Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V)
Luspatercept (reassessment of an orphan drug after exceeding the EUR 30 million turnover limit: myelodysplastic syndromes with transfusion-dependent anaemia, pretreated)

of 2 November 2023

At its session on 2 November 2023, 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 by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII is amended as follows:

1. **The information on Luspatercept in the version of the resolution of 21 January 2021 on the therapeutic indication myelodysplastic syndromes (BAnz AT 02.03.2021 B3) is repealed.**
2. **In Annex XII, the following information shall be added after No. 5 to the information on the benefit assessment of Luspatercept in accordance with the resolution of 2 November 2023**:

Luspatercept

Resolution of: 2 November 2023
Entry into force on: 2 November 2023
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.

Therapeutic indication of the resolution (resolution of 2 November 2023):

See therapeutic indication according to marketing authorisation.

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

Adults 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

Appropriate comparator therapy for luspatercept:

- A transfusion therapy on demand with red blood cell concentrates in combination with chelation therapy in accordance with the marketing authorisation

Extent and probability of the additional benefit of luspatercept compared to the appropriate comparator therapy

An additional benefit is not proven.

Study results according to endpoints[1]:

Adults 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

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	↔	No relevant difference for the benefit assessment; advantage in the deterioration of the insomnia endpoint, disadvantage in the deterioration of the fatigue endpoint.
Health-related quality of life	↔	No relevant difference for the benefit assessment; disadvantage in the deterioration of physical functioning
Side effects	↔	No relevant differences for the benefit assessment. In detail, disadvantage in the AE (CTCAE grade ≥ 3) of the system organ class "Nervous system disorders"
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		

MEDALIST study: Luspatercept + BSC vs placebo + BSC

Data cut-off: 26.11.2020 (final data cut-off)

[1] Data from the dossier evaluation of the Institute for Quality and Efficiency in Health Care (IQWiG) (A23-44) unless otherwise indicated.

Mortality

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 (%)*	Hazard ratio [95% CI] p value[a]
Overall survival[b]					
	153	46.0 [42.0; n.c.] 45 (29.4)	76	n.r. [43.1, n.c.] 24 (31.6)	0.99 [0.59; 1.64]; 0.958

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[c]
Transfusion avoidance ≥ 24 weeks[d]					
	153	20 (13.1)	76	1 (1.3)	9.84 [1.36; 71.31]; 0.024
Symptomatology (EORTC QLQ-C30 symptom scales)					
Improvement by ≥ 10 points (start of study compared to week 25)[e]					
Fatigue	109	32 (29.4)	54	24 (44.4)	0.67 [0.44; 1.01]; 0.056
Nausea and vomiting	110	17 (15.5)	54	5 (9.3)	1.71 [0.67; 4.38]; 0.263
Pain	109	25 (22.9)	54	14 (25.9)	0.86 [0.49; 1.50]; 0.591
Dyspnoea	106	24 (22.6)	54	16 (29.6)	0.77 [0.45; 1.31]; 0.335
Insomnia	108	27 (25.0)	54	18 (33.3)	0.77 [0.47; 1.25]; 0.290
Appetite loss	109	22 (20.2)	53	9 (17.0)	1.21 [0.59; 2.46]; 0.602
Constipation	110	31 (28.2)	53	13 (24.5)	1.16 [0.67; 2.01]; 0.601
Diarrhoea	110	11 (10.0)	53	6 (11.3)	0.84 [0.33; 2.15]; 0.718

Endpoint	Luspatercept + BSC		Placebo + BSC		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value[c]
Deterioration by ≥ 10 points (start of study compared to week 25)[f]					
Fatigue	109	50 (45.9)	54	14 (25.9)	1.76 [1.07; 2.89]; 0.026
Nausea and vomiting	110	17 (15.5)	54	7 (13.0)	1.19 [0.51; 2.74]; 0.690
Pain	109	27 (24.8)	54	14 (25.9)	0.99 [0.56; 1.73]; 0.962
Dyspnoea	106	30 (28.3)	54	10 (18.5)	1.56 [0.81; 3.01]; 0.186
Insomnia	108	19 (17.6)	54	18 (33.3)	0.53 [0.30; 0.93]; 0.028
Appetite loss	109	22 (20.2)	53	10 (18.9)	1.06 [0.53; 2.14]; 0.860
Constipation	110	15 (13.6)	53	5 (9.4)	1.42 [0.54; 3.76]; 0.477
Diarrhoea	110	16 (14.5)	53	5 (9.4)	1.59 [0.57; 4.40]; 0.376
Hospitalisation (up to and including week 24)					
Due to any cause	153	34 (22.2)	76	17 (22.4)	0.99 [0.60; 1.64]; 0.977

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[c]
EORTC QLQ-C30					
Improvement by ≥ 10 points (start of study compared to week 25)[g]					
Global health status	110	31 (28.2)	53	12 (22.6)	1.24 [0.69; 2.25]; 0.476
Physical functioning	110	25 (22.7)	54	18 (33.3)	0.70 [0.42; 1.16]; 0.163
Role functioning	110	30 (27.3)	54	18 (33.3)	0.82 [0.50; 1.34]; 0.425
Emotional functioning	110	18 (16.4)	53	11 (20.8)	0.81 [0.41; 1.59]; 0.542
Cognitive functioning	110	29 (26.4)	53	14 (26.4)	1.01 [0.58; 1.76]; 0.968
Social functioning	110	26 (23.6)	53	16 (30.2)	0.76 [0.45; 1.30]; 0.322
Deterioration by ≥ 10 points (start of study compared to week 25)[h]					
Global health status	110	33 (30.0)	53	11 (20.8)	1.47 [0.80; 2.67]; 0.213
Physical functioning	110	34 (30.9)	54	7 (13.0)	2.33 [1.12; 4.87]; 0.024
Role functioning	110	35 (31.8)	54	19 (35.2)	0.90 [0.58; 1.41]; 0.652
Emotional functioning	110	28 (25.5)	53	14 (26.4)	0.99 [0.57; 1.72]; 0.973
Cognitive functioning	110	29 (26.4)	53	17 (32.1)	0.83 [0.50; 1.36]; 0.458
Social functioning	110	36 (32.7)	53	16 (30.2)	1.10 [0.68; 1.79]; 0.687

Side effects[d]

Endpoint	Luspatercept + BSC		Placebo + BSC		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value
Total adverse events[i] (presented additionally)					
	153	145 (94.8)	76	70 (92.1)	–
Serious adverse events (SAE)[i]					
	153	40 (26.1)	76	16 (21.1)	1.25 [0.75; 2.08]; 0.395
Severe adverse events (CTCAE grade ≥ 3)[i, j]					
	153	55 (35.9)	76	27 (35.5)	1.01 [0.70; 1.45]; 0.978
Therapy discontinuation due to adverse events[i]					
	153	12 (7.8)	76	4 (5.3)	1.54 [0.50; 4.79]; 0.454
Nervous system disorders (SOC, severe AEs[j, k]**)**					
	153	8 (5.2)	76	0 (0)	8.50 [0.50; 145.34]; 0.044[l,m]

[a] HR and CI: Cox regression model, p value: log-rank test, each stratified by IPSS-R risk group at baseline (very low or low vs intermediate) and average transfusion burden at baseline (≥ 6 red blood cell concentrate units/ 8 weeks vs < 6 red blood cell concentrate units/ 8 weeks).
[b] Evaluation refers to the period from 1st dose of study medication (day 1, cycle 1) until the final data cut-off (26.11.2020).
[c] RR, CI and p value using the CMH method, stratified by IPSS-R risk group at baseline (very low or low vs intermediate) and average transfusion burden at baseline (≥ 6 red blood cell concentrate units/ 8 weeks vs < 6 red blood cell concentrate units/ 8 weeks).
[d] Evaluation refers to the period from 1st dose of study medication (day 1, cycle 1) up to and including week 24.
[e] Percentage of patients with a decrease in the score by ≥ 10 points compared to the start of study at week 25 with a scale range of 0 to 100. Lower (decreasing) values mean an improvement of symptomatology.
[f] Percentage of patients with an increase in the score by ≥ 10 points compared to the start of study at week 25 with a scale range of 0 to 100. Higher (increasing) values mean a deterioration of symptomatology.
[g] Percentage of patients with an increase in the score by ≥ 10 points compared to the start of study at week 25 with a scale range of 0 to 100. Higher (increasing) values mean an improvement of health-related quality of life.
[h] Percentage of patients with a decrease in the score by ≥ 10 points compared to the start of study at week 25 with a scale range of 0 to 100. Lower (decreasing) values mean a deterioration of the health-related quality of life.
[i] Contains events of the underlying disease.
[j] 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).
[K] Mainly comprises the following events (coded according to MedDRA): syncope (PT) and presyncope (PT).
[L] IQWiG calculation of RR, CI (asymptotic) and p value (unconditional exact test, CSZ method according to Martín Andrés A and Silva Mato A); in the case of 0 events in one study arm, the correction factor 0.5 was used in both study arms when calculating the effect and CI.

[m]Discrepancy between p value (exact) and CI (asymptotic) due to different calculation methods.

Abbreviations used:
CMH = Cochran-Mantel-Haenszel; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; HR = hazard ratio; IPSS-R = Revised International Prognostic Scoring System; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; PT = preferred term; QLQ-C30 = Quality of Life Questionnaire – Core 30; RR = relative risk; SOC = system organ class; SAE = serious adverse event; AE = adverse event; vs = versus

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

Adults 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

approx. 790 – 1860 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: 29 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 specialists in internal medicine, haematology and oncology experienced in the treatment of patients with myelodysplastic syndromes with transfusion-dependent anaemia.

In accordance with the requirements of the EMA regarding additional risk minimisation measures, the pharmaceutical company must provide all healthcare professionals who may use luspatercept with an information package. The information package contains information on where to get the current product information as well as a checklist for healthcare professionals to use before starting any treatment, at each administration and then at regular intervals during follow-up visits. The information package also contains a patient card, which healthcare professionals must hand over to women in reproductive 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 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 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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Luspatercept	€ 62,446.51 - € 124,893.02
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:

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:

Adults 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

– No active ingredient 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.

I. **The resolution will enter into force on the day of its publication on the website of the G-BA on 2 November 2023.**

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

Berlin, 2 November 2023

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken