation was observed in 1.1% (5/449), and tachycardia in 4.7% (21/449) of the patients. Cardiac disorders led to treatment discontinuations in 1.3% (6/449) β-thalassaemia patients.

(See “Warnings and precautions”).

Immunogenicity

In clinical studies in MDS, an analysis of 395 MDS patients who were treated with luspatercept and who were evaluable for the presence of anti-luspatercept antibodies showed that 36 (9.1%) patients tested positive for treatment-emergent anti-luspatercept antibodies, including 18 (4.6%) patients who had neutralising antibodies against luspatercept.

In clinical studies in transfusion dependent and non-transfusion dependent β-thalassaemia, an analysis of 380 β-thalassaemia patients who were treated with luspatercept and who were evaluable for the presence of anti-luspatercept antibodies showed that 7 (1.84%) patients tested positive for

treatment emergent anti-luspatercept antibodies, including 5 (1.3%) patients who had neutralising antibodies against luspatercept.

Luspatercept serum concentration tended to decrease in the presence of anti-luspatercept 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. Patients with treatment-emergent anti-luspatercept antibodies were more likely to report a serious treatment-emergent adverse event (69.4% [25/36] for anti-luspatercept antibodies-positive patients vs. 45.7% [164/359] for anti-luspatercept antibodies-negative patients) or a Grade 3 or 4 treatment emergent adverse event (77.8% [28/36] for anti-luspatercept antibodies-positive patients vs. 56.8% [204/359] for anti-luspatercept antibodies-negative patients) compared to patients without anti-luspatercept antibodies in the TD MDS pool.

Other special population

MDS patients without ring sideroblast (RS-)
RS- patients are more likely to experience serious adverse events, Grade 5 treatment emergent adverse events, adverse events leading to drug discontinuation or dose reduction compared to patients with ring sideroblasts (RS+). In ACE536-MDS-002 study, RS- patients showed higher incidence of some adverse reactions compared to RS+ patients in both treatment arms. When comparing RS subgroups in the luspatercept arm, asthenia, nausea, vomiting, dyspnoea, cough, thromboembolic events, alanine aminotransferase increased, aspartate aminotransferase increased, and thrombocytopenia occurred more frequently in the RS-subgroup.

MDS patients with mutational status SF3B1 non-mutated
Patients with mutational status SF3B1 non-mutated are more likely to experience Grade 3 or 4 treatment emergent adverse events, serious adverse events, Grade 5 treatment emergent adverse events, adverse events leading to drug discontinuation, dose reduction as well as dose interruption compared to patients with mutational status SF3B1 mutated. Known luspatercept adverse reactions with a frequency ≥ 3% higher in the non-mutated SF3B1 luspatercept arm subgroup included vomiting, dyspnoea, and hypertension.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Overdose with luspatercept may cause an increase of Hb values above the desired level. In the event of an overdose, treatment with luspatercept should be delayed until Hb is ≤ 11 g/dL.

Properties/Effects

ATC code

B03XA06

Mechanism of action

Luspatercept, an erythroid maturation agent, is a recombinant fusion protein that binds selected transforming growth factor-β (TGF-β) superfamily ligands. By binding to specific endogenous ligands (e.g. GDF-11, activin B) luspatercept inhibits Smad2/3 signalling, resulting in erythroid maturation through expansion and differentiation of late-stage erythroid precursors (normoblasts) in the bone marrow, thereby restoring effective erythropoiesis. Smad2/3 signalling is abnormally high in disease models characterised by ineffective erythropoiesis, i.e. MDS and β-thalassaemia, and in the bone marrow of MDS patients.

Somatic mutations in MDS patients

Luspatercept demonstrated clinical benefit and favourability over epoetin alfa across multiple genomic mutations that are frequently observed in lower-risk MDS with the exception of CBL gene mutations.

Pharmacodynamics

Hb response

In patients who received < 4 units of RBC transfusion within 8 weeks prior to the study, Hb increased within 7 days of treatment initiation, and the increase correlated with the time to reach luspatercept C_{max}. The greatest mean Hb increase was observed after the first dose, with additional smaller increases observed after subsequent doses. Hb levels returned to baseline value approximately 6 to 8 weeks from the last dose (0.6 to 1.75 mg/kg). Increasing luspatercept serum exposure (AUC) was associated with a greater Hb increase in patients with ESA-refractory or -intolerant MDS or β-thalassaemia.

In non-transfusion-dependent β-thalassaemia patients who had a baseline transfusion burden of 0 to 5 units within 24 weeks, increasing luspatercept serum exposure (time-averaged AUC) was associated with a greater probability of achieving a Hb increase (≥ 1 g/dL or ≥ 1.5 g/dL) and a longer

duration of such Hb increases. The luspatercept serum concentration achieving 50% of the maximum stimulatory effect on Hb production was estimated to be 7.6 µg/mL.

Clinical efficacy

Myelodysplastic syndromes in ESA-naïve patients

The efficacy and safety of luspatercept were evaluated in a Phase 3 multicentre, randomised, open-label, active-controlled study COMMANDS (ACE-536-MDS-002) comparing luspatercept *versus* epoetin alfa in patients with anaemia due to International Prognostic Scoring System-Revised (IPSS-R) very low-, low- or intermediate-risk MDS or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN RS-T) in ESA-naïve patients (with endogenous serum erythropoietin (sEPO) levels of < 500 U/L) who require red blood cell transfusions. For eligibility, patients were required to have had 2 to 6 RBC units/8 weeks confirmed for a minimum of 8 weeks immediately preceding randomization. Patients with deletion 5q (del5q) MDS were excluded from the study.

Patients were treated for at least 24 weeks, unless the patient experienced unacceptable toxicities, withdrew the consent or met any other treatment discontinuation criteria. The treatment was continued beyond week 24 in case of clinical benefit (defined as a transfusion reduction of ≥ 2 pRBC units/8 weeks compared with baseline) and absence of disease progression. Based on the outcome of these assessments, patients either were discontinued from treatment and entered into the Post-Treatment Follow-up Period or continued open-label treatment (with luspatercept or epoetin alfa) as long as the above criteria continued to be met or until the patient experienced unacceptable toxicities, withdrew consent, or met any other discontinuation criteria.

A total of 363 patients were randomized to receive subcutaneously luspatercept (N=182) or epoetin alfa (N=181) at 1 mg/kg every 3 weeks or at 450 U/kg every week, respectively. Randomization was stratified by RBC transfusion burden, RS status, and sEPO level at baseline. Two dose level increases were allowed for luspatercept (to 1.33 mg/kg and to 1.75 mg/kg). Doses were held and subsequently reduced for adverse reactions, reduced if the haemoglobin increased by ≥ 2 g/dL from the prior cycle, and held if the pre-dose haemoglobin was ≥ 12 g/dL. All patients received best supportive care, which included RBC transfusions, use of antibiotic, antiviral and antifungal therapy, and nutritional support as needed. BSC for this study excluded the use of ESAs outside of the study treatment.

The mean age of the 363 study participants was 73.4 years (range: 31, 93 years). The trial population was 55.4% male and 44.6% female; 79.6% were White, 0.6% Black or African American, 12.1% Asian, and race was not reported in 7.7% of patients. Ethnicities were reported as 85.7% for Not

Hispanic or Latino patients, 6.3% for Hispanic or Latino patients, 7.4% for patients with no ethnicity reported, and 0.6% were unknown.
The median haemoglobin (Hb) levels were identical between the two groups with both showing a median of 7.80 g/dL. The range for the Luspatercept group was 4.7 to 9.2 g/dL, and the range in the epoetin alfa group was 4.5 to 10.2 g/dL. The median time since the original diagnosis of MDS was 7.97 months for the luspatercept group and 5.13 months for the epoetin alfa group.
In the luspatercept group 79.7% had a sEPO levels ≤200 U/L, and 20.3% had levels >200 U/L to <500 U/L, with a median sEPO of 77.245 U/L. In the Epoetin Alfa group 79.6% had sEPO levels ≤200 U/L and 20.4% with >200 U/L to <500 U/L, with a median sEPO of 85.370 U/L. Serum ferritin had a median of 623.00 µg/L (range 12.4 to 3170.0 µg/L) in the Luspatercept group and 650.00 µg/L (range 39.4 to 6960.5 µg/L) in the Epoetin Alfa group.
The baseline transfusion burden over 8 weeks showed that 64.8% of patients in the Luspatercept group received less than 4 while 35.2% received 4 or more units of RBC transfusions. In the Epoetin Alfa group, 61.3% received less than 4 and 38.7% received 4 or more units of RBC transfusions.
According to the WHO 2016 classification of MDS, in the Luspatercept group, 0.5% had MDS with single lineage dysplasia (MDS-SLD), 27.5% had MDS with multilineage dysplasia (MDS-MLD), 1.1% had MDS with ring sideroblasts with single lineage dysplasia (MDS-RS-SLD), 69.8% had MDS with ring sideroblasts with multilineage dysplasia (MDS-RS-MLD), and 1.1% had myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T). There were no missing data in this group. For Epoetin Alfa, the distribution was 2.2% for MDS-SLD, 26.0% for MDS-MLD, 3.3% for MDS-RS-SLD, 65.2% for MDS-RS-MLD, 2.8% for MDS/MPN-RS-T, and for 0.6% data were missing.
Based on the IPSS-R classification, 8.8% of the Luspatercept patients were classified as very low risk, 71.4% as low risk, 18.7% as intermediate risk, and 1.1% were categorized as other/missing. For the Epoetin Alfa patients, 9.4% were very low risk, 73.5% were low risk, 16.0% were intermediate risk, and 1.1% were categorized as other/missing.
According to WHO criteria (2016), 73.1% of the patients in the luspatercept group were with ring sideroblasts (RS+), and 26.9% were without (RS-). There were no missing data in this group. In the Epoetin Alfa group, 71.8% were RS+, 27.6% were RS-, and for 0.6% data were missing.
In the Luspatercept group 62.6% of the patients had mutated Splicing Factor 3B Subunit 1A (SF3B1) gene, 35.7% non-mutated, and 1.6% missing data. In the Epoetin Alfa group, 55.8% had the SF3B1 mutation, 39.8% were non-mutated, and 4.4% were missing.

The primary endpoint was achieving RBC transfusion independence (RBC-TI) for 12 weeks with a concurrent mean Hb increase of at least 1.5 g/dL (Weeks 1 - 24). The response rate was 60.4% (110/182) in patients receiving Luspatercept (95% CI of 52.9% to 67.6%) versus 34.8% (63/181) in patients receiving Epoetin alfa (95% CI of 27.9% to 42.2%). The common risk difference in response

rate between the two groups was 25.4% in favor of Luspatercept (95% CI: 15.8% to 35.0%, p-value < 0.0001, the odds ratio for this comparison was 3.1, with a 95% CI of 2.0 to 4.8).
The treatment effect of luspatercept on RBC-TI ≥12 weeks and Hb increase of ≥1.5 g/dL was higher than epoetin alfa across all clinically relevant baseline demographic and most disease characteristic subgroups, except in patients without ring sideroblasts, where the treatment effect of luspatercept was comparable to epoetin alfa.

For the secondary endpoints, the rate of hematological improvement – erythroid (HI-E) for at least 8 weeks (Weeks 1 - 24) was 74.2% (135 /182) in patients treated with Luspatercept versus 53% (96/181) patients treated with Epoetin alfa. The common risk difference was 21.5% (95% CI: 12.2% to 30.7%), p-value < 0.0001.
Myelodysplastic syndromes in ESA-refractory or -intolerant patients
The efficacy and safety of luspatercept were evaluated in a Phase 3 multicentre, randomised, double-blind, placebo-controlled study MEDALIST (ACE-536-MDS-001) in adult patients with anaemia requiring RBC transfusions (≥ 2 units/8 weeks) due MDS as defined by the WHO/FAB classification that meets IPSS-R classification of very low-, low-, or intermediate-risk disease who have ring sideroblasts (≥ 15%). All patients had less than 5% of blasts in the bone marrow. The MEDALIST trial excluded patients with deletion 5q (del 5q), white blood cell count > 13 Gi/L, neutrophils < 0.5 Gi/L, platelets < 50 Gi/L, or with prior use of a disease modifying agent for treatment of MDS. 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 > 200 U/L.

A total of 229 patients were randomised to receive luspatercept 1 mg/kg (N=153) or placebo (N=76) subcutaneously every 3 weeks. Randomization was stratified by baseline RBC transfusion burden and baseline IPSS-R. Treatment was started at 1 mg/kg subcutaneously every 3 weeks
Dose titration up to 1.75 mg/kg was permitted. The dose could be delayed or reduced depending on the Hb level. All patients were eligible to receive best supportive care (BSC), which included RBC transfusions, iron-chelating agents, antibiotic, antiviral and antifungal therapy, and nutritional support, as needed.
Patients in both arms were treated for 24 weeks, then continued treatment if they had demonstrated clinical benefit and absence of disease progression. The study was unblinded for analyses when all patients had at least received 48 weeks of treatment or discontinued treatment.
A total of 128 (83.7%) and 68 (89.5%) patients receiving luspatercept and placebo respectively completed 24 weeks of treatment. A total of 78 (51%) and 12 (15.8%) patients receiving luspatercept and placebo respectively completed 48 weeks of treatment.

The efficacy of REBLOZYL 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.

The median age of the 229 study participants was 71 years (range: 26, 95 years). The trial population was 63% male and 69% White. At baseline, among the luspatercept patients 57.5% had sEPO levels below 200 U/L, 28.1% had levels between 200–500 U/L, 13.7% had levels greater than 500 U/L, and 0.7% had missing values. Among placebo patients, 65.8% had sEPO levels below 200 U/L, 19.7% had levels between 200–500 U/L, and 14.5% had levels greater than 500 U/L, with no missing values. Median serum ferritin was 1089.2 µg/L (range 64–5968) in the luspatercept group and 1122.1 µg/L (range 165–5849) in the placebo group.
The IPSS-R classification revealed that 11.8% of luspatercept patients were categorized as “Very Low Risk,” 71.2% as “Low Risk,” 16.3% as “Intermediate Risk,” and 0.7% as “Other.” For placebo patients, the respective proportions were 7.9%, 75.0%, 17.1% in “Intermediate Risk,” and none as “Other.” According to the WHO 2016 classification of MDS, 14 patients (9.2%) in the luspatercept group and 9 patients (11.8%) in the placebo group were diagnosed with myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).

Assessment of baseline RBC transfusion burden over an 8 week period (collected over 16 weeks prior to randomization) revealed that 43.1% of the luspatercept patients required 6 or more units and 56.9% required less than 6 units. In the placebo group, 43.4% required 6 or more units and 56.6% required less than 6 units. Median Hb levels were 7.6 g/dL (range 6–10) in the luspatercept group and 7.6 g/dL (range 5–9) in the placebo group.
In the luspatercept group, 92.2% had the SF3B1 mutation, 7.8% were unmutated. Among placebo patients, 85.5% were mutated, 13.2% were unmutated.
The primary endpoint of RBC-TI for 8 weeks or more (Weeks 1-24) response rate was 37.9% (58/153) in luspatercept treated patients versus 13.2% (10/76) in the placebo group. The common risk difference in response rate was 24.56% (95% CI of 14.48 to 34.64) and the p-value < 0.0001.
Secondary endpoints included achieving RBC-TI for 12 weeks (Weeks 1-24). There were 43 responders (28.1%) with luspatercept versus 6 responders (7.9%) with placebo, resulting in a common risk difference of 20% (95% CI: 10.92 to 29.08 with a p-value of 0.0002). RBC-TI of 12 weeks (weeks 1-48) had 51 responders (33.3%) on luspatercept compared to 9 (11.8%) on placebo. The common risk difference was 21.37% (95% CI: 11.23 to 31.51 with the p-value at 0.0003).

Only limited data are available for the group with transfusion burden of ≥ 8 units/8 weeks. Efficacy has not been established in patients with a transfusion burden of > 12 units/8 weeks.

Transfusion dependent β-thalassaemia

The efficacy and safety of luspatercept were evaluated in a Phase 3 multicentre, randomised, doubleblind, placebo-controlled study BELIEVE (ACE-536-BTHAL-001) in adult patients with transfusiondependent β–thalassaemia–associated anaemia who require RBC transfusions (6-20 RBC units/24 weeks) with no transfusion-free period > 35 days during that period.

Patients in both the luspatercept and placebo arms were treated for at least 48 and up to 96 weeks. After unblinding, placebo patients were able to cross-over to luspatercept.

A total of 336 adult patients were randomised to receive luspatercept 1 mg/kg (N=224) or placebo (N=112) subcutaneously every 3 weeks. Dose titration to 1.25 mg/kg was allowed. Dose could be delayed or reduced depending upon Hb level. All patients were eligible to receive BSC, which included RBC transfusions, iron-chelating agents, use of antibiotic, antiviral and antifungal therapy, and nutritional support, as needed. The study excluded patients with Hb S/β-thalassaemia or alpha (α)-thalassaemia or who had major organ damage (liver disease, heart disease, lung disease, renal insufficiency). Patients with recent DVT 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. Disease characteristics included pretransfusion Hb thresholds during a 12-week run-in period, with median Hb values of 9.30 g/dL (range: 4.6-11.4) in the luspatercept cohort and 9.14 g/dL (range: 6.2-11.5) in the placebo cohort. The baseline transfusion burden over 12 weeks showed median values of 6.12 units for the luspatercept group (range 3.0, 14.0) and 6.27 units for the placebo group (range 3.0-12.0). In the luspatercept cohort 77.7% were diagnosed with β-thalassemia, 13.8% had HbE/β-thalassemia, 8% had β-thalassemia combined with α-thalassemia and for 0.4% diagnostic information was missing. In the placebo group 74.1% were diagnosed with β-thalassemia, 18.8% had HbE/β-thalassemia, and 7.1% had β-thalassemia combined with α-thalassemia.

Regarding β-thalassemia gene mutation groupings in the luspatercept cohort, β0/β0 mutations were present in 30.4% of patients, non-β0/β0 mutations in 69.2%. In the placebo cohort, 31.3% had β0/β0 mutations, 68.8% non-β0/β0 mutations.

The efficacy of Reblozyl in adult patients with β-thalassemia 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. In the luspatercept group, 21.0% (47 / 224) of patients achieved this reduction, compared to 4.5% (5 / 112) in the placebo group. The difference in proportions was calculated as 16.5 (95% CI: 10.0 to 23.1) with a p-value of less than 0.0001. A total of 77.2% of luspatercept treated patients achieved ≥ 33% reduction in RBC transfusion burden from baseline during any rolling 12-week interval, compared with 34.8% of subjects in the placebo treated group (nominal $p < 0.0001$).
Furthermore, a total of 50.0% of luspatercept treated patients achieved ≥ 50% reduction in RBC transfusion burden from baseline during any rolling 12-week interval, compared with 8.0% of subjects in the placebo treated patients (nominal $p < 0.0001$).

Paediatric population

Myelodysplastic syndromes
Swissmedic has waived the obligation to submit the results of studies with Reblozyl in all subsets of the paediatric population in myelodysplastic syndromes (see “Dosage/Administration” for information on paediatric use).

β-thalassaemia
Swissmedic has deferred the obligation to submit the results of studies with Reblozyl in one or more subsets of paediatric population older than 6 years of age in β-thalassaemia (see “Dosage/Administration” for information on paediatric use).

Pharmacokinetics

Absorption

In healthy volunteers and patients, luspatercept is slowly absorbed following subcutaneous administration, with the C_{max} in serum often observed approximately 7 days post-dose across all dose levels. Population pharmacokinetic (PK) analysis suggests that the absorption of luspatercept into the circulation is linear over the range of studied doses, and the absorption is not significantly affected by the subcutaneous injection location (upper arm, thigh or abdomen). Interindividual variability in AUC was approximately 37% in both β-thalassaemia and MDS patients.

Distribution

At the recommended doses, the geometric mean apparent volume of distribution was 9.56 L for MDS patients and 7.26 L for β-thalassaemia patients. The small volume of distribution indicates that luspatercept is confined primarily in extracellular fluids, consistent with its large molecular mass.

Metabolism

Luspatercept is expected to be catabolised into amino acids by general protein degradation process.

Elimination

Luspatercept is not expected to be excreted into urine due to its large molecular mass that is above the glomerular filtration size exclusion threshold. At the recommended doses, the geometric mean apparent total clearance was 0.47 L/day for MDS patients and 0.44 L/day for β-thalassaemia. The geometric mean half-lives in serum were approximately 14.1 days for MDS patients and 11 days for β-thalassaemia patients.

Linearity/non-linearity

The increase of luspatercept Cmax and AUC in serum is approximately proportional to increases in dose from 0.125 to 1.75 mg/kg. Luspatercept clearance was independent of dose or time.

When administered every three weeks, luspatercept serum concentration reaches the steady state after 3 doses, with an accumulation ratio of approximately 1.5.

Kinetics in specific patient groups

Elderly

Population PK analysis for luspatercept included patients with ages ranging from 27 to 95 and 18 to 71 years, for MDS and β–thalassaemia patients, respectively, with a median age of 72.5 years for MDS patients and of 33 years for β-thalassaemia patients. No clinically significant difference in AUC or clearance was found across age groups in MDS patients (≤ 64, 65-74, and ≥ 75 years) or in β–thalassaemia patients (18 to 71 years).

Hepatic impairment

Population PK analysis for luspatercept included patients with normal hepatic function (BIL, ALT, and AST ≤ ULN; N=62 for β–thalassaemia patients and N=311 for MDS patients), mild hepatic impairment (BIL > 1 – 1.5 x ULN, and ALT or AST > ULN; N=89 for β–thalassaemia patients and N=126 for MDS patients), moderate hepatic impairment (BIL > 1.5 – 3 x ULN, any ALT or AST; N= 157 for β–thalassaemia patients and N=32 for MDS patients), or severe hepatic impairment (BIL > 3 x ULN, any ALT or AST; N=73 for β–thalassaemia patients and N=1 for MDS patients) as defined by the National Cancer Institute criteria of hepatic dysfunction. Effects of hepatic function categories, elevated liver enzymes (ALT or AST, up to 3 x ULN) and elevated total BIL (4 – 246 μmol/L) on

luspatercept clearance were not observed. No clinically significant difference in mean steady state C_{max} and AUC was found across hepatic function groups. PK data are insufficient for patients with liver enzymes (ALT or AST) ≥ 3 x ULN. No PK data are available for patients with liver cirrhosis (Child-Pugh Classes A, B and C) as no dedicated study was performed.

Renal impairment

Population PK analysis for luspatercept included patients with normal renal function (individual eGFR ≥ 90 mL/min N=302 for β–thalassaemia patients and N=169 for MDS patients), mild renal impairment (individual eGFR 60 to 89 mL/min; N= 74 β–thalassaemia patients and N=204 for MDS patients), or moderate renal impairment (individual eGFR 30 to 59 mL/min; N=4 for β–thalassaemia patients and N=88 for MDS patients) as defined by Modification of Diet in Renal Disease (MDRD) formula. Luspatercept steady-state serum exposure (AUC) was 24% to 41% higher in patients with mild to moderate renal impairment than in patients with normal renal function. PK data are insufficient for patients with severe renal impairment (individual eGFR < 30 mL/min) or end-stage kidney disease.

Other intrinsic factors

The following population characteristics have no clinically significant effect on luspatercept AUC or clearance: sex and race (Asian *vs.* White).

The following baseline disease characteristics had no clinically significant effect on luspatercept clearance: Serum erythropoietin level (2.4 – 1680 U/L for β–thalassaemia patients and 7.80-2920 U/L for MDS patients), RBC transfusion burden (0 – 43.4 units/24 weeks), MDS ring sideroblasts, β-thalassaemia genotype (β0/β0 *vs.* non-β0/β0) and splenectomy.

The volume of distribution and clearance of luspatercept increased with increase of body weight (33 – 124 kg), supporting the body weight-based dosing regimen.

Preclinical data

Single and repeat-dose toxicity

Following repeated administration of luspatercept in rats, toxicities included: membranoproliferative glomerulonephritis; congestion, necrosis and/or mineralisation of the adrenal glands; hepatocellular vacuolation and necrosis; mineralisation of the glandular stomach; and decreased heart and lung weights with no associated histology findings. A clinical observation of swollen hindlimbs/feet was noted in several studies in rats and rabbits (including juvenile and reproductive toxicity studies). In one juvenile rat, this correlated histopathologically with new bone formation, fibrosis, and inflammation. Membranoproliferative glomerulonephritis was also seen in monkeys. Additional

toxicities in monkeys included: vascular degeneration and inflammatory infiltrates in the choroid plexus.

For the 6-month toxicity study, the longest duration study in monkeys, the no-observed-adverse-effect level (NOAEL) was 0.3 mg/kg (0.3-fold of clinical exposure at 1.75 mg/kg every 3 weeks). A NOAEL was not identified in rats and the lowest-observed-adverse-effect-level (LOAEL) in the rat 3-month study was 1 mg/kg (0.9-fold of clinical exposure at 1.75 mg/kg every 3 weeks).

Carcinogenesis and mutagenesis

Neither carcinogenicity nor mutagenicity studies with luspatercept have been conducted. Haematological malignancies were observed in 3 out of 44 rats examined in the highest dose group (10 mg/kg) in the definitive juvenile toxicity study. The occurrence of these tumours in young animals is unusual and the relationship to luspatercept therapy cannot be ruled out. At the 10 mg/kg dose, at which tumours were observed, the exposure represents an exposure multiple of approximately 4 times the estimated exposure at a clinical dose of 1.75 mg/kg every three weeks.

No other proliferative or pre-neoplastic lesions, attributable to luspatercept, have been observed in any species in other non-clinical safety studies conducted with luspatercept, including the 6-month study in monkeys.

Fertility

In a fertility study in rats, administration of luspatercept to females at doses higher than the currently recommended highest human dose reduced the average number of corpora lutea, implantations and viable embryos. No such effects were observed when exposure in animals was at 1.5 times the clinical exposure. Effects on fertility in female rats were reversible after a 14-week recovery period.

Administration of luspatercept to male rats at doses higher than the currently recommended highest human dose had no adverse effect on male reproductive organs or on their ability to mate and produce viable embryos. The highest dose tested in male rats yielded an exposure approximately 7 times the clinical exposure.

Embryo-foetal development (EFD)

Embryo-foetal developmental toxicology studies (range-finding and definitive studies) were conducted in pregnant rats and rabbits. In the definitive studies, doses of up to 30 mg/kg or 40 mg/kg every week were administered twice during the period of organogenesis. Luspatercept was a selective developmental toxicant (dam not affected; foetus affected) in the rat and a maternal and foetal

developmental toxicant (doe and foetus affected) in the rabbit. Embryofoetal effects were seen in both species and included reductions in numbers of live foetuses and foetal body weights, increases in resorptions, post-implantation loss and skeletal variations and, in rabbit foetuses, malformations of the ribs and vertebrae. In both species, effects of luspatercept were observed in the EFD studies at the lowest dose tested, 5 mg/kg, which corresponds to an estimated exposure in rats and rabbits of approximately 2.7 and 5.5 times greater, respectively, than the estimated clinical exposure.

Pre- and post-natal development

In a pre- and post-natal development study, with dose levels of 3, 10, or 30 mg/kg administered once every 2 weeks from gestational day (GD) 6 through post-natal day (PND) 20, adverse findings at all doses consisted of lower F_1 pup body weights in both sexes at birth, throughout lactation, and post weaning (PND 28); lower body weights during the early premating period (Weeks 1 and 2) in the F_1 females (adverse only at the 30 mg/kg/dose) and lower body weights in F_1 males during the premating, pairing and post-mating periods; and microscopic kidney findings in F_1 pups. Additionally, non-adverse findings included delayed male sexual maturation at the 10 and 30 mg/kg/dose. The delay in growth and the adverse kidney findings, in the F_1 generation, precluded the determination of a NOAEL for F_1 general and developmental toxicity. However, there was no effect on behavioural indices, fertility or reproductive parameters at any dose level in either sex, therefore the NOAEL for behavioural assessments, fertility and reproductive function in the F_1 animals was considered to be the 30 mg/kg/dose. Luspatercept is transferred through the placenta of pregnant rats and rabbits and is excreted into the milk of lactating rats.

Juvenile toxicity

In a study in juvenile rats, luspatercept was administered from postnatal day (PND) 7 to PND 91 at 0, 1, 3, or 10 mg/kg. Many of the findings seen in repeat-dose toxicity studies in adult rats were repeated in the juvenile rats. These findings included glomerulonephritis in the kidney, haemorrhage/congestion, necrosis and mineralization of the adrenal gland, mucosal mineralization in the stomach, lower heart weights, and swollen hindlimbs/feet. Luspatercept-related findings unique to juvenile rats included tubular atrophy/hypoplasia of the kidney inner medulla, delays in the mean age of sexual maturation in males, effects on reproductive performance (lower mating indices), and non-adverse decreases in bone mineral density in both male and female rats. The effects on reproductive performance were observed after a greater than 3-month recovery period, suggesting a permanent effect. Although reversibility of the tubular atrophy/hypoplasia was not examined, these effects are also considered to be irreversible. Adverse effects on the kidney and reproductive system were observed at clinically relevant exposure levels and seen at the lowest dose tested and, thus, a NOAEL was not established. In addition, haematological malignancies were observed in 3 out of 44

rats examined in the highest dose group (10 mg/kg). These findings are all considered potential risks in paediatric patients.

Other information

Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Shelf life

Unopened vial:
Do not use this medicine after the expiry date ("EXP") stated on the container.

After reconstitution
When stored in the original container, chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated for up to 8 hours at room temperature (≤ 25°C) or for up to 24 hours at 2°C -8°C.

From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C - 8°C.

Do not freeze the reconstituted solution.

Special precautions for storage

Store in a refrigerator (2°C -8°C).
Do not freeze.
Store in the original carton in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see “Shelf life”.

Instructions for handling

Reblozyl must be reconstituted gently prior to administration. Aggressive shaking should be avoided.

Reconstitution of the product

Reblozyl is supplied as a lyophilised powder for reconstitution before use. Only water for injections (WFI) should be used when reconstituting Reblozyl.

The appropriate number of Reblozyl vials should be reconstituted to achieve the desired dose. A syringe with appropriate graduations must be used for reconstitution to ensure accurate dose.

The following steps should be followed for reconstitution:

1. Remove the coloured cap from the vial and wipe the top with an alcohol wipe.

2. Reblozyl 25 mg powder for solution for injection
   Add 0.68 mL WFI into the vial by means of a syringe with appropriate graduations with a needle directing the flow onto the lyophilised powder. Allow to stand for one minute. Each 25 mg single-dose vial will deliver at least 0.5 mL of 50 mg/mL luspatercept.

   Reblozyl 75 mg powder for solution for injection
   Add 1.6 mL WFI into the vial by means of a syringe with appropriate graduations with a needle directing the flow onto the lyophilised powder. Allow to stand for one minute. Each 75 mg single-dose vial will deliver at least 1.5 mL of 50 mg/mL luspatercept.

3. Discard the needle and syringe used for reconstitution. Do not use them for subcutaneous injection.
4. 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.
5. Inspect the vial for undissolved powder in the solution. If undissolved powder is observed, repeat step 4 until the powder is completely dissolved.
6. 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.
7. Repeat step 6 seven more times to ensure complete reconstitution of material on the sides of the vial.
8. Visually inspect the reconstituted solution prior to administration. When properly mixed, Reblozyl reconstituted solution is a colourless to slightly yellow, clear to slightly opalescent solution which is free of visible foreign particulate matter. Do not use if undissolved product or foreign particulate matter is observed.
9. If the reconstituted solution is not used immediately, see “shelf life” for storage conditions.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

69’592 (Swissmedic).

Packs

Reblozyl 25 mg powder for solution for injection: 1 vial (A)
Reblozyl 75 mg powder for solution for injection: 1 vial (A)

Marketing authorisation holder

Bristol-Myers Squibb SA, Steinhausen

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