Luspatercept (new therapeutic indication: β-thalassaemia, non-transfusion-dependent anaemia)

Resolution of: 21 September 2023 Valid until: unlimited
Entry into force on: 21 September 2023
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New therapeutic indication (according to the marketing authorisation of 27 February 2023):

Reblozyl is indicated in adults for the treatment of anaemia associated with transfusion-dependent and non-transfusion-dependent beta-thalassaemia.

Therapeutic indication of the resolution (resolution of 21 September 2023):

Reblozyl is indicated in adults for the treatment of anaemia associated with non-transfusion-dependent beta-thalassaemia.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

Adults with non-transfusion-dependent anaemia due to β-thalassaemia

Appropriate comparator therapy:

Transfusion therapy on demand with red blood cell concentrates in combination with a chelation therapy according to the marketing authorisation, preferably as monotherapy

Extent and likelihood of additional benefit of luspatercept compared to transfusion therapy on demand with red blood cell concentrates in combination with chelation therapy according to the marketing authorisation, preferably as monotherapy:

Indication of a minor additional benefit

Study results according to endpoints:[1]

Adults with non-transfusion-dependent anaemia due to β-thalassaemia

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑↑	Advantages in case of symptomatology related to fatigue/ weakness, shortness of breath and β-thalassaemia.
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↑	Advantage in the endpoint of serious adverse events (SAE) borne by the subgroup of patients with previous splenectomy; in detail, disadvantage in the SAE of bone pain.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

Double-blind, randomised phase III study BEYOND:

- Luspatercept + Best Supportive Care (BSC) vs placebo + BSC
- Data cut-off from 14.09.2020

Mortality

Endpoint	Luspatercept + BSC		Placebo + BSC		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value[a]
Overall mortality[b]					
	96	0 (0)	49	0 (0)	n.a.

[1] Data from the dossier assessment of the IQWiG (A23-20) and from the addendum (A23-80), unless otherwise indicated.

Morbidity

Endpoint	Luspatercept + BSC		Placebo + BSC		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value[a]
Symptomatology (NTDT-PRO) - percentage of patients with improvement at week 24					
Fatigue/ weakness[c]	76	27 (35.5)	39	7 (17.9)	2.06 [1.02; 4.17] 0.043
Shortness of breath[c]	76	21 (27.6)	39	4 (10.3)	2.87 [1.09, 7.59] 0.033
β-thalassaemia-related symptomatology - percentage of patients with improvement					
PGIS – change at week 24[c]	76	23 (30.3)	39	4 (10.3)	3.08 [1.19; 7.95] 0.020
PGIC – change at week 48[d]	73	38 (52.1)	40	3 (7.5)	7.08 [2.29; 21.87] 0.001
Transfusion avoidance at week 48 (presented additionally)					
	96	81 (84.4)[k]	49	30 (61.2)[k]	1.36 [1.08; 1.72] 0.009
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Hazard ratio [95% CI][i] p value[j]
Total hospitalisation					
	96	n.r. [125.29; n.c.] 16 (16.7)	49	n.r. [84.71; n.c.] 12 (24.5)	0.50 [0.23; 1.08] 0.070

Health-related quality of life

Endpoint	Luspatercept + BSC		Placebo + BSC		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value[a]
FACIT-F - percentage of patients with improvement at week 48					
Total score[e]	74	9 (12.2)	40	1 (2.5)	4.99 [0.67; 36.94] 0.116
Subscales (presented additionally)					
Physical well-being	74	8 (10.8)	40	1 (2.5)	4.43 [0.59; 33.41]
Social/ family well-being	74	8 (10.8)	40	4 (10.0)	1.10 [0.36; 3.31]
Emotional well-being	74	9 (12.2)	40	3 (7.5)	1.66 [0.51; 5.43]
Functional well-being	74	5 (6.8)	40	1 (2.5)	2.77 [0.33; 23.02]
FACT-G total score	74	5 (6.8)	40	1 (2.5)	2.77 [0.35; 22.04]
Fatigue-specific scale	74	17 (23.0)	40	4 (10.0)	2.35 [0.88; 6.28]
SF-36v2 - percentage of patients with improvement at week 48					
Physical Component Summary (PCS) score[f]	73	5 (6.8)	39	2 (5.1)	1.31 [0.27; 6.26] 0.736
Mental Component Summary (MCS) score[g]	73	11 (15.1)	39	1 (2.6)	5.93 [0.79; 44.22] 0.083

Side effects[h]

Endpoint	Luspatercept + BSC		Placebo + BSC		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI][i] p value[j]
Adverse events (presented additionally)					
	96	0.10 [0.07; 0.13] 96 (100.0)	49	0.76 [0.46; 0.89] 48 (98.0)	-
Serious adverse events (SAE)					
	96	n.r. 11 (11.5)	49	n.r. [18.00; n.c.] 12 (24.5)	0.29 [0.12; 0.69] 0.003
Severe adverse events (CTCAE grade ≥ 3)					
	96	n.r. 27 (28.1)	49	n.r. [16.62; n.c.] 12 (24.5)	1.07 [0.54; 2.14] 0.842
Discontinuation due to adverse events					
	96	n.r. 3 (3.1)	49	n.r. 4 (8.2)	0.29 [0.06; 1.34] 0.092
Bone pain (preferred term)					
	96	n.r. 35 (36.5)	49	n.r. 3 (6.1)	7.11 [2.18; 23.15] < 0.001

a RR: calculated using Mantel-Haenszel method, adjusted for baseline Hb value and baseline NTDT-PRO total score in the fatigue/ weakness domain; CI and p value were calculated using normal approximation.
b Deaths were recorded as part of the adverse events; period until 14.09.2020
c Percentage of patients with a decrease in the relevant score by ≥ 1.5 points compared to the start of the study at week 24 with a scale range of 0 to 10. Lower (decreasing) values mean an improvement of symptomatology.
d Percentage of patients who rated their β-thalassaemia-related symptomatology as very much better or much better compared to the start of the study.
e Percentage of patients with an increase in the FACIT-F score by ≥ 24 points compared to the start of the study at week 48 with a scale range of 0 to 160. Higher (increasing) values mean an improvement of health-related quality of life.
f Percentage of patients with an increase in the PCS score by ≥ 9.4 points compared to the start of the study at week 48 with a scale range of 7 to 63. Higher (increasing) values mean an improvement of health-related quality of life.

g Percentage of patients with an increase in the MCS score by ≥ 9.6 points compared to the start of the study at week 48 with a scale range of 6 to 64. Higher (increasing) values mean an improvement of health-related quality of life.
h Events that occurred from the day of the first dose of study medication until 9 weeks after the last dose, also beyond week 48, if applicable.
i Cox regression model stratified by baseline Hb value and baseline NTDT-PRO total score in the fatigue/ weakness domain.
j Log-rank test stratified by baseline Hb value and baseline NTDT-PRO total score in the fatigue/ weakness domain.
k Patients without complete observation until week 48 were not considered transfusion-free (in both treatment arms, this concerns 3 patients each).

CTCAE: Common Terminology Criteria for Adverse Events; FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue; FACT-G: Functional Assessment of Cancer Therapy – General; HR: hazard ratio; CI: confidence interval; MCS: Mental Component Summary; n: number of patients with (at least 1) event; N: number of patients evaluated; n.c.: not calculable; n.r. = not reached; NTDT-PRO: Nontransfusion-Dependent Thalassemia-Patient Reported Outcomes; PCS: Physical Component Summary; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PT: preferred term; RCT: randomised controlled trial; RR: relative risk; SF 36v2: Short Form-36 Health Survey Version 2.

2. Number of patients or demarcation of patient groups eligible for treatment

Adults with non-transfusion-dependent anaemia due to β-thalassaemia

approx. 470 – 560 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Reblozyl (active ingredient: luspatercept) at the following publicly accessible link (last access: 26 April 2023):

https://www.ema.europa.eu/en/documents/product-information/reblozyl-epar-product-information_en.pdf

Treatment with luspatercept should only be initiated and monitored by doctors experienced in treating patients with haematological diseases.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients including patient identification card (only for women of reproductive age). The training material includes, among other things, a checklist for healthcare professionals to use before starting any treatment, at each administration and then at regular intervals during follow-up visits. The patient identification card must be given to women of reproductive age at the time of the start of treatment. Treatment with luspatercept must not be started if a woman is pregnant. Luspatercept is contraindicated during pregnancy. Patients must use highly effective contraceptives during treatment with Luspatercept. If a patient becomes pregnant, luspatercept should be discontinued.

Treatment with luspatercept should be discontinued if patients do not show an increase in Hb from baseline after nine weeks of treatment (three doses) with the highest dose, without transfusions, unless other explanations for the lack of response are found (e.g. bleeding, surgery, other comorbidities) or whenever unacceptable toxicity occurs.

4. Treatment costs

Annual treatment costs:

Adults with non-transfusion-dependent anaemia due to β-thalassaemia

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Luspatercept	€ 42,740.66 - € 83,816.84
Appropriate comparator therapy:	
Transfusion therapy on demand with red blood cell concentrates in combination with chelation therapy in accordance with the marketing authorisation	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 September 2023

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed					
Luspatercept	Surcharge for production of a Reblozyl-containing parenteral solution	€ 81	1	17.4	€ 1,409.40
Appropriate comparator therapy					
Transfusion therapy on demand with red blood cell concentrates	Different from patient to patient				
Chelation therapy					
Deferoxamine	Surcharge for production of another parenteral solution	€ 54	Different from patient to patient		

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

<u>Adults with non-transfusion-dependent anaemia due to β-thalassaemia</u>

- No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.