1. NAME OF THE MEDICINAL PRODUCT

Reblozyl 25 mg
Reblozyl 75 mg

Powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Reblozyl 25 mg powder for solution for injection
Each vial contains 25 mg of luspatercept. After reconstitution, each mL of solution contains 50 mg luspatercept.

Reblozyl 75 mg powder for solution for injection
Each vial contains 75 mg of luspatercept. After reconstitution, each mL of solution contains 50 mg luspatercept.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

White to off-white lyophilised powder.

4. CLINICAL PARTICULARS

Patient Safety Information Card
The marketing of Reblozyl is subject to risk management plan (RMP) including a 'Patient Card (for Women of Childbearing Potenial)', emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the card before starting treatment.

Prescriber's Checklist
This product is marketed with a prescriber's checklist providing important safety information.
Please ensure you are familiar with this material as it contains important safety information.

4.1 Therapeutic indications

Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy (see section 5.1).

Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia associated with beta-thalassaemia (see section 5.1).

4.2 Posology and method of administration

Reblozyl treatment should be initiated by a physician experienced in treatment of haematological diseases.

Posology
Prior to each Reblozyl administration, the haemoglobin (Hb) level of patients should be assessed. In case of a red blood cell (RBC) transfusion occurring prior to dosing, the pre-transfusion Hb level must be considered for dosing purposes.

The recommended starting dose of Reblozyl is 1.0 mg/kg administered once every 3 weeks.

Myelodysplastic syndromes
In patients who are not RBC transfusion-free after at least 2 consecutive doses at the 1.0 mg/kg starting dose, the dose should be increased to 1.33 mg/kg. If patients are not RBC transfusion-free after at least 2 consecutive doses at the 1.33 mg/kg dose level, the dose should be increased to 1.75 mg/kg. The dose increase should not occur more frequently than every 6 weeks (2 administrations) and should not exceed the maximum dose of 1.75 mg/kg every 3 weeks. The dose should not be increased immediately after a dose delay. For patients with a pre-dose Hb level of > 9 g/dL and who have not yet achieved transfusion independence, a dose increase may be required at the physician's discretion; the risk of Hb increasing above the target threshold with concomitant transfusion cannot be excluded.

If a patient loses response (i.e., transfusion independence), the dose should be increased by one dose level (see Table 1).

β-thalassaemia

In patients who do not achieve a response, defined as a reduction in RBC transfusion burden of at least a third after ≥ 2 consecutive doses (6 weeks), at the 1.0 mg/kg starting dose, the dose should be increased to 1.25 mg/kg. The dose should not be increased beyond the maximum dose of 1.25 mg/kg every 3 weeks.

If a patient loses response (if the RBC transfusion burden increases again after an initial response) the dose should be increased by one dose level (see Table 2).

Increase to next dose level

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

Table 1: 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 2: Increase to next dose level for β-thalassaemia

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

MDS and 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, Reblozyl dose should be reduced by one dose level.

If the Hb is ≥ 11.5 g/dL in the absence of transfusion for at least 3 weeks, the dose should be delayed until the Hb is ≤ 11.0 g/dL. If there is also a concomitant rapid increase in Hb 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.

Reduced dose during treatment with luspatercept are provided below.

Table 3: 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 4: Reduced dose for β-thalassaemia

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

Dose modification due to adverse reactions
Instructions on dose interruptions or reductions for luspatercept treatment-related adverse reactions are outlined in Table 5.

Table 5: Dose modification instructions

Treatment-related adverse reactions*	Dose instructions
Grade ≥ 3 hypertension (see sections 4.4 and 4.8)	• Interrupt treatment • Restart at reduced dose once the blood pressure is controlled as per dose reduction guidance
Other persistent Grade ≥ 3 adverse reactions (see section 4.8)	• Interrupt treatment • Restart at previous dose or at reduced dose when adverse reaction has improved or returned to baseline as per dose reduction guidance

* 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 1 and Table 2).

Discontinuation
Reblozyl should be discontinued if patients do not experience a reduction in transfusion burden after 9 weeks of treatment (3 doses) at the maximum dose level if no alternative explanations for response

failure are found (e.g. bleeding, surgery, other concomitant illnesses) or if unacceptable toxicity occurs at any time.

Special populations

Elderly
No starting dose adjustment is required for Reblozyl (see section 5.2).

Hepatic impairment
No starting dose adjustment is required for patients with total bilirubin (BIL) > upper limit of normal (ULN) and/or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) < 3 x ULN (see section 5.2). No specific dose recommendation can be made for patients with ALT or AST ≥ 3 x ULN or liver injury CTCAE Grade ≥ 3 due to lack of data (see section 5.2).

Renal impairment
No starting dose adjustment is required for patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] < 90 and ≥ 30 mL/min/1.73 m^2). No specific dose recommendation can be made for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) due to lack of clinical data (see section 5.2). Patients with renal impairment at baseline should be closely monitored for renal function as per standard of care.

Paediatric population
Reblozyl is not indicated for for children and adolescents under 18 years old.

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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded.
It is recommended to record the batch number as well.

Thromboembolic events
In β-thalassaemia patients, thromboembolic events (TEEs) were reported in 3.6% (8/223) of patients treated with luspatercept in a controlled clinical study. Reported TEEs included deep vein thrombosis (DVT), portal vein thrombosis, pulmonary emboli and ischaemic stroke (see section 4.8). 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.

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 5 mmHg from baseline (see section 4.8).

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 5 in section 4.2). The potential benefit of treatment with Reblozyl should be re-evaluated in case of persistent hypertension or exacerbations of preexisting hypertension.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and 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.

Pregnancy
Treatment with Reblozyl should not be started if the woman is pregnant (see section 4.3).
There are no data from the use of Reblozyl in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Reblozyl is contraindicated during pregnancy (see section 4.3). 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 section 5.3). 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 section 5.3).

4.7 Effects on ability to drive and use machines

Reblozyl may have 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 section 4.8). Therefore, patients should be advised to exercise caution until they know of any impact on their ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Myelodysplastic syndromes
The most frequently reported adverse drug reactions in patients receiving Reblozyl (at least 15% of patients) were fatigue, diarrhoea, asthenia, nausea, dizziness, back pain and headache. The most commonly reported Grade ≥ 3 adverse drug reactions (at least 2% of patients) included syncope/presyncope, fatigue, hypertension and asthenia. The most commonly reported serious adverse drug reactions (at least 2% of patients) were urinary tract infection, back pain and syncope.

Asthenia, fatigue, dizziness and headache occurred more frequently during the first 3 months of treatment.

Treatment discontinuation due to an adverse reaction occurred in 2.0% of patients treated with luspatercept. The adverse reactions leading to treatment discontinuation in the luspatercept treatment arm were fatigue and headache.

β-thalassaemia
The most frequently reported adverse drug reactions in patients receiving Reblozyl (at least 15% of patients) were headache, bone pain and arthralgia. The most commonly reported Grade ≥ 3 adverse drug reaction was hyperuricaemia. The most serious adverse reactions reported included thromboembolic events of deep vein thrombosis, ischaemic stroke portal vein thrombosis and pulmonary embolism (see section 4.4).

Bone pain, asthenia, fatigue, dizziness and headache occurred more frequently during the first 3 months of treatment.

Treatment discontinuation due to an adverse reaction occurred in 2.6% of patients treated with luspatercept. The adverse reactions leading to treatment discontinuation in the luspatercept treatment arm were arthralgia, back pain, bone pain and headache .

Tabulated list of adverse reactions
The highest frequency for each adverse reaction that was observed and reported in patients in the pivotal studies in MDS, β-thalassaemia and the long-term follow-up study is shown in Table 6 below. The adverse reactions are listed below by body system organ class and preferred term. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).

Table 6. Adverse drug reactions (ADRs) in patients treated with Reblozyl for MDS and / or β-thalassaemia in the pivotal studies

System organ class	Preferred term	Frequency (all grades) for MDS	Frequency (all grades) for β-thalassaemia
Infections and infestations	bronchitis	Very common	Common[a]
	urinary tract infection	Very common	Common[a]
	upper respiratory tract infection	Common	Very common[a]

System organ class	Preferred term	Frequency (all grades) for MDS	Frequency (all grades) for β-thalassaemia
	influenza	Common	Very common
Immune system disorders	hypersensitivity [I, IV]	Common	Common
Metabolism and nutrition disorders	hyperuricaemia	Common	Common
Psychiatric disorders	insomnia	Common	
	anxiety		Common
	irritability		Common
Nervous system disorders	dizziness	Very common	Very common
	headache	Very common	Very common
	syncope/presyncope	Common	Common[a]
Ear and labyrinth disorders	vertigo/vertigo positional	Common	Common[a]
Vascular disorders	hypertension[II, VI]	Common	Very common
	thromboembolic events[IV, VI]	Common	Common
Respiratory, thoracic and mediastinal disorders	cough	Very common	
	epistaxis	Common	
	dyspnoea	Very common	Common
Gastrointestinal disorders	abdominal pain	Common	
	diarrhoea	Very common	Very common[a]
	nausea	Very common	Very common
Hepatobiliary disorders	alanine aminotransferase increased		Common[V]
	aspartate aminotransferase increased		Very common[V]
	blood bilirubin increased		Very common[V]
Musculoskeletal and connective tissue disorders	back pain	Very common	Very common
	arthralgia[VI]	Common	Very common
	bone pain[VI]	Common	Very common
General disorders and administration site conditions	influenza-like illness	Common	
	fatigue	Very common	Very common[a]
	asthenia	Very common	Very common
	injection site reactions [III, VI]	Common	Common

*The pivotal studies are ACE-536-MDS-001(MDS) and ACE-536-B-THAL-001 (transfusion-dependent β-thalassaemia).

[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] Thromboembolic events include deep vein thrombosis, portal vein thrombosis, ischaemic stroke and pulmonary embolism.
[V] Frequency is based on laboratory values of any grade.
[VI] See section 4.8 Description of selected adverse reactions.
[VII] Reported only in post-marketing.

[a] ADRs observed in transfusion-dependent β-thalassaemia study ACE-536-B-THAL-001.

Description of selected adverse reactions

Bone pain
Bone pain was reported in 19.7% of β-thalassaemia patients treated with luspatercept (placebo 8.3%) and in 2.6% of MDS patients treated with luspatercept (placebo 3.9%). In β-thalassaemia patients treated with luspatercept, bone pain was most common in the first 3 months (16.6%) compared to months 4-6 (3.7%). Most events (41/44 events) were Grade 1-2, with 3 events Grade 3. One of the 44 events was serious, and 1 event led to treatment discontinuation.

Arthralgia
Arthralgia was reported in 19.3% of β-thalassaemia patients treated with luspatercept (placebo 11.9%) and in 5.2% of MDS patients treated with luspatercept (placebo 11.8%). In the β-thalassaemia patients treated with luspatercept, arthralgia led to treatment discontinuation in 2 patients (0.9%).

Hypertension
Patients treated with luspatercept had an average increase in systolic and diastolic blood pressure of 5 mmHg from baseline not observed in patients receiving placebo. Hypertension was reported in 8.5% of MDS patients treated with luspatercept (placebo 9.2%) and in 8.1% of β-thalassaemia patients treated with luspatercept (placebo 2.8%). See section 4.4.

Grade 3 hypertension events were reported in MDS patients, for 5 patients (3.3%) treated with luspatercept and in 3 patients (3.9%) receiving placebo.

In β-thalassaemia patients, Grade 3 events were reported in 4 patients (1.8%) treated with luspatercept (0.0% placebo). See section 4.4.

Hypersensitivity
Hypersensitivity-type reactions (including eyelid oedema, drug hypersensitivity, swelling face, periorbital oedema, face oedema, angioedema, lip swelling, drug eruption) were reported in 4.6% of MDS (placebo 2.6%) and in 4.5% of β-thalassaemia patients treated with luspatercept (placebo 1.8%). In clinical studies, all events were Grade 1-2. In β-thalassaemia patients treated with luspatercept, hypersensitivity led to treatment discontinuation in 1 patient (0.4%).

Injection site reactions
Injection site reactions (including injection site erythema, injection site pruritus, injection site swelling and injection site rash) were reported in 3.9% of MDS patients (placebo 0.0%) and in 2.2% of β-thalassaemia patients (placebo 1.8%). In clinical studies, all events were Grade 1 and none led to discontinuation.

Thromboembolic events
Thromboembolic events (including deep vein thrombosis, portal vein thrombosis, ischaemic stroke and pulmonary embolism) occurred in 3.6% of β-thalassaemia patients receiving luspatercept (placebo 0.9%). All events were reported in patients who had undergone splenectomy and had at least one other risk factor. No difference in TEEs was observed between luspatercept and placebo arms in MDS patients. See section 4.4.

Traumatic fracture
Traumatic fracture occurred in 1 (0.4%) β-thalassaemia patient receiving luspatercept (placebo 0.0%).

Immunogenicity
In clinical studies in MDS, an analysis of 260 MDS patients who were treated with luspatercept and who were evaluable for the presence of anti-luspatercept antibodies showed that 23 (8.8%) MDS patients tested positive for treatment-emergent anti-luspatercept antibodies, including 9 (3.5%) MDS patients who had neutralising antibodies against luspatercept.

In clinical studies in β-thalassaemia, an analysis of 284 β-thalassaemia patients who were treated with luspatercept and who were evaluable for the presence of anti-luspatercept antibodies showed that

4 (1.4%) β-thalassaemia patients tested positive for treatment-emergent anti-luspatercept antibodies, including 2 (0.7%) β-thalassaemia patients who had neutralising antibodies against luspatercept.

Luspatercept serum concentration tended to decrease in the presence of neutralising antibodies. There were no severe systemic hypersensitivity reactions reported for patients with anti-luspatercept antibodies. There was no association between hypersensitivity type reactions or injection site reactions and presence of anti-luspatercept antibodies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse event should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antianaemic preparations, other antianaemic preparations, 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 differentiation of late-stage erythroid precursors (normoblasts) in the bone marrow. 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.

Clinical efficacy and safety

Myelodysplastic syndromes
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 to International Prognostic Scoring System-Revised (IPSS-R) very low-, low- or intermediate-risk MDS who have ring sideroblasts (≥ 15%). Patients were required to have either received prior treatment with an erythropoiesis-stimulating agent (ESA) with inadequate response, to be ineligible for ESAs (determined to be unlikely to respond to ESA treatment with serum erythropoietin (EPO) > 200 U/L), or intolerant to ESA treatment. Patients with deletion 5q (del5q) MDS were excluded from the study.

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 229 patients were randomised to receive luspatercept 1.0 mg/kg (n=153) or placebo (n=76) subcutaneously every 3 weeks. 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. Dose titration up to 1.75 mg/kg was allowed. Dose could be delayed or reduced depending upon Hb level. All patients were eligible to receive best supportive care (BSC), which included RBC transfusions, iron-chelating agents, use of antibiotic, antiviral and antifungal therapy, and nutritional support, as needed. The key baseline disease characteristics in patients with MDS in study ACE-536-MDS-001 are shown in Table 7.

Table 7. Baseline characteristics in MDS patients with <5% marrow blasts in study ACE-536-MDS-001

	Luspatercept (N=153)	**Placebo (N=76)**
Demographics		
Age[a] (years)		
Median (min, max)	71 (40, 95)	72 (26, 91)
Age categories, n (%)		
<64 years	29 (19.0)	16 (21.1)
65-74 years	72 (47.1)	29 (38.2)
≥75	52 (34.0)	31 (40.8)
Sex, n (%)		
Male	94 (61.4)	50 (65.8)
Female	59 (38.6)	26 (34.2)
Race, n (%)		
Black	1 (0.7)	0 (0.0)
White	107 (69.9)	51 (67.1)
Not collected or reported	44 (28.8)	24 (31.6)
Other	1 (0.7)	1 (1.3)
Disease characteristics		
Serum EPO (U/L) categories[b], n (%)		
< 200	88 (57.5)	50 (65.8)
200 to 500	43 (28.1)	15 (19.7)
> 500	21 (13.7)	11 (14.5)
Missing	1 (0.7)	0
Serum ferritin (µg/L)		
Median (min,max)	1089.2 (64, 5968)	1122.1 (165, 5849)
IPSS-R classification risk category, n (%)		
Very low	18 (11.8)	6 (7.9)
Low	109 (71.2)	57 (75.0)
Intermediate	25 (16.3)	13 (17.1)
Other	1 (0.7)	0
Baseline RBC Transfusion burden/ 8 weeks[c], n (%)		
≥ 6 units	66 (43.1)	33 (43.4)
≥ 6 and < 8 units	35 (22.9)	15 (20.2)
≥ 8 and < 12 units	24 (15.7)	17 (22.4)
≥ 12 units	7 (4.6)	1 (1.3)
< 6 units	87 (56.9)	43 (56.6)
≥ 4 and < 6 units	41 (26.8)	23 (30.3)
< 4 units	46 (30.1)	20 (26.3)

	Luspatercept (N=153)	Placebo (N=76)
Hb[d] (g/dL) Median (min, max)	7.6 (6, 10)	7.6 (5, 9)
SF3B1, n (%) Mutated Unmutated Missing	149 (92.2) 12 (7.8) 0	65 (85.5) 10 (13.2) 1 (1.3)

EPO=erythropoietin; Hb=haemoglobin; IPSS-R=International Prognostic Scoring System-Revised

[a] Age was calculated based on the informed consent signing date.

[b] Baseline EPO was defined as the highest EPO value within 35 days of the first dose of study drug.

[c] Collected over 16 weeks prior to randomisation.

[d] Baseline Hb was defined as the last value measured on or before the date of the first dose of investigational product (IP).After applying the 14/3 day rule, baseline Hb was defined as the lowest Hb value that was within 35 days on or prior to the first dose of IP.

The efficacy results are summarised below.

Table 8. Efficacy results in patients with MDS in study ACE-536-MDS-001

Endpoint	Luspatercept (N=153)	Placebo (N=76)
Primary endpoint		
• **RBC-TI ≥ 8 weeks (Week 1-24)** Number of responders (response rate %)	58 (37.9)	10 (13.2)
• Common risk difference on response rate (95% CI)	24.56 (14.48, 34.64)	
Odds ratio (95% CI)[a]	5.065 (2.278, 11.259)	
p-value[a]	< 0.0001	
Secondary endpoints		
• **RBC-TI ≥ 12 weeks (Weeks 1-24)** Number of responders (response rate %)	43 (28.1)	6 (7.9)
• Common risk difference on response rate (95% CI)	20.00 (10.92, 29.08)	
Odds ratio (95% CI)[a]	5.071 (2.002, 12.844)	
p-value[a]	0.0002	
• **RBC-TI ≥ 12 weeks (Weeks 1-48)** Number of responders (response rate %)[b]	51 (33.3)	9 (11.8)
• Common risk difference on response rate (95% CI)	21.37 (11.23, 31.51)	
Odds ratio (95% CI)[a]	4.045 (1.827, 8.956)	
p-value[a]	0.0003	

Endpoint	Luspatercept (N=153)	Placebo (N=76)
Transfusion event frequency[c]		
• **Weeks 1-24**		
Interval transfusion rate (95% CI)	6.26 (5.56, 7.05)	9.20 (7.98, 10.60)
Relative risk *vs.* placebo	0.68 (0.58, 0.80)	
• **Weeks 25-48**		
Interval transfusion rate (95% CI)	6.27 (5.47, 7.19)	8.72 (7.40, 10.28)
Relative risk *vs.* placebo	0.72 (0.60, 0.86)	
RBC Transfusion units[c]		
• **Weeks 1-24**		
Baseline transfusion burden <6 units/8 weeks		
LS Mean (SE)	7.2 (0.58)	12.8 (0.82)
95% CI for LS mean	6.0, 8.3	11.1, 14.4
LS mean difference (SE) (luspatercept *vs.* placebo)	-5.6 (1.01)	
95% CI for LS mean difference	-7.6, -3.6	
Baseline transfusion burden ≥6 units/8 weeks		
LS Mean (SE)	18.9(0.93)	23.7(1.32)
95% CI for LS mean	17.1, 20.8	21.1, 26.4
LS mean difference (SE) (luspatercept *vs.* placebo)	-4.8 (1.62)	
95% CI for LS mean difference	-8.0, -1.6	
• **Weeks 25-48**		
Baseline transfusion burden <6 units/8 weeks		
LS Mean (SE)	7.5 (0.57)	11.8(0.82)
95% CI for LS mean	6.3, 8.6	10.1, 13.4
LS mean difference (SE) (luspatercept *vs.* placebo)	-4.3 (1.00)	
95% CI for LS mean difference	-6.3, -2.3	
Baseline transfusion burden ≥6 units/8 weeks		
LS Mean (SE)	19.6(1.13)	22.9(1.60)
95% CI for LS mean	17.4, 21.9	19.7, 26.0
LS mean difference (SE) (luspatercept *vs.* placebo)	-3.3(1.96)	
95% CI for LS mean difference	-7.1, 0.6	

RBC-TI: RBC Transfusion Independent; CI: confidence interval; CMH = Cochran-Mantel-Haenszel;
[a] CMH test stratified for average baseline transfusion burden (≥ 6 units *vs.* < 6 units per 8 weeks), and baseline IPSS-R score (very low or low *vs.*intermediate).
[b] After the Week 25 disease assessment visit, patients who were no longer deriving benefit discontinued therapy; few placebo patients contributed data for evaluation at the later timepoint compared with luspatercept (n=12 vs. n=78 respectively).
[c] Post-hoc analysis using baseline imputation.

A treatment effect in favour of luspatercept over placebo was observed in most subgroups analysed using transfusion independence ≥12 weeks (during week 1 to week 24), including patients with high baseline endogenous EPO level (200-500 U/L) (23.3% *vs.* 0%, explorative analysis).

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

Exploratory findings

Table 9. Exploratory efficacy results in patients with MDS in study ACE-536-MDS-001

Endpoint	Luspatercept (N=153)	Placebo (N=76)
mHI-E[a]		
• **Weeks 1-24**		
Number of responders (response rate %)	81 (52.9)	9 (11.8)
(95% CI)	(44.72, 61.05)	(5.56, 21.29)
RBC transfusion reduction of 4 units/8 weeks, n (%)	52/107 (48.6)	8/56 (14.3)
Mean Hb increase of ≥ 1.5 g/dL for 8 weeks, n (%)	29/46 (63.0)	1/20 (5.0)

• **Weeks 1-48** Number of responders (response rate %)	90 (58.8)	13 (17.1)
(95% CI)	(50.59, 66.71)	(9.43, 27.47)
RBC transfusion reduction of 4 units/8 weeks, n (%)	58/107 (54.2)	12/56 (21.4)
Mean Hb increase of ≥ 1.5 g/dL for 8 weeks, n (%)	32/46 (69.6)	1/20 (5.0)
Mean change from baseline in mean serum ferritin with imputation by baseline (ITT population)		
Mean change from baseline in mean serum ferritin averaged over Weeks 9 through 24 (µg/L)[b] LS Mean (SE)	9.9 (47.09)	190.0 (60.30)
95% CI for LS Mean	-82.9, 102.7	71.2, 308.8
Treatment comparison (luspatercept vs. placebo)[c]		
LS mean difference (SE)	-180.1 (65.81)	
95% CI for LS mean difference	-309.8, -50.4	

Hb=haemoglobin

[a] mHI-E = modified haematological improvement – erythroid. The proportion of patients meeting the HI-E criteria as per International Working Group (IWG) 2006 criteria sustained over a consecutive 56-day period during the indicated treatment period. For patients with baseline RBC transfusion burden of ≥ 4 units/8 weeks, mHI-E was defined as a reduction in RBC transfusion of at least 4 units/8 weeks. For patients with baseline RBC transfusion burden of < 4 units/8 weeks, mHI-E was defined as a mean increase in Hb of ≥ 1.5 g/dL for 8 weeks in the absence of RBC transfusions.

[b] If a patient did not have a serum ferritin value within the designated postbaseline interval, the serum ferritin is imputed from the baseline value.

[c] Analysis of covariance was used to compare the treatment difference between groups (including nominal p-value), with the change in serum ferritin as the dependent variable, treatment group (2 levels) as a factor, and baseline serum ferritin value as covariates, stratified by average baseline RBC transfusion requirement (≥ 6 units *vs.*< 6 units of RBC per 8 weeks), and baseline IPSS-R (very low or low *vs.*intermediate).

The median duration of the longest RBC Transfusion Independent (RBC-TI) period among responders in the luspatercept treatment arm was 30.6 weeks.

A total of 62.1% (36/58) of the luspatercept responders who achieved RBC-TI ≥ 8 weeks from Week 1-24 had 2 or more episodes of RBC-TI at the time of analysis.

β-thalassaemia

The efficacy and safety of luspatercept were evaluated in a Phase 3 multicentre, randomised, double-blind, placebo-controlled study BELIEVE (ACE-536-B-THAL-001) in adult patients with 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 1.0 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 key baseline disease characteristics in patients with β-thalassaemia in study ACE-536-B-THAL-001 are shown in Table 10.

Table 10. Baseline characteristics in patients with β-thalassaemia in study ACE-536-B-THAL-001

	Luspatercept (N=224)	Placebo (N=112)
Demographics		
Age (years) Median (min, max)	30.0 (18, 66)	30.0 (18, 59)
Age categories, n (%) ≤ 32 > 32 to ≤ 50 > 50	129 (57.6) 78 (34.8) 17 (7.6)	63 (56.3) 44 (39.3) 5 (4.5)
Sex, n (%) Male Female	92 (41.1) 132 (58.9)	49 (43.8) 63 (56.3)
Race, n (%) Asian Black White Not collected or reported Other	81 (36.2) 1 (0.4) 122 (54.5) 5 (2.2) 15 (6.7)	36 (32.1) 0 60 (53.6) 5 (4.5) 11 (9.8)
Disease characteristics		
Pretransfusion Hb threshold[a], 12 week run-in (g/dL) Median (min, max)	9.30 (4.6, 11.4)	9.16 (6.2, 11.5)
Baseline transfusion burden 12 weeks Median (min, max) (units/12 weeks) (Week -12 to Day 1)	6.12 (3.0, 14.0)	6.27 (3.0, 12.0)
β-thalassaemia gene mutation grouping, n (%) β0/β0 Non-β0/β0 Missing[b]	68 (30.4) 155 (69.2) 1 (0.4)	35 (31.3) 77 (68.8) 0

[a]The 12-week pretransfusion threshold was defined as the mean of all documented pretransfusions Hb values for a patient during the 12 weeks prior to Cycle 1 Day 1.
[b] "Missing" category includes patients in the population who had no result for the parameter listed.

The study was unblinded for analyses when all patients had at least received 48 weeks of treatment or discontinued treatment.

The efficacy results are summarised below.

Table 11. Efficacy results in patients with β-thalassaemia in study ACE-536-B-THAL-001

Endpoint	Luspatercept (N=224)	Placebo (N=112)
Primary endpoint		
≥ 33% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks compared to the 12-week interval prior to treatment		
Weeks 13-24	48 (21.4)	5 (4.5)
Difference in proportions (95% CI)[a]	17.0 (10.4, 23.6)	
p-value[b]	< 0.0001	
Secondary endpoints		
Weeks 37-48	44 (19.6)	4 (3.6)
Difference in proportions (95% CI)[a]	16.1 (9.8, 22.3)	
p-value[b]	< 0.0001	

Endpoint	Luspatercept (N=224)	Placebo (N=112)
≥ 50% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks compared to the 12-week interval prior to treatment		
Weeks 13-24	17 (7.6)	2 (1.8)
Difference in proportions (95% CI)[a]	5.8 (1.6, 10.1)	
p-value[b]	0.0303	
Weeks 37-48	23 (10.3)	1 (0.9)
Difference in proportions (95% CI)[a]	9.4 (5.0, 13.7)	
p-value[b]	0.0017	

CI: confidence interval.
[a] Difference in proportions (luspatercept + BSC – placebo + BSC) and 95% CIs estimated from the unconditional exact test.
[b] P-value from the Cochran Mantel-Haenszel test stratified by the geographical region.

Exploratory findings

Table 12. Exploratory efficacy results in patients with β-thalassaemia in study ACE-536-B-THAL-001

Endpoint	Luspatercept (N=224)	Placebo (N=112)
≥ 33% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks compared to the 12-week interval prior to treatment		
Any consecutive 12 weeks*	158 (70.5)	33 (29.5)
Difference in proportions (95% CI)[a]	41.1 (30.7, 51.4)	
Any consecutive 24 weeks*	92 (41.1)	3 (2.7)
Difference in proportions (95% CI)[a]	38.4 (31.3, 45.5)	
≥ 50% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks compared to the 12-week interval prior to treatment		
Any consecutive 12 weeks*	90 (40.2)	7 (6.3)
Difference in proportions (95% CI)[a]	33.9 (26.1, 41.8)	
Any consecutive 24 weeks*	37 (16.5)	1 (0.9)
Difference in proportions (95% CI)[a]	15.6 (10.5, 20.8)	
Least square (LS) mean change from baseline in transfusion burden (RBC units/48 weeks)		
Weeks 1 to Week 48 LS mean	-4.67	+1.16
LS mean of difference (luspatercept-placebo) (95% CI)[b]	-5.83 (-7.01, -4.6)	
Weeks 49 to Week 96 LS mean	-5.66	+2.19
LS mean of difference (luspatercept-placebo) (95% CI)[b]	-7.84 (-14.44, -1.25)	

ANCOVA = analysis of covariance; CI: confidence interval.
[a] Difference in proportions (luspatercept + BSC – placebo + BSC) and 95% CIs estimated from the unconditional exact test.
[b] Estimates are based on ANCOVA model with geographical regions and baseline transfusion burden as covariates

A reduction in mean serum ferritin levels was observed from baseline in the luspatercept arm compared to an increase in the placebo arm at Week 48 (-233.51 µg/L *vs.* +114.28 µg/L which resulted in a least square mean treatment difference of -347.8 µg/L (95% CI: -516.95, -178.65).

A total of 80.4% (127/158) of luspatercept responders who achieved at least a 33% reduction in transfusion burden during any consecutive 12-week interval achieved 2 or more episodes of response at the time of analysis.

5.2 Pharmacokinetic properties

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 38% in MDS patients and 36% in β-thalassaemia patients.

Distribution
At the recommended doses, the mean apparent volume of distribution was 9.68 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.

Biotransformation
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 mean apparent total clearance was 0.516 L/day for MDS patients and 0.441 L/day for β-thalassaemia. The mean half-life in serum was approximately 13 days for MDS patients and 11 days for β-thalassaemia patients.

Linearity/non-linearity
The increase of luspatercept C_{max} 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.

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 MDS or β-thalassaemia.

Special populations

Elderly
Population PK analysis for luspatercept included patients with ages ranging from 18 to 95 years old, with a median age of 72 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 (< 65, 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 = 207), mild hepatic impairment (BIL > 1 – 1.5 x ULN, and ALT or AST > ULN; N = 160), moderate hepatic impairment (BIL > 1.5 – 3 x ULN, any ALT or AST; N = 138), or severe hepatic impairment (BIL > 3 x ULN, any ALT or AST; N = 40) 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 (eGFR ≥ 90 mL/min/1.73 m^2; N = 315), mild renal impairment (eGFR 60 to 89 mL/min/1.73 m^2; N = 171), or moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m^2; N = 59). Luspatercept serum exposure (AUC) was 27% to 41% higher in patients with mild to moderate renal impairment than in patients with normal renal function. PK data are not available for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) 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, RBC transfusion burden, 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, supporting the body weight-based dosing regimen.

5.3 Preclinical safety 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 (Week 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, an 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Tri-sodium citrate dihydrate
Polysorbate 80
Citric acid monohydrate
Hydrochloric acid
Sodium hydroxide

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial
The expiry date of the product is indicated on the packaging materials.

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.

6.4 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 section 6.3.

6.5 Nature and contents of container

Reblozyl 25 mg powder for solution for injection
3 mL Type I glass vial with a hydrophobic inner coating closed with a bromobutyl rubber stopper and aluminium seal with yellow polypropylene flip-off cap.

Reblozyl 75 mg powder for solution for injection
3 mL Type I glass vial with a hydrophobic inner coating closed with a bromobutyl rubber stopper and aluminium seal with orange polypropylene flip-off cap.

Pack size: 1 vial

6.6 Special precautions for disposal and other 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 dosage.

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 section 6.3 for storage conditions.

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

7. MANUFACTURER
Celgene Corporation
86 Morris Avenue, Summit, New Jersey 07901, USA

8. REGISTRATION HOLDER
Bristol-Myers Squibb (Israel) Ltd,
18 Aharon Bart st., POB 3361, Kiryat Arye, Petach Tikva 4951448

9. REGISTRATION NUMBERS
Reblozyl 25 mg: 169-03-36646-00
Reblozyl 75 mg: 169-04-36647-00

Revised on May 2023 according to the MOH's guidelines