Justification

Gemeinsamer Bundesausschuss

to the Resolution 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

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation in accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy need not be submitted (Section 35a paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, Nos. 2 and 3 SGB V in conjunction with Chapter 5, Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT, exceeds € 50 million during the last 12 calendar months. In accordance with Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence in accordance with Chapter 5, Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5, Section 6 VerfO and prove the additional benefit compared with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). On the basis of the statutory requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is deemed to have been proven through the grant of marketing authorisation, the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, in the case of orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit provided is assessed exclusively on the basis of the pivotal studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (*cf* Section 35a, paragraph 1, sentence 12 SGB V). According to Section 35a, paragraph 2 SGB V, the assessment of the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient luspatercept in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 August 2020. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, number 1 VerfO on 28 July 2020.

Luspatercept for the treatment of an anaemia as a result of myelodysplastic syndromes is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed by the G-BA on the basis of the pivotal studies.

The G-BA carried out the benefit assessment and commissioned the IQWiG to assess the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 2 November 2020 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G20-16) prepared by the IQWiG, and the written statements submitted in the written and oral hearing procedure as well as the amendment to the benefit assessment prepared by the G-BA.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for marketing authorisation with regard to their therapeutic relevance (qualitative) according to the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1–4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not set aside in the benefit assessment of luspatercept.

In light of the above and taking into account the written statements received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of luspatercept (Reblozyl) in accordance with the product information

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.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

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.

2.1.2 Extent of the additional benefit and significance of the evidence

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

In summary, the additional benefit of luspatercept is assessed as follows:

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

Justification:

For the benefit assessment of the active ingredient luspatercept, the pharmaceutical company presented results from the ongoing pivotal MEDALIST study (ACE-536-MDS-001). This is a double-blind, randomised, controlled, multi-centre Phase III study.

Patients with anaemia as a result of myelodysplastic syndromes (MDS) with very low, low, or intermediate risk in accordance with IPSS-R (International Prognostic Scoring System – revised), with ring sideroblasts and transfusion dependence were included in the MEDALIST study on which the benefit assessment was based.

229 patients were randomised 2:1 to treatment with luspatercept + best supportive care (BSC) (153 patients) or to the control arm with placebo + BSC (76 patients). Randomisation was stratified by the number of transfusions at baseline (≥ 6 erythrocyte concentrate (EC) units/8 weeks vs < 6 EC units/8 weeks) and the IPSS-R risk score (very low or low vs intermediate)) at baseline.

Information on the implementation of the BSC (e.g. the type of therapy or the number and frequency of EC transfusions) could not be identified in the study documents.

Patients had a median age of 71 years and had received a median of 6 EC transfusions within the last 8 weeks at baseline.

The MEDALIST study is divided into a screening phase, a treatment phase (primary and extension phase), and a follow-up phase. The primary treatment phase lasted up to 24 weeks, and the extension phase of treatment started from week 25 and extended until treatment discontinuation. Long-term follow-up is planned for up to 3 years after the last administration of the study medication. Following the primary treatment phase (Week 25), the clinical benefit of treatment with luspatercept was assessed by the medical personnel. If no clinical benefit was observed or if there was a progression of MDS, the administration of the study medication was stopped, and the patients entered long-term follow-up. If there was a clinical benefit and no progression of MDS was detectable, patients entered the extension phase in which randomised treatment allocation and blinding were maintained.

After reviewing the clinical benefit after Study week 24, a large number of patients discontinued treatment with the study medication. This occurred more frequently in the placebo arm than in the luspatercept arm.

Switching between treatment arms (cross-over) was not allowed during the course of the study.

Analyses were submitted by the pharmaceutical company at three data cut-offs (8 May 2018, 7 January 2019, and 1 July 2019). The benefit assessment is based on the planned data cut-

off of 8 May 2018. At this time, all patients had already reached Study week 48 or had prematurely discontinued study participation, and results for the primary treatment phase (up to study week 24) were available for all endpoints on the basis of a study report. According to the pharmaceutical company, no structured results reports were available for the benefit assessment for the data cut-offs of 7 January 2019 and 1 July 2019, which were subsequently requested by the European Medicines Agency (EMA) as part of the approval process. Also, no information on study course, patient flow, exposure to the study medication, concomitant medication, or follow-up therapies could be identified. Because of the resulting uncertainties, the data cut-offs of 7 January 2019 and 1 July 2019 were not used for the benefit assessment.

A transfusion-free period ≥ 8 weeks (Weeks 1 to 24) was the primary endpoint of the MEDALIST study. In addition, overall survival and endpoints in the categories of morbidity (symptomatology, hospitalisation, further endpoints on transfusion-free periods), health-related quality of life, and adverse events were surveyed. Except for the results for the endpoint overall survival, the pharmaceutical company did not provide adequate effect estimators in the dossier taking into account the stratification factors. Within the framework of the written statement procedure, evaluations on stratified relative risks were submitted by the pharmaceutical company; these are used accordingly for the present assessment.

Mortality

Overall survival

Overall survival is defined as the time from randomisation to death from any cause or censoring of the patient.

There was no statistically significant difference between the treatment arms.

Morbidity

Transfusion-free period

The endpoint transfusion-free period is defined as a period without receiving erythrocyte concentrate (EC) transfusions over a certain duration in the course of the study. Evaluations were submitted by the pharmaceutical company on different transfusion-free periods between study week 1 to 24. A transfusion-free period ≥ 8 weeks is the primary endpoint of the MEDALIST study.

Patients in the present therapeutic indication require frequent and lifelong EC transfusions. Despite iron chelation therapy, the required transfusions can lead to increasing organ iron overload and subsequent long-term complications in patients.

In the MEDALIST study, in the case of low Hb values, symptoms associated with anaemia, or comorbidities, EC transfusions are administered at the discretion of the investigator.

In the present therapeutic indication, a long-term or sustained avoidance of transfusions (transfusion-free period) while maintaining a defined minimum haemoglobin value represents a primary therapy goal with which anaemia and anaemia-related symptoms are controlled with simultaneous freedom from EC transfusions.

With regard to the evaluations on the different transfusion-free periods, a transfusion-free period ≥ 24 weeks is considered the relevant period for the present assessment in order to be able to assume a long-term avoidance of transfusions (freedom from transfusion). Thus, a transfusion-free period ≥ 24 weeks may represent a patient-relevant endpoint in the present therapeutic indication.

Regarding the proportion of patients with a transfusion-free period ≥ 24 weeks, there is a statistically significant difference between the treatment arms for the advantage of treatment with luspatercept + BSC compared with placebo + BSC. A transfusion-free period ≥ 24 weeks was observed in 20 patients (13.1%) in the intervention arm and in one patient (1.3%) in the control arm.

However, this advantage is not reflected in other endpoints that may in principle be associated with a transfusion-free period. In particular, there is a disadvantageous effect on health-related quality of life (physical functioning sub-scale of the EORTC QLQ-C30).

Data on a transfusion-free period over the entire study period are not available.

Overall, based on these results on a transfusion-free period ≥ 24 weeks, a statistically significant difference to the advantage of treatment with luspatercept + BSC can be observed with regard to long-term avoidance of transfusions (transfusion-free period).

In any case, the extent of this difference in the present case, taking into account the results for the other endpoints, is assessed as too minor to justify the derivation of an additional benefit at the endpoint level in the overall assessment.

Other endpoints related to the avoidance of transfusions (e.g. reduction of the transfusion burden) are not presented in the resolution because these are not per se patient-relevant and no information is derived from the data that goes beyond the data on the endpoint freedom from transfusion ≥ 24 weeks.

Symptomatology

Disease symptomology was surveyed using the symptom scales of the cancer-specific questionnaire EORTC QLQ-C30.

Among other things, responder analyses based on a Minimal Important Difference (MID) of 10 points on the proportion of patients with an improvement of the symptomatology for the primary treatment phase (Weeks 1–24) were submitted by the pharmaceutical company.

The evaluations of the deterioration of symptomatology by at least 10 points, which were also planned according to the statistical analysis plan, were not part of the dossier.

With the written statement, the pharmaceutical company submitted additional responder analyses on the deterioration of symptomatology; these were taken into account for the present assessment.

There is no statistically significant difference for the improvement of symptomatology between the study arms.

With respect to the deterioration of symptomatology, there are statistically significant differences between the treatment arms for the endpoints fatigue and insomnia. For the deterioration of fatigue, there is a disadvantage of luspatercept + BSC compared with placebo + BSC. In contrast, for the deterioration of insomnia, an advantage can be found for the treatment of luspatercept + BSC.

Hospitalisation

The endpoint hospitalisation was defined as the proportion of patients hospitalised for any cause (total hospitalisation) from randomisation to the time of data analysis.

There was no statistically significant difference in hospitalisation for any cause between the treatment arms.

Because this is a multi-centre study, it remains unclear whether there are regional differences that could lead to a bias in the number of hospitalisations. The pharmaceutical company does not provide any further information on this. Stratified randomisation at study centre or country level was not included in the MEDALIST study. There are uncertainties with regard to the operationalisation of the endpoint because there is no information on when the admission to hospital was counted as hospitalisation (e.g. with regard to outpatient, partial inpatient admission). Furthermore, it cannot be conclusively assessed to what extent events of the endpoint are also recorded in the context of serious adverse events and would thus be considered twice.

In the overall consideration of the results on patient-relevant endpoints in the morbidity category, treatment with luspatercept + BSC leads to an advantage in the endpoint insomnia and a disadvantage in the endpoint fatigue with regard to the deterioration of symptomatology.

Quality of life

The health-related quality of life was assessed using the functional scales and the global health status scale (global impression) of the cancer-specific EORTC QLQ-C30 questionnaire.

Among other things, responder analyses based on an MID of 10 points on the proportion of patients with improvement of health-related quality of life for the primary treatment phase (Weeks 1–24) were submitted by the pharmaceutical company.

The evaluations of the deterioration of health-related quality of life by at least 10 points, which were also planned according to the statistical analysis plan, were not part of the dossier.

With the written statement, the pharmaceutical company submitted additional responder analyses on the deterioration of health-related quality of life; these were taken into account for the present assessment.

There is no statistically significant difference in the improvement of health-related quality of life between the treatment arms. In contrast, there is a statistically significant difference to the disadvantage of therapy with luspatercept with respect to the deterioration of physical functioning.

In the overall view, a disadvantage of luspatercept + BSC compared with placebo + BSC for health-related quality of life is shown in the deterioration of physical functioning.

Side effects

Total adverse events (AE)

Almost all study participants experienced AE. The results are presented additionally.

Serious AE (SAE), severe AE (CTCAE grade ≥ 3), therapy discontinuations because of AE

For the endpoints SAE, severe AE (CTCAE grade ≥ 3), and therapy discontinuations because of AE, there are no statistically significant differences between the treatment arms.

AE of special interest

Regarding the AE of special interest “pre-malignant disease” (SOC, AE), two events occurred in the intervention arm and three in the control arm. The AE of special interest “malignancies” (SOC, AE) occurred in five patients in the intervention arm and in one in the control arm. Because of the low number of events, no comparative analyses were carried out.

In the overall view of the results for the endpoint category side effects, neither an advantage nor a disadvantage can be derived for luspatercept + BSC compared with placebo + BSC.

Overall assessment

For the assessment of the additional benefit of luspatercept 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, results on the endpoint categories mortality, morbidity, quality of life, and side effects from the MEDALIST study are available.

In the ongoing study luspatercept + best supportive care (BSC) is compared with placebo + BSC.

For the overall survival, there is no statistically significant difference between the treatment arms.

In the endpoint category morbidity, with regard to the deterioration of symptomology, luspatercept + BSC showed an advantage in the endpoint insomnia and a disadvantage in the endpoint fatigue.

For the endpoint category morbidity, there are results on transfusion-free periods. For the patients in the therapeutic indication, a long-term or sustained avoidance of transfusions (transfusion-free period) represents a primary therapy goal with which anaemia and anaemia-related symptoms are controlled with simultaneous freedom from erythrocyte concentrate transfusions. For the present assessment, a transfusion-free period ≥ 24 weeks is considered the relevant period to assume long-term avoidance of transfusions (transfusion-free period).

With respect to the proportion of patients with a transfusion-free period ≥ 24 weeks, there is a statistically significant difference to the advantage of treatment with luspatercept + BSC compared with placebo + BSC. However, this advantage is not reflected in other endpoints that may in principle be associated with a transfusion-free period. In particular, there is a disadvantageous effect on health-related quality of life (physical functioning sub-scale of the EORTC QLQ-C30). Therefore, overall, based on these results on a transfusion-free period ≥ 24 weeks, a statistically significant difference to the advantage of treatment with luspatercept + BSC can be observed with regard to long-term avoidance of transfusions (transfusion-free period). Data on a transfusion-free period over the entire study period are not available. In any case, the extent of this difference in the present case, taking into account the results for the other endpoints, is assessed as too minor to justify the derivation of an additional benefit at the endpoint level in the overall assessment.

In terms of side effects, neither an advantage nor a disadvantage can be found for luspatercept + BSC compared with placebo + BSC.

In the overall assessment of the results on patient-relevant endpoints, the G-BA classifies the extent of the additional benefit of luspatercept in 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 on the basis of the criteria in Section 5, paragraph 8, sentences 1 and 2 in conjunction with Section 5, paragraph 7, sentence 1, number 4 AM-NutzenV as non-quantifiable because the scientific data basis does not allow quantification.

Significance of the evidence

This assessment is based on results from the blinded, randomised, placebo-controlled MEDALIST Phase III study. The results from the MEDALIST study do not allow a quantification of the extent of the additional benefit in the overall assessment. The significance of the results for the observed additional benefit is low overall; the significance of the evidence is therefore classified in the “hint” category.

2.1.3 Summary of the assessment

The present assessment refers to the benefit assessment of the new medicinal product Reblozyl with the active ingredient luspatercept. Luspatercept was approved as an orphan drug. Luspatercept is approved 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.

For the benefit assessment, results of the double-blind, randomised, controlled MEDALIST Phase III study in which luspatercept + best supportive care (BSC) was compared with placebo + BSC are available.

In overall survival, there was no difference between the treatment arms.

In the endpoint category morbidity, there is an advantage for luspatercept in the endpoint insomnia and a disadvantage in the endpoint fatigue.

For the results on a transfusion-free period ≥ 24 weeks taken as a basis for the assessment, a difference to the advantage of a treatment with luspatercept + BSC can be determined with regard to a long-term avoidance of transfusions (freedom from transfusion). However, this advantage is not reflected in other endpoints that may in principle be associated with a transfusion-free period. In particular, there is a disadvantageous effect on health-related quality of life in physical functioning. Data on a transfusion-free period over the entire study period are not available. In any case, the extent of this difference in the present case, taking into account the results for the other endpoints, is assessed as too minor to justify the derivation of an additional benefit at the endpoint level in the overall assessment.

There was no difference in side effects between the treatment arms.

In the overall assessment of the results on patient-relevant endpoints, the G-BA classifies the extent of the additional benefit of luspatercept in 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 on the basis of the criteria in Section 5, paragraph 8, sentences 1 and 2 in conjunction with Section 5, paragraph 7, sentence 1, number 4 AM-NutzenV as non-quantifiable because the scientific data basis does not allow quantification. The significance of the evidence is classified in the “hint” category.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The resolution will be based on the information from the dossier of the pharmaceutical company. However, the stated range is subject to uncertainties; these are due, in particular, to the unclear calculation of the starting point.

Accordingly, patients who developed MDS before 2013 and are still alive in 2018 are not taken into account for the estimation of the lower limit.

In addition, the pharmaceutical company transfers the risk distribution in accordance with IPSS-R; this is also applied to prevalent patients in a later step, to newly ill patients for the estimation of the starting point. Because of the more favourable prognosis in terms of survival associated with low risk in accordance with IPSS-R, there could be a different proportion of patients at low risk in accordance with IPSS-R when referring to incidence than when referring to prevalence.

On one hand, further uncertainties arise because the development of new cases of MDS was based on the average annual rate of increase in the incidence of myeloid leukaemia. On the

other hand, with regard to the calculation of the upper limit, among other things, the extrapolation of the care structure data analysis is not completely comprehensible.

2.3 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.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 December 2020).

Treatment duration:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is different for each individual patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Luspatercept	1 × every 21 days	17.4	1	17.4

Usage and consumption:

The active ingredient luspatercept is dosed depending on body weight. For the calculation of the dosages as a function of body weight, the average body measurements from the official representative statistics "Microcensus 2017– Questions about Health – body measurements of the population" were used as a basis (average body weight): 77.0 kg)[2].

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consump-tion by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Luspatercept	1 × 0.8 mg/kg = 61.6 mg – 1 × 1.75 mg/kg = 134.8 mg	61.6 g – 134.8 g	1 × 75 mg – 2 × 75 mg	17.4	17.4 × 75 mg – 34.8 × 75 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated based on the pharmacy sales price level as well as less the statutory rebates according to Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined based on consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Luspatercept 75 mg	1 PIJ	€ 5,492.14	€ 1.77	€ 310.38	€ 5,179.99
Abbreviations: PIJ = powder for the preparation of an injection solution					

Pharmaceutical selling price (LAUER-TAXE®) as last revised: 1 January 2021

[2] German Federal Office For Statistics (2018). Microcensus 2017: Fragen zur Gesundheit; Körpermaße der Bevölkerung [Questions about health; body measurements of the population] [online, access: 24 November 2020] https://www.destatis.de/DE/Methoden/Qualitaet/Qualitaetsberichte/Bevoelkerung/mikrozensus-2017.pdf;jsessionid=B922CBC0E7D233E5ACE6BA7FAD0CC37A.internet8731?__blob=publicationFile

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be assessed in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

No additionally required SHI services are taken into account for the cost representation.

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (*Hilfstaxe*; contract on price formation for substances and preparations of substances; Sections 4 and 5 Pharmaceutical Price Ordinance) of 1 October 2009 is not fully used to calculate the costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the *Hilfstaxe* in its currently valid version, surcharges for the production of parenteral preparations containing cytostatic agents of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit are to be payable. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating the *Hilfstaxe*. The cost representation is based on the pharmacy sales price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy sales price of the active ingredient, the invoicing of discards, the calculation of application containers and carrier solutions according to the regulations in Annex 3 of the *Hilfstaxe*.

In accordance with Annex 3, Part 7b, a surcharge of € 81 is billable for the preparation of solutions containing luspatercept in deviation from Annex 3, Part 7, Item 6 per ready-to-use unit.

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 28 July 2020, the pharmaceutical company submitted a dossier for the benefit assessment of luspatercept to the G-BA in due time in accordance with Chapter 5, Section 8, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 2 November 2020 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 23 November 2020.

The oral hearing was held on 7 December 2020.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI

umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 12 January 2021, and the proposed resolution was approved.

At its session on 21 January 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	10 November 2020	Information of the benefit assessment of the G-BA
Working group Section 35a	1 December 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	7 December 2020	Conduct of the oral hearing
Working group Section 35a	15 December 2020 5 January 2021	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee on Medicinal Products	12 January 2021	Concluding discussion of the draft resolution
Plenum	21 January 2021	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 21 January 2021

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

Prof. Hecken