# 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 (Myelodysplastic Syndrome (MDS))

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. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of luspatercept in accordance with the resolution of 21 January 2021:**

**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 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.



## 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 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

**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]

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

**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 | ↔ | No difference relevant for the benefit assessment; advantage in the deterioration of the endpoint insomnia, disadvantage in the deterioration of the endpoint fatigue. |
| Health-related quality of life | ↓ | Disadvantage in the deterioration of physical functioning. |
| Side effects | ↔ | No difference relevant for the benefit assessment. |
| Explanations:<br>↑: statistically significant and relevant positive effect with low/unclear reliability of data<br>↓: statistically significant and relevant negative effect with low/unclear reliability of data<br>↑↑: statistically significant and relevant positive effect with high reliability of data<br>↓↓: statistically significant and relevant negative effect with high reliability of data<br>↔: no statistically significant or relevant difference<br>∅: There are no usable data for the benefit assessment.<br>n.a.: not assessable | | |



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

MEDALIST study: Luspatercept + best supportive care (BSC) vs placebo + BSC
Study design: double-blind, randomised (2:1), Phase III
Data cut-off: 8 May 2018 (primary treatment phase Study weeks 1 to 24)

**Mortality**

| **Endpoint** | **Luspatercept + BSC** | | **Placebo + BSC** | | Intervention vs control |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>*Patients with event n (%)* | N | Median time to event in months [95% CI]<br>*Patients with event n (%)* | Hazard ratio[a] [95% CI] p value |
| **Overall survival**[b] | | | | | |
| | 153 | n.a.<br>*12 (7.8)* | 76 | n.a.<br>*9 (11.8)* | 0.76<br>[0.32; 1.83]<br>0.54 |

**Morbidity**

| **Endpoint** | **Luspatercept + BSC** | | **Placebo + BSC** | | Intervention vs control |
|---|---|---|---|---|---|
| | N | Patients with event n (%) | N | Patients with event n (%) | Relative risk[b] [95% CI] p value Absolute difference (AD)[c] |
| **Transfusion-free period ≥ 8 weeks**[d, e] | | | | | |
| | 153 | 58 (37.9) | 76 | 10 (13.2) | 2.85<br>[1.59; 5.12]<br>< 0.001<br>AD: 24.7% |
| **Transfusion-free period ≥ 24 weeks**[d] | | | | | |
| | 153 | 20 (13.1) | 76 | 1 (1.3) | 9.84<br>[1.36; 71.31]<br>0.003<br>AD: 11.8% |

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| | | | | | |
|---|---|---|---|---|---|
| **Symptomatology (EORTC QLQ-C30 symptom scales)**[f] | | | | | |
| Improvement by ≥ 10 points | | | | | |
| Fatigue | 110[g] | 32 (29.1) | 54[g] | 24 (44.4) | 0.79<br>[0.60; 1.03]<br>0.06 |
| Nausea and vomiting | 111[g] | 17 (15.3) | 54[g] | 5 (9.3) | 1.19<br>[0.92; 1.55]<br>0.26 |
| Pain | 110[g] | 25 (22.7) | 54[g] | 14 (25.9) | 0.93<br>[0.72; 1.21]<br>0.58 |
| Dyspnoea | 107[g] | 24 (22.4) | 54[g] | 16 (29.6) | 0.87<br>[0.65; 1.16]<br>0.33 |
| Loss of appetite | 110[g] | 22 (20.0) | 53[g] | 9 (17.0) | 1.07<br>[0.83; 1.38]<br>0.62 |
| Insomnia | 109[g] | 28 (25.7) | 54[g] | 18 (33.3) | 0.89<br>[0.68; 1.15]<br>0.35 |
| Constipation | 111[g] | 31 (27.9) | 53[g] | 13 (24.5) | 1.06<br>[0.84; 1.34]<br>0.62 |
| Diarrhoea | 111[g] | 11 (9.9) | 53[g] | 6 (11.3) | 0.93<br>[0.65; 1.35]<br>0.71 |
| Financial difficulties | 109[g] | 13 (11.9) | 53[g] | 9 (17.0) | 0.86<br>[0.59; 1.24]<br>0.37 |
| Deterioration by ≥ 10 points[f] | | | | | |
| Fatigue | 110[g] | 51 (46.4) | 54[g] | 14 (25.9) | 1.32<br>[1.06; 1.62]<br>0.01<br>AD: 20.5% |
| Nausea and vomiting | 111[g] | 17 (15.3) | 54[g] | 7 (13.0) | 1.06<br>[0.79; 1.41]<br>0.70 |
| Pain | 110[g] | 28 (25.5) | 54[g] | 14 (25.9) | 1.01<br>[0.79; 1.28]<br>0.96 |

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| | | | | | |
|---|---|---|---|---|---|
| Dyspnoea | 107[g] | 30 (28.0) | 54[g] | 10 (18.5) | 1.19<br>[0.94; 1.50]<br>0.17 |
| Loss of appetite | 110[g] | 22 (20.0) | 53[g] | 10 (18.9) | 1.02<br>[0.78; 1.34]<br>0.88 |
| Insomnia | 109[g] | 19 (17.4) | 54[g] | 18 (33.3) | 0.72<br>[0.51; 1.01]<br>0.03<br>AD: 15.9% |
| Constipation | 111[g] | 15 (13.5) | 53[g] | 5 (9.4) | 1.12<br>[0.84; 1.48]<br>0.48 |
| Diarrhoea | 111[g] | 16 (14.4) | 53[g] | 5 (9.4) | 1.15<br>[0.88; 1.49]<br>0.37 |
| Financial difficulties | 109[g] | 10 (9.2) | 53[g] | 6 (11.3) | 0.93<br>[0.63; 1.38]<br>0.71 |
| **Hospitalisation**[d] | | | | | |
| By any cause | 153 | 34 (22.2) | 76 | 17 (22.4) | 0.99<br>[0.60; 1.64]<br>0.98 |



**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[b] [95% CI] p value Absolute difference (AD) |
| **EORTC QLQ-C30 functional scales**[f] | | | | | |
| Improvement by ≥ 10 points | | | | | |
| Physical functioning | 111[g] | 25 (22.5) | 54[g] | 18 (33.3) | 0.83<br>[0.62; 1.11]<br>0.16 |
| Role functioning | 111[g] | 30 (27.0) | 54[g] | 18 (33.3) | 0.90<br>[0.71; 1.16]<br>0.41 |

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| | | | | | |
|---|---|---|---|---|---|
| Emotional functioning | 111[g] | 18 (16.2) | 53[g] | 11 (20.8) | 0.91<br>[0.67; 1.24]<br>0.53 |
| Cognitive functioning | 111[g] | 29 (26.1) | 53[g] | 14 (26.4) | 1.00<br>[0.78; 1.28]<br>0.99 |
| Social functioning | 111[g] | 26 (23.4) | 53[g] | 16 (30.2) | 0.88<br>[0.67; 1.15]<br>0.31 |
| Overall assessment | 111[g] | 31 (27.9) | 53[g] | 12 (22.6) | 1.09<br>[0.87; 1.36]<br>0.49 |
| Deterioration by ≥ 10 points[f] | | | | | |
| Physical functioning | 111[g] | 34 (30.6) | 54[g] | 7 (13.0) | 1.33<br>[1.09; 1.62]<br>0.02<br>AD: 17.6% |
| Role functioning | 111[g] | 35 (31.5) | 54[g] | 20 (37.0) | 0.92<br>[0.73; 1.16]<br>0.48 |
| Emotional functioning | 111[g] | 29 (26.1) | 53[g] | 13 (24.5) | 1.04<br>[0.82; 1.32]<br>0.75 |
| Cognitive functioning | 111[g] | 29 (26.1) | 53[g] | 17 (32.1) | 0.91<br>[0.70; 1.17]<br>0.45 |
| Social functioning | 111[g] | 37 (33.3) | 53[g] | 16 (30.2) | 1.06<br>[0.84; 1.33]<br>0.63 |
| Overall assessment | 111[g] | 33 (29.7) | 53[g] | 10 (18.9) | 1.20<br>[0.97; 1.49]<br>0.13 |

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**Side effects**[h]

| Endpoint | Luspatercept + BSC | | Placebo + BSC | | Intervention vs control |
|---|---|---|---|---|---|
| | N | Patients with event n (%) | N | Patients with event n (%) | Relative risk[b] [95% CI] p value |
| **Total adverse events** (presented additionally) | | | | | |
| | 153 | 145 (94.8) | 76 | 70 (92.1) | - |
| **Serious adverse events (SAE)** | | | | | |
| | 153 | 40 (26.1) | 76 | 16 (21.1) | 1.25 [0.75; 2.08] 0.40 |
| **Severe adverse events (CTCAE grade ≥ 3)** | | | | | |
| | 153 | 54 (35.3) | 76 | 27 (35.5) | 0.99 [0.68; 1.42] 0.97 |
| **Therapy discontinuations because of adverse events** | | | | | |
| | 153 | 12 (7.8) | 76 | 4 (5.3) | 1.54 [0.50; 4.79] 0.47 |
| **AE of special interest** | | | | | |
| Pre-malignant disease (SOC, AE) | 153 | 2 (1.3) | 76 | 3 (3.9) | - |
| Malignancies (SOC, AE) | 153 | 5 (3.3) | 76 | 1 (1.3) | - |
| Transforma-tion to AML (PT, AE) | 153 | 2 (1.3) | 76 | 1 (1.3) | - |
| Progression to high-risk MDS (PT, AE) | 153 | 1 (0.7) | 76 | 1 (1.3) | - |



(Continuation)

| Endpoint<br><br>SOC<br>PT | Luspatercept + BSC | | Placebo + BSC | | Intervention vs control |
|---|---|---|---|---|---|
| | N | Patients with event n (%) | N | Patients with event n (%) | Relative risk[b] [95% CI] p value |
| **SAE according to SOC/PT with incidence ≥ 5% in one treatment arm** | | | | | |
| Infections and infestations | 153 | 14 (9.2) | 76 | 8 (10.5) | 0.89 [0.40; 1.99] 0.74 |
| Injury, poisoning, and procedural complications | 153 | 8 (5.2) | 76 | 3 (3.9) | 1.29 [0.34; 4.91] 0.67 |
| **Severe AE (CTCAE grade ≥ 3) according to SOC/PT with incidence ≥ 5% in one treatment arm** | | | | | |
| Blood and lymphatic system disorders | 153 | 13 (8.5) | 76 | 8 (10.5) | 0.76 [0.33; 1.75] 0.62 |
| Anaemia | 153 | 9 (5.9) | 76 | 4 (5.3) | 1.07 [0.33; 3.39] 0.85 |
| Neutropoenia | 153 | 5 (3.3) | 76 | 5 (6.6) | 0.46 [0.14; 1.52] 0.25 |
| Infections and infestations | 153 | 14 (9.2) | 76 | 7 (9.2) | 1.03 [0.44; 2.42] 0.99 |
| General disorders and administration site conditions | 153 | 12 (7.8) | 76 | 3 (3.9) | 1.97 [0.57; 6.77] 0.26 |
| Metabolism and nutrition disorders | 153 | 12 (7.8) | 76 | 3 (3.9) | 1.97 [0.58; 6.70] 0.26 |
| Injury, poisoning, and procedural complications | 153 | 8 (5.2) | 76 | 3 (3.9) | 1.29 [0.34; 4.91] 0.67 |

(Continuation)

| | | | | | |
|---|---|---|---|---|---|
| Nervous system disorders | 153 | 8 (5.2) | 76 | 0 | - |

[a] Hazard ratio calculated using Cox proportional hazard model with transfusion burden (≥ 6 EC units/8 weeks vs < 6 EC units/8 weeks) and IPSS-R risk score (very low or low vs intermediate) as co-variables.
[b] Relative risk with 95% CI and p value calculated by Cochran-Mantel-Haenszel test stratified by the number of transfusions at baseline (≥ 6 EC units/8 weeks vs < 6 EC units/8 weeks) and IPSS-R score at baseline (very low or low vs intermediate)
[c] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[d] Intention-to-treat (ITT) population
[e] Data from the written statement of the pharmaceutical company
[f] Health-related Quality of Life-Population: Luspatercept + BSC: n = 149; placebo + BSC: n = 76
[g] The reference value is the number of patients with an indication at Week 24
[h] Safety population: Luspatercept + BSC: n = 153; placebo + BSC: n = 76

Abbreviations used:
AML = acute myeloid leukaemia; BSC = best supportive care; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; CI = confidence interval; N = number of patients assessed; n = number of patients with (at least one) event; n.c. = not calculable; PT = preferred term; SOC = system organ class; vs = versus

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

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

approx. 840–1,870 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 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 |
|---|---|
| Luspatercept | € 90,131.83 – 180,263.65 |

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 | Cost/ 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