Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Luspatercept (β-thalassaemia)

of 21 January 2021

At its session on 21 January 2021 the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive, (AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient luspatercept as follows:

Luspatercept

Resolution of: 21 January 2021
Entry into force on: 21 January 2021
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 25 June 2020):

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.

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

Therapeutic indication of the resolution (resolution of 21 January 2021):

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

1. Extent of the additional benefit and significance of the evidence

Luspatercept is approved as a medicinal product for the treatment of a rare disease in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

Adult patients with transfusion-dependent anaemia associated with beta-thalassaemia

Extent of the additional benefit and significance of the evidence for luspatercept:

Hint for a non-quantifiable additional benefit because the scientific data does not allow quantification

Study results according to endpoints:[1]

BELIEVE study: Luspatercept + best supportive care (BSC) vs placebo + BSC

Study design: double-blind, randomised, Phase III

Data cut-offs: 11 May 2018 (evaluation time: 48-week treatment phase); 7 January 2019 (evaluation time: Time of unblinding at the level of the participating study centres on 1 August 2018)

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No difference relevant for the benefit assessment.
Morbidity	↓	Disadvantage in the endpoint hospitalisation.
Health-related quality of life	↔	No difference relevant for the benefit assessment.
Side effects	↓	Disadvantages in the endpoints serious AE, severe AE (CTCAE-grade ≥ 3), therapy discontinuations because of AE.

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
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

Mortality[a]

Endpoint	Luspatercept + BSC		Placebo + BSC		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value Absolute difference (AD)[b]
Overall mortality					
Deaths	224	1 (0.4)	112	1 (0.9)	–[c]

[1] Data from the dossier assessment by the G-BA (published on 2 November 2020) as well as from the amendment unless indicated otherwise.

Morbidity[a]

Endpoint	Luspatercept + BSC		Placebo + BSC		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value Absolute difference (AD)[b]
Transfusion burden					
Reduction of EC units by ≥ 33% with at least two EC-units[d] (presented additionally)					
In week 13–24 compared with the screening phase[e]	224	48 (21.4)	122	5 (4.5)	4.80 [1.97; 11.72] < 0.001 AD: 16.9%
Transfusion-free period ≥ 24 weeks					
	224	5 (2.2)	112	0	–[c]
Hospitalisation					
By any cause	224	41 (18.3)	112	5 (4.5)	4.08 [1.66; 10.02] < 0.001 AD: 13.8%

Health-related quality of life[f]

Endpoint	Luspatercept + BSC		Placebo + BSC		Intervention vs control
	N	Mean change LS Mean [95% CI]	N	Mean change LS Mean [95% CI]	Mean difference (MD) [95% CI] p value Absolute difference (AD)[b]
TranQoL – total score[g]					
Baseline and Week 48	179	−0.2 [−2.1; 1.7]	88	0.4 [−2.3; 3.1]	−0.6 [−3.8; 2.7] 0.73

Endpoint	Luspatercept + BSC		Placebo + BSC		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value Absolute difference (AD)[b]
SF-36 score[h]					
Improvement by ≥ 5 points at Week 48					
Physical component score (PCS)	210	37 (17.6)	103	11 (10.7)	1.19 [0.99; 1.43] 0.10
Mental component score (MCS)	210	40 (19.0)	103	15 (14.6)	1.10 [0.92; 1.33] 0.33
Deterioration by ≥ 5 points at Week 48					
Physical component score (PCS)	210	76 (36.2)	103	28 (27.2)	1.14 [0.97; 1.34] 0.12
Mental component score (MCS)	210	81 (38.6)	103	43 (41.8)	0.95 [0.81; 1.13] 0.57

Side effects[a]

Endpoint	Luspatercept + BSC		Placebo + BSC		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value Absolute difference (AD)[b]
Total 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] 0.02 AD: 9.3%
Severe adverse events (CTCAE grade ≥ 3)					
	223	70 (31.4)	109	19 (17.4)	1.80 [1.15; 2.83] 0.007 AD: 14.0%

(Continuation)

Therapy discontinuations because of adverse events					
	223	15 (6.7)	109	1 (0.9)	7.32 [0.98; 54.57] 0.02 AD: 5.8%
Adverse events of special interest					
Malignancies and pre-malignant diseases (SMQ)	223	2 (0.9)	109	0	–[c]
Other relevant safety events[i]					
Thromboembolic and thrombophlebitic events (SMQ)	223	9 (4.0)	109	1 (0.9)	4.39 [0.57; 33.97] 0.12
Bone pain (PT)	223	44 (19.7)	109	9 (8.3)	2.39 [1.23; 4.67] 0.007 AD: 11.4%
SAE according to SOC/PT with incidence ≥ 5% in one treatment arm or ≥ 1% and 10 persons with event in one treatment arm					
Infections and infestations (SOC)	223	14 (6.3)	109	5 (4.6)	1.36 [0.50; 3.69] 0.53
Severe AE (CTCAE grade ≥ 3) according to SOC/PT with incidence ≥ 5% or ≥ 1% and 10 persons with event in one treatment arm					
Infections and infestations (SOC)	223	15 (6.7)	109	8 (7.3)	0.91 [0.40; 2.08] 0.84
Investigations (SOC)	223	13 (5.8)	109	7 (6.4)	0.91 [0.37; 2.21] 0.83
Blood and lymphatic system disorders (SOC)	223	11 (4.9)	109	0 (0)	no data available
Metabolism and nutrition disorders (SOC)	223	11 (4.9)	109	1 (0.9)	5.33 [0.70; 40.51] no data available
Musculoskeletal and connective tissue disorders (SOC)	223	10 (4.5)	109	1 (0.9)	4.90 [0.63; 38.06] no data available
Nervous system disorders (SOC)	223	10 (4.5)	109	1 (0.9)	4.91 [0.64; 37.98] no data available

(Continuation)

[a] Evaluation time: Unblinding at participating study centre level on 1 August 2018 as part of the data cut-off of 7 January 2019
[b] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[c] The number of events is low. The calculation of relative effect estimators would not allow a reliable statement.
[d] Data from the dossier on luspatercept Module 4A of 27 July 2020
[e] Screening phase: 12 weeks before randomisation
[f] Evaluation time: 48-week treatment phase as part of the data cut-off of 11 May 2018
[g] The TranQoL total score can have a value between 0 and 100. A higher value corresponds to a higher quality of life.
[h] A higher score represents a higher quality of life.
[i] Pre-specified AEs requiring safety analysis

Abbreviations used:
AD = absolute difference; BSC = best supportive care; CTCAE = Common Terminology Criteria for Adverse Events; CI = confidence interval; MD = mean difference; MCS = mental component score; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; PCS = physical component score; PT = preferred term; RR = relative risk; SOC = system organ class; SMQ = Standardised MedDRA Query; TranQoL = Transfusion-dependent Quality of Life Questionnaire; vs = versus

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

approx. 170–300 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: 3 December 2020):

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

Treatment with luspatercept should only be initiated and monitored by specialists who are experienced in the therapy of patients with haematological diseases.

In accordance with the specifications of the EMA regarding additional measures for risk minimisation, the pharmaceutical company must provide training materials to all healthcare professionals who are likely to use luspatercept. The information pack contains information on where to obtain the current product information as well as a check-list for healthcare professionals to use before starting any treatment, at each administration, and then at regular intervals during follow-up visits. Furthermore, the information package includes a patient card that healthcare professionals must give to women of childbearing age at 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 experience a 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 concomitant diseases) or whenever unacceptable toxicity occurs.

4. Treatment costs

Annual treatment costs:

Adult patients with transfusion-dependent anaemia associated with beta-thalassaemia

Designation of the therapy	Annual treatment costs/patient
Luspatercept	€ 90,131.83 – 120,820.90

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 January 2021

Costs for additionally required SHI services: not applicable.

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Luspatercept	Surcharge for the preparation of a parenteral solution	€ 81	1	17.4	€ 1,409.40

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 21 January 2021.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 21 January 2021

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken