אוקטובר 2024

<u>רבלוזיל 25 מ"ג, רבלוזיל 75 מ"ג – אבקה להכנת תמיסה להזרקה</u>
<u>Reblozyl 25 mg, Reblozyl 75 mg - powder for solution for injection</u>

רופא/ה ,רוקח/ת יקר/ה,

חברת בריסטול-מאיירס סקוויב (ישראל) שמחה להודיע על הרחבת התוויה, 1 line myelodysplastic syndromes לתכשירים שבנדון.

התוויות התכשירים כפי שאושרו ע"י משרד הבריאות:

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.

המרכיב הפעיל: Luspatercept 25 mg, Luspatercept 75 mg per vial

העלונים לרופא ולצרכן עודכנו בהתאם. בנוסף עודכנו העלונים עם מידע בטיחותי חדש ומידע PK עדכני.

העדכונים המהותיים בעלונים מפורטים בעמודים הבאים (ללא פירוט שינויים עריכתיים).

תוספת טקסט מסומנת <u>בקו תחתון אדום</u>, מחיקת טקסט ~~בקו אמצעי אדום~~, <u>החמרה מודגשת בצהוב</u>.

העלון לרופא והעלון לצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפס על ידי פנייה לבעל הרישום בריסטול-מאיירס סקוויב (ישראל) בע"מ.

בברכה,
יפעת זלינגר בן דוד
רוקחת ממונה
בריסטול-מאיירס סקוויב (ישראל)

למידע מלא על התרופה יש לעיין בעלון לרופא ובעלון לצרכן כפי שנשלחו למשרד הבריאות.

עדכונים מהותיים בעלון לרופא:

4.1 Therapeutic indications

Reblozyl is indicated in adults for the treatment of ~~adults patient 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 in adults for the treatment of anaemia associated with transfusion-dependent and non-transfusion-dependent beta-thalassaemia (see section 5.1).

4.2 Posology and method of administration

[…]

- *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 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 1.0 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 treatment effect of luspatercept on RBC-TI ≥12 weeks and Hb increase of ≥1.5 g/dL was comparable to epoetin alfa in patients without ring sideroblasts, and higher than epoetin alfa in patients with ring sideroblasts

[…]

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~~12 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.

[…]

Discontinuation
Reblozyl should be discontinued if patients do not experience a reduction in transfusion burden (for transfusion-dependent ~~MDS or~~ 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.
[…]

5.1 Pharmacodynamic properties

[…]

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.

[…]

Clinical efficacy and safety

Myelodysplastic syndromes
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 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 1.0 mg/kg every 3 weeks or at 450 U/kg every week, respectively. Randomization was stratified by RBC transfusion burden, RS status, and endogenous serum erythropoietin (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 key baseline disease characteristics in MDS patients in ACE-536-MDS-002 are shown in Table 8.

Table 8: Baseline demographics and disease characteristics of MDS patients in ACE-536-MDS-002

-	- **Luspatercept** - **(N = 182)**	- **Epoetin alfa** - **(N = 181)**
- **Demographics**		

-	- **Luspatercept** - **(N = 182)**	- **Epoetin alfa** - **(N = 181)**
Age[a] (years)	-	-
- **Median (min, max)**	- 74 (46, 93)	- 74 (31, 91)
Age categories, n (%)	-	-
≤64 years	- 27 (14.8)	- 25 (13.8)
65-74 years	- 68 (37.4)	- 66 (36.5)
- ≥75	87 (47.8)	- 90 (49.7)
Sex, n (%)	-	-
Male	- 109 (59.9)	- 92 (50.8)
- Female	73 (40.1)	- 89 (49.2)
Race, n (%)	-	-
Asian	- 19 (10.4)	- 25 (13.8)
Black	- 2 (1.1)	0
White	- 146 (80.2)	143 (79)
Not collected or reported	- 15 (8.2)	13 (7.2)
- **Disease Characteristics**		
Hb (g/dL), n (%)[b]		
Median (min, max)	7.80 (4.7, 9.2)	7.80 (4.5, 10.2)
Time since original MDS diagnosis (months)[c]		
Median	7.97	5.13
Serum EPO (U/L) categories, n (%)[d]		
≤200	145 (79.7)	144 (79.6)
>200	37 (20.3)	37 (20.4)
Median serum EPO	77.245	85.370
Serum ferritin (µg/L)	623.00	650.00
Median (min, max)	(12.4, 3170.0)	(39.4, 6960.5)
Baseline transfusion burden / 8 weeks[e] (pRBC units), n (%)		
<4 units	118 (64.8)	111 (61.3)
≥4 units	64 (35.2)	70 (38.7)
MDS Classification WHO 2016 at baseline, n (%)		
MDS-SLD	1 (0.5)	4 (2.2)
MDS-MLD	50 (27.5)	47 (26.0)
MDS-RS-SLD	2 (1.1)	6 (3.3)
MDS-RS-MLD	127 (69.8)	118 (65.2)
MDS/MPN-RS-T	2 (1.1)	5 (2.8)
Missing	0	1 (0.6)
IPSS-R classification risk category, n (%)		
Very low	16 (8.8)	17 (9.4)
Low	130 (71.4)	133 (73.5)
Intermediate	34 (18.7)	29 (16.0)
Other / missing	2 (1.1)	2 (1.1)
Ring sideroblast status (per WHO criteria), n (%)		
RS+	133 (73.1)	130 (71.8)
RS-	49 (26.9)	50 (27.6)
Missing	0	1 (0.6)
SF3B1 mutation status, n (%)		
Mutated	114 (62.6)	101 (55.8)
Non-mutated	65 (35.7)	72 (39.8)
Missing	3 (1.6)	8 (4.4)

Hb = haemoglobin; IPSSR = International Prognostic Scoring System-Revised; MDS-SLD = MDS with single lineage dysplasia; MDS-MLD = MDS with multilineage dysplasia; MDS-RS-SLD = MDS with ring sideroblasts with single lineage dysplasia; MDS-RS-MLD = MDS with ring sideroblasts with multilineage dysplasia; MDS/MPN-RS-T = myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and

thrombocytosis; RS+ = with ring sideroblasts; RS-= without ring sideroblasts; SF3B1 = Splicing Factor 3B Subunit 1A MDS mutation
[a] Age was calculated based on the informed consent signing date.
[b] After applying the 14/3-day rule (only Hb values that are measured at least 14 days after a transfusion may be used unless there is another transfusion within 3 days after the Hb assessment. If a transfusion within 3 days after the Hb assessment occurs, that Hb value will be used despite being < 14 days after the previous transfusion), the baseline Hb value (efficacy) is defined as the lowest Hb value from the central, or local laboratory, or pre-transfusion Hb from transfusion records that is within the 35 days prior to the first dose of study drug, if it was available.
[c] The number of months from the date of original diagnosis to the date of informed consent.
[d] Baseline EPO was defined as the highest EPO value within the 35 days preceding the first dose of study drug.
[e] Collected over 8 weeks prior to randomisation.

The efficacy results are summarised below.

Table 9: Efficacy results in MDS patients in ACE-536-MDS-002

- **Endpoint**	**Luspatercept (N = 182)**	**Epoetin alfa (N = 181)**
Primary endpoint		
• **RBC-TI for 12 weeks with associated concurrent mean Hb increase of ≥ 1.5 g/dL (Weeks 1-24)**		
Number of responders (response rate %) (95% CI)	110 (60.4) (52.9, 67.6)	63 (34.8) (27.9, 42.2)
Common Risk Difference (95% CI)[a]	25.4 (15.8, 35.0)	
p-value	< 0.0001	
Odds Ratio (95% CI)[a]	3.1 (2.0, 4.8)	
Secondary endpoints		
• **HI-E per IWG ≥8 weeks (Weeks 1-24)[b]**		
Number of responders (response rate %) (95% CI)	135 (74.2) (67.2, 80.4)	96 (53.0) (45.5, 60.5)
Common Risk Difference (95% CI)[a]	21.5 (12.2, 30.7)	
p-value	< 0.0001	
Odds Ratio (95% CI)[a]	2.8 (1.8, 4.5)	
• **RBC-TI for 24 weeks (Weeks 1-24)**		
Number of responders (response rate %) (95% CI)	87 (47.8) (40.4, 55.3)	56 (30.9) (24.3, 38.2)
Common Risk Difference (95% CI)[a]	16.3 (7.1, 25.4)	
p-value	0.0003	
Odds Ratio (95% CI)[a]	2.3 (1.4, 3.7)	
• **RBC-TI for ≥24 weeks (Weeks 1-48)**	163	167
Number of responders (response rate %) (95% CI)	99 (60.7) (52.8, 68.3)	66 (39.5) (32.1, 47.4)
Common Risk Difference (95% CI)[a]	20.7 (10.8, 30.6)	
p-value	p < 0.0001[c]	
Odds Ratio (95% CI)[a]	2.6 (1.6, 4.3)	

Hb = haemoglobin; RBC = red blood transfusion
[a] Based on CMH test stratified by baseline RBC transfusion burden (< 4, ≥ 4 pRBC units), RS status (RS+, RS-) and sEPO level (≤ 200, > 200 U/L). 1-sided p-value is presented.
[b] HI-E = 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, HI-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, HI-E was defined as a mean increase in Hb of ≥ 1.5 g/dL for 8 weeks in the absence of RBC transfusions.
[c] Nominal p-value

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.

- *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 to ~~International Prognostic Scoring System Revised (~~IPSS-R~~)~~ very low-, low- or intermediate-risk MDS who have ring sideroblasts (≥ 15%). Patients with del5q MDS or without ring sideroblasts (RS-) were not included in the study. 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.~~

[…]

Table 10: Baseline demographics and disease characteristics of 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 65-74 years ≥ 75	 29 (19.0) 72 (47.1) - 52 (34.0)	 16 (21.1) 29 (38.2) - 31 (40.8)

[…]

5.2 Pharmacokinetic properties

[…]

Distribution

At the recommended doses, the geometric mean apparent volume of distribution was 9.56~~57~~ 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.

[…]

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.

[…]

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.

[…]

Special populations

Elderly
Population PK analysis for luspatercept included patients with ages ranging from 27 to 95 and 18 to ~~95~~71 years old, for MDS and b-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 (~~< 65~~ ≤ 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 = ~~373~~ 62 for b-thalassaemia patients and N = 311 for MDS patients), mild hepatic impairment (BIL > 1 – 1.5 x ULN, and ALT or AST > ULN; N = ~~216~~ 89 for b-thalassaemia patients and N = 126 for MDS patients), moderate hepatic impairment (BIL > 1.5 – 3 x ULN, any ALT or AST; N = ~~189~~ 157 for b-thalassaemia patients and N = 32 for MDS patients), or severe hepatic impairment (BIL > 3 x ULN, any ALT or AST; N = ~~74~~ 73 for b-thalassaemia patients and N = 1 for MDS patients) as defined by the National Cancer Institute criteria of hepatic dysfunction.

[…]

Renal impairment
Population PK analysis for luspatercept included patients with normal renal function (individual eGFR ≥ 90 mL/min N = ~~471~~ 302 for b-thalassaemia patients and N = 169 for MDS patients), mild renal impairment (individual eGFR 60 to 89 mL/min; N = ~~278~~ 74 for b-thalassaemia patients and N = 204 for MDS patients), or moderate renal impairment (individual eGFR 30 to 59 mL/min; N = ~~93~~ 4 for b-thalassaemia patients and N = 88 for MDS patients) as defined by Modification of Diet in Renal Disease (MDRD) formula.

[…]

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 b-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.

[…]

עדכונים מהותיים בעלון לצרכן

1. למה מיועדת התרופה?

- רבלוזיל מותווית לטיפול במבוגרים עם אנמיה התלויה בעירויי דם בשל תסמונות מיאלודיספלסטיות (MDS) בסיכון נמוך מאוד, נמוך או בינוני, ~~עם טבעת סידרובלסטית, אשר הגיבו בצורה לא מספקת או שאינם יכולים לקבל טיפול מבוסס אריתרופויאטין~~.
- רבלוזיל מותווית לטיפול במבוגרים עם אנמיה הקשורה עם בטא תלסמיה התלויה או שאינה תלויה בעירויי דם.