Luspatercept (reassessment of an orphan drug after exceeding the EUR 30 million turnover limit: β-thalassaemia, transfusion-dependent anaemia)

Resolution of: 2 November 2023 valid until: unlimited
Entry into force on: 2 November 2023
Federal Gazette, BAnz AT 07 12 2023 B2

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 2 November 2023):

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

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

Adults with transfusion-dependent anaemia associated with 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:

An additional benefit is not proven.

Study results according to endpoints:[1]

Adults with transfusion-dependent anaemia associated with β-thalassaemia

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↓	Disadvantage in the total hospitalisation endpoint.
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↓	Disadvantages in the endpoints of SAEs and severe AEs (CTCAE grade ≥ 3); in detail, disadvantage in the AE 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 BELIEVE study:

- Luspatercept + Best Supportive Care (BSC) vs placebo + BSC
- Final data cut-off from 5 January 2021 (evaluation time points: at week 48; until unblinding)

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]					
	224	1 (0.4)	112	1 (0.9)	0.50 [0.03; 7.92] 0.736[c]

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A23-43) 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] AD [r]
Transfusion avoidance ≥ 24 weeks[d]							
	224	5 (2.2)		112	0 (0)		5.52 [0.31; 99.03] 0.120[c]
Reduction of the transfusion burden by ≥ 50% over ≥ 24 weeks compared to the start of study (presented additionally)[e]							
	224	40 (17.9)		112	1 (0.9)		20.02 [2.78, 144.31] 0.003 AD: 17%
Total hospitalisation[c]							
	224	40 (17.9)		112	5 (4.5)		4.00 [1.62, 9.85] < 0.001 AD: 13.4%
	N[o]	Values at start of study[p] MV (SD)	Change to unblinding MV [95% CI]	N[o]	Values at start of study[p] MV (SD)	Change to unblinding MV [95% CI]	MD [95% CI] p value
Transfusion burden / 24 weeks, continuous analysis (presented additionally)							
	223	14.5 (3.6)	-2.35 [-2.75; -1.96]	111	14.8 (3.5)	0.43 [-0.12; 0.99]	–2.79 [–3.46, –2.12] < 0.001[q]

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]
SF-36v2 (percentage of patients with improvement at week 48)					
Physical Component Summary (PCS) score[f, g]	183	12 (6.6)	91	5 (5.5)	1.21 [0.44, 3.34] 0.714
Mental Component Summary (MCS) score[g, i]	183	17 (9.3)	91	7 (7.7)	1.20 [0.52, 2.77] 0.674
TranQoL (percentage of patients with improvement at week 48)					
Total score [h, j]	186	20 (10.8)	91	7 (7.7)	1.38 [0.61, 3.13] 0.436
Physical health	186	34 (18.3)	91	11 (12.1)	1.52 [0.81; 2.85] –
Emotional health	186	33 (17.7)	91	10 (11.0)	1.60 [0.83; 3.10] –
Sexual activity	No usable data available[k]				
Family situation	186	35 (18.8)	91	12 (13.2)	1.43 [0.78; 2.61] –
School and work	186	39 (21.0)	90	21 (23.3)	0.90 [0.56; 1.45] –

Side effects[l]

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] AD [r]
Adverse events (presented additionally)					
	223	216 (96.9)	109	102 (93.6)	–
Serious adverse events (SAE)					
	223	37 (16.6)	109	8 (7.3)	2.26 [1.09; 4.69] 0.029[m] AD: 9.3%
Severe adverse events (CTCAE grade ≥ 3)[n]					
	223	70 (31.4)	109	19 (17.4)	1.80 [1.15; 2.83] 0.011[m] AD: 14%
Discontinuation due to AEs					
	223	15 (6.7)	109	2 (1.8)	3.67 [0.85; 15.77] 0.080[m]
Bone pain (preferred term)					
	223	44 (19.7)	109	9 (8.3)	2.39 [1.23; 4.67] 0.011[m] AD: 11.4%

a Unless otherwise specified: Mantel-Haenszel method adjusted by geographical region; CIs and p value were calculated using normal approximation.
b Fatalities were collected as part of AEs.
c IQWiG calculation: RR, CI (asymptotic) and p value (unconditional exact test, CSZ method)
d Defined as the percentage of patients who did not require a transfusion of a red blood cell concentrate for ≥ 24 weeks until the study was unblinded.
e Defined as the percentage of patients with a reduction in transfused red blood cell concentrates over ≥ 24 weeks by ≥ 50% compared to the start of study (based on the 24 weeks before the start of treatment) in the period up to unblinding of the study.
f Percentage of patients with an increase in the PCS score by ≥ 9.4 points compared to the start of 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 Supplementary sensitivity analyses by the pharmaceutical company with replacement of missing values as non-responders (RR [95% CI], p-value): PCS: 1.20 [0.43; 3.32]; p = 0.731; MCS: 1.19 [0.51; 2.76], p = 0.691
h Percentage of patients with an increase in the total score by ≥ 15 points compared to the start of study at week 48 with a scale range of 0 to 100. Higher (increasing) values mean an improvement of health-related quality of life.
i Percentage of patients with an increase in the MCS score by ≥ 9.6 points compared to the start of study at week 48 with a scale range of 6 to 64. Higher (increasing) values mean an improvement of health-related quality of life.

j Supplementary sensitivity analysis of the pharmaceutical company with replacement of missing values as non-responders (RR [95% CI], p-value): Total score: 1.39 [0.61; 3.17], p = 0.431
k Only 31% and 33% of the randomised patients in the intervention and comparator arms, respectively, are included in the analysis, thus rendering the data unusable.
l Events that occurred from the date of 1st dose of the study medication until 9 weeks after the last dose,
m stratified by geographical region
n operationalised as CTCAE grade ≥ 3; the severity grade of AEs for which no CTCAE criteria are defined was classified by the principal investigator using a 5-point scale (grade 1: mild; grade 2: moderate; grade 3: severe; grade 4: life-threatening; grade 5: fatal).
o Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at start of study can be based on other patient numbers.
p Transfused red blood cell concentrates within 24 weeks based on the 24-week interval before or on the day of the 1st dose of the study medication
q ANCOVA model adjusted by geographical region and baseline value
r AD, absolute difference only in case of statistically significant difference, own calculation

Abbreviations used:
CTCAE = Common Terminology Criteria for Adverse Events; CI = confidence interval; MCS = Mental Component Summary; MD = mean difference; MV = mean value; N = number of patients analysed; n = number of patients with (at least one) event; PCS = Physical Component Summary; SD = standard deviation; SF-36v2 = Short Form-36 Health Survey Version 2; SAE = serious adverse event; TranQoL = Transfusion-dependent Quality of Life Questionnaire; AE = adverse event; vs = versus

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

Adults with transfusion-dependent anaemia associated with β-thalassaemia

approx. 250 – 330 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: 24 August 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 any reduction in transfusion burden after nine weeks of treatment (three doses) with the highest dose, 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 transfusion-dependent anaemia associated with β-thalassaemia

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Luspatercept	€ 62,446.51 – € 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: 15 October 2023)

Costs for additionally required SHI services: not applicable

Other SHI services: Production of ready-to-use units

Designation of the therapy	Type of service	Costs/ unit	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed				
Luspatercept	Surcharge for production of a Reblozyl-containing parenteral solution	€ 81	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 transfusion-dependent anaemia associated with 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.