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 (new therapeutic indication: myelodysplastic syndromes with transfusion-dependent anaemia, non-pretreated, and without ring sideroblasts, pretreated)

of 17 October 2024

At its session on 17 October 2024, 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. **In Annex XII, the following information is added after No. 5 to the information on the benefit assessment of Luspatercept in accordance with the resolution of 2 November 2023 on the therapeutic indication "...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":**

Luspatercept

Resolution of: 17 October 2024
Entry into force on: 17 October 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 27 March 2024):

Reblozyl is indicated in adults for the treatment of transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS).

Therapeutic indication of the resolution (resolution of 17 October 2024):

Reblozyl is indicated in adults for the treatment of transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS)[1], who have not received previous erythropoietin (EPO)-based therapy and are eligible for it.

Reblozyl is indicated in adult patients for the treatment of transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) without ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin -based therapy.

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

a) Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), who have not yet received any erythropoiesis-stimulating agents (ESA)-based therapy and are eligible for it; and adults with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS without ring sideroblasts, who had an unsatisfactory response to or are ineligible for ESA-based therapy.

Appropriate comparator therapy:

Patient-individual therapy with selection of:

- Erythropoiesis-stimulating agents (erythropoietin alfa/ erythropoietin zeta; only in patients with an erythropoietin serum level of < 200 U/L)
- A transfusion therapy on demand with red blood cell (RBC) concentrates in combination with chelation therapy
- Lenalidomide (only for patients with an isolated 5q deletion if other treatment options are insufficient or inappropriate)

1 Referred to as "myelodysplastic neoplasms" according to the WHO classification 2022, abbreviated also as MDS. In ICD-10 coding, the term "myelodysplastic syndromes" is also used, which is to be regarded as a synonym for "myelodysplastic neoplasms".

taking into account the erythropoietin serum level, cytogenetics and previous therapy

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

a1) Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), who have not yet received any erythropoiesis-stimulating agents (ESA)-based therapy and are eligible for it

Hint for a minor additional benefit

a2) Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS without ring sideroblasts, who had an unsatisfactory response to or are ineligible for ESA-based therapy

An additional benefit is not proven.

Study results according to endpoints:[2]

a1) Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), who have not yet received any erythropoiesis-stimulating agents (ESA)-based therapy and are eligible for it

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant differences for the benefit assessment.
Morbidity	↑	Advantage in transfusion independence
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↔	Overall, no relevant differences for the benefit assessment. In detail, disadvantage in the AEs of the system organ class of eye 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		

[2] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A24-50) unless otherwise indicated.

Open-label, randomised phase III COMMANDS study, ongoing

- Luspatercept vs epoetin alfa
- Patients who have not received previous ESA-based therapy and are eligible for it; relevant sub-population: serum erythropoietin (sEPO) level < 200 U/L (approx. 79.6% of the study population)
- Primary data cut-off from 31 March 2023, after treatment phase (24 weeks) for symptomatology, health-related quality of life and side effects
- Fourth data cut-off from 22 September 2023 for transfusion independence, overall survival

Mortality

Endpoint	**Luspatercept**		**Epoetin alfa**		Luspatercept vs epoetin alfa
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	Hazard ratio [95% CI] p value [a]
Overall survival[b]					
	145	n.r. [37.2; n.c.] 34 (23.4)	144 [c]	46.7 [42.4; n.c.] 33 (22.9)[c]	0.97 [0.60; 1.59] 0.907

Morbidity

Endpoint	**Luspatercept**		**Epoetin alfa**		Luspatercept vs epoetin alfa
	N	Patients with event n (%)	N	Patients with event n (%)[c]	Relative risk [95% CI] p value [d] Absolute difference (AD)[e]
Transfusion independence for 24 weeks (week 1–24) [b, f]					
	145	79 (54.5)	144	55 (38.2)	1.41 [1.10; 1.80] 0.007 +16.3%

Endpoint	Luspatercept			Epoetin alfa			Luspatercept vs epoetin alfa
	N	Values at the start of the study MV (SD)	Change over the course of study weeks 1–24 MV [g] (SE)	N	Values at the start of the study MV (SD)	Change over the course of study weeks 1–24 MV [g] (SE)	MD [95% CI] p value [g]
Symptomatology (EORTC QLQ-C30 [h]; week 1–24 [i])							
Fatigue	128	41.1 (23.9)	-4.0 (1.7)	115	46.7 (25.4)	-7.5 (1.8)	3.55 [-0.89; 7.98] 0.116
Nausea and vomiting	128	3.9 (9.2)	1.3 (0.9)	115	4.7 (12.3)	-0.6 (0.9)	1.94 [-0.30; 4.18] 0.089
Pain	128	21.4 (24.4)	-2.0 (1.6)	115	20.9 (23.9)	-3.7 (1.7)	1.62 [-2.57; 5.80] 0.447
Dyspnoea	128	27.1 (28.3)	-3.4 (2.0)	115	31.9 (27.8)	-6.1 (2.1)	2.77 [-2.29; 7.83] 0.282
Insomnia	128	30.7 (28.9)	-2.9 (2.1)	115	29.2 (29.5)	-4.0 (2.2)	1.16 [-4.22; 6.54] 0.672
Appetite loss	128	17.7 (26.1)	-2.6 (1.7)	115	18.4 (24.3)	-0.4 (1.8)	-2.24 [-6.56; 2.09] 0.310
Constipation	128	13.5 (23.5)	-4.1 (1.5)	115	16.1 (25.2)	-2.9 (1.6)	-1.22 [-5.20; 2.76] 0.547
Diarrhoea	128	5.5 (15.0)	2.5 (1.2)	115	5.0 (13.5)	0.6 (1.3)	1.83 [-1.39; 5.06] 0.263

Health-related quality of life

Endpoint	Luspatercept			Epoetin alfa			Luspatercept vs epoetin alfa
	N	Values at the start of the study MV (SD)	Change over the course of study weeks 1–24 MV [g] (SE)	N	Values at the start of the study MV (SD)	Change over the course of study weeks 1–24 MV [g] (SE)	MD [95% CI] p value [g]
EORTC QLQ-C30 [j] (week 1–24 [i])							
Global health status	128	60.4 (18.0)	2.0 (1.4)	115	59.3 (20.4)	2.1 (1.5)	-0.12 [-3.71; 3.46] 0.946
Physical functioning	128	68.6 (20.5)	1.7 (1.4)	115	63.1 (21.7)	3.3 (1.5)	-1.61 [-5.19; 1.97] 0.376
Role functioning	128	72.4 (25.3)	2.3 (1.8)	115	72.2 (25.4)	0.4 (1.9)	1.94 [-2.78; 6.65] 0.420
Emotional functioning	128	77.3 (19.2)	3.5 (1.4)	115	73.0 (20.8)	4.5 (1.4)	-1.08 [-4.62; 2.47] 0.550
Cognitive functioning	128	79.6 (22.4)	2.8 (1.3)	115	79.1 (22.3)	1.2 (1.4)	1.56 [-1.84; 4.97] 0.366
Social functioning	128	82.7 (20.2)	-1.2 (1.6)	115	79.5 (22.2)	0.4 (1.7)	-1.61 [-5.86; 2.65] 0.458
FACT-An [k]							
Total score	134	128.8 (25.3)	3.8 (1.1)	131	122.4 (27.3)	3.8 (1.1)	-0.01 [-2.93; 2.91] 0.995
Physical well-being	134	22.1 (4.3)	0.3 (0.2)	131	21.4 (4.9)	0.5 (0.2)	-0.22 [-0.78; 0.33]
Social/ family well-being	134	19.7 (5.2)	0.3 (0.3)	131	18.9 (5.5)	-0.4 (0.3)	0.68 [-0.00; 1.36]
Emotional well-being	134	17.4 (4.3)	1.1 (0.2)	131	17.1 (4.3)	0.5 (0.2)	0.52 [0.03; 1.00]

Endpoint	Luspatercept			Epoetin alfa			Luspatercept vs epoetin alfa
	N	Values at the start of the study MV (SD)	Change over the course of study weeks 1–24 MV [g] (SE)	N	Values at the start of the study MV (SD)	Change over the course of study weeks 1–24 MV [g] (SE)	MD [95% CI] p value [g]
Functional well-being	134	16.3 (5.5)	0 (0.3)	131	14.9 (5.4)	-0.1 (0.3)	0.08 [-0.56; 0.72]
Anaemia-specific subscale	134	53.3 (13.4)	2.2 (0.6)	131	50.1 (15.2)	3.0 (0.6)	-0.73 [-2.26; 0.79]

Side effects

Endpoint	Luspatercept		Epoetin alfa		Luspatercept vs epoetin alfa
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value [d] Absolute difference (AD)[e]
Adverse events (AEs, presented additionally, week 1–24[f, i])					
	145	131 (90.3)	143	117 (81.8)	-
Serious adverse events (SAEs, week 1–24[f, i])					
	145	29 (20.0)	143	32 (22.4)	0.94 [0.60; 1.46] 0.770
Severe adverse events (CTCAE grade ≥ 3, week 1–24[f, i])					
	145	56 (38.6)	143	50 (35.0)	1.13 [0.84; 1.53] 0.415
Therapy discontinuation due to AEs (week 1–24[f, i])					
	145	4 (2.8)	143	5 (3.5)	0.84 [0.23; 3.03] 0.785
Specific AEs (week 1–24[f, i])					
Thromboembolic events (severe AEs)	145	1 (0.7)	143	1 (0.7)	0.96 [0.06; 15.01] 0.976

Endpoint	Luspatercept		Epoetin alfa		Luspatercept vs epoetin alfa
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value [d] Absolute difference (AD)[e]
Eye disorders (SOC, AEs)	145	23 (15.9)	143	3 (2.1)	7.70 [2.31; 25.69] < 0.001 + 13,8%

a) HR and CI: Cox proportional hazards model; p value: log-rank test; each stratified by average transfusion burden (< 4 red blood cell concentrate units/ 8 weeks vs ≥ 4 red blood cell concentrate units/ 8 weeks) and ring sideroblast status (with vs without ring sideroblasts)
b) Data cut-off from 22 September 2023
c) Information from the dossier of the pharmaceutical company. Number possibly reduced by one subject with missing ring sideroblast status
d) RR, CI and p value: Cochran-Mantel-Haenszel method; stratified by average transfusion burden (< 4 red blood cell concentrate units/ 8 weeks vs ≥ 4 red blood cell concentrate units/ 8 weeks) and ring sideroblast status (with vs without ring sideroblasts)
e) Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
f) from the day after the first dose of study medication up to and including day 169 (transfusion independence) or from the day of the first dose of study medication up to and including day 168 (side effects)
g) MV and SE (per treatment group) as well as MD, CI and p value (group comparison): MMRM; adjusted for average transfusion burden (< 4 red blood cell concentrate units/ 8 weeks vs ≥ 4 red blood cell concentrate units/ 8 weeks) and ring sideroblast status (with vs without ring sideroblasts); based on all collections from the dose visits up to and including week 25 day 1. Effect represents the difference in mean changes (compared to baseline) between the treatment groups over the course of study weeks 1–24.
h) Lower (decreasing) values mean better symptomatology; negative effects (intervention minus control) mean an advantage for the intervention (scale range: 0 to 100)
i) Data cut-off from 31 March 2023
j) Higher (increasing) values mean better health-related quality of life; positive effects (intervention minus comparison) mean an advantage for the intervention (scale range: 0 to 100)
k) Higher (increasing) values mean better health-related quality of life; positive effects (intervention minus comparison) mean an advantage for the intervention (scale range: 0 to 188)

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; FACT-An = Functional Assessment of Cancer Therapy – Anaemia; HR = hazard ratio; CI = confidence interval; MD = mean difference; MMRM = mixed model for repeated measures; MV = mean value; N = number of evaluated patients; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; RR = relative risk; SD = standard deviation; SE = standard error; SOC = system organ class; SAE = serious adverse event; AE = adverse event; vs = versus

a2) Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS without ring sideroblasts, who had an unsatisfactory response to or are ineligible for ESA-based therapy

No data are available to allow an assessment of the additional benefit.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.

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

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

a1) Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), who have not yet received any erythropoiesis-stimulating agents (ESA)-based therapy and are eligible for it

Approx. 3,980 – 5,680 patients

a2) Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS without ring sideroblasts, who had an unsatisfactory response to or are ineligible for ESA-based therapy

Approx. 980 – 1,400 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: 12 June 2024):

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.

Patients with an isolated deletion on chromosome 5q (MDS del(5q)) were excluded from the COMMANDS study. Accordingly, luspatercept was not investigated in this patient group.

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, including no increase in initial haemoglobin value, 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:

a) Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), who have not yet received any erythropoiesis-stimulating agents (ESA)-based therapy and are eligible for it; and adults with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS without ring sideroblasts, who had an unsatisfactory response to or are ineligible for ESA-based therapy.

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Luspatercept	€ 47,038.99 - € 94,077.97

Designation of the therapy	Annual treatment costs/ patient
Appropriate comparator therapy:	
Erythropoietin alfa	€ 15,671.33 - € 31,342.67
Transfusion therapy on demand with red blood cell concentrates in combination with chelation therapy	Different from patient to patient
Lenalidomide	€ 463.41

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 September 2024)

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 in combination with chelation 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:

a) Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), who have not yet received any erythropoiesis-stimulating agents (ESA)-based therapy and are eligible for it; and adults with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS without ring sideroblasts, who had an unsatisfactory response to or are ineligible for ESA-based therapy.

– No medicinal product with new active ingredients that can be used in a combination therapy and 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.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 17 October 2024.

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

Berlin, 17 October 2024

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

Prof. Hecken