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 (β-thalassaemia)

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 a β-thalassaemia 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 G20-15) 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 associated with beta-thalassaemia.

2.1.2 Extent of the additional benefit and significance of the evidence

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

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 BELIEVE Phase III study (ACE-536-B-THAL-001). This is a double-blind, randomised, controlled, multi-centre study that was conducted in 15 countries and 65 study centres.

The BELIEVE study (on which the benefit assessment was based) included adult patients with β-thalassaemia or haemoglobin E/β-thalassaemia who receive regular transfusions (defined as 6–20 erythrocyte concentrate [EC] units and no transfusion-free period ≥ 35 days within the 24 weeks prior to randomisation).

A total of 336 patients were randomised 2:1 to treatment with luspatercept + best supportive care (BSC) (N = 224 patients) or to the control arm with placebo + BSC (N = 112 patients). The BSC includes EC transfusions and iron chelation therapies as well as antibiotic therapies, antiviral and antifungal therapies, and/or nutritional support as needed. Randomisation was stratified by region (North America and Europe/Middle East and North Africa/Asia-Pacific).

The patients had a median age of approx. 32 years at the time of study inclusion and received a median of approx. 15 EC units within the last 24 weeks.

The BELIEVE study includes a 12-week screening phase, a 48-week treatment phase that has already been completed, and a long-term treatment phase in which patients continued to receive treatment at the discretion of the investigator in accordance with the initial allocation. The long-term treatment phase ended after all patients had completed the 48-week treatment phase. This was followed by the unblinding of the study. In the still ongoing open extension phase, patients from both study arms continued to be treated with luspatercept + BSC. At the time of unblinding, 84.4% of patients in the originally allocated control arm were switched to treatment with luspatercept + BSC.

A total of three data cut-offs are available for the study (11 May 2018, 7 January 2019, and 1 July 2019). The first data cut-off of 11 May 2018 is the *a priori* planned primary analysis. At the time of this data cut-off, 81.2% of patients in the intervention arm and 78.0% of patients in the control arm were receiving therapy. However, no information is available on the proportion of patients who discontinued treatment at the discretion of the investigator at the end of the 48-week treatment phase. The later data cut-offs were requested by the European Medicines Agency (EMA) as part of the approval process. Based on the second data cut-off of 7 January 2019, the pharmaceutical company submitted evaluations at the time of unblinding at the level of the participating centres; this took place on 1 August 2018, as part of the written statement procedure. This evaluation is used for the present assessment because of the longer observation time. Later evaluation times are based on non-comparative data and are not used for the present assessment.

The primary endpoint of the BELIEVE study is the reduction of the transfusion burden by ≥ 33% EC-units with at least two EC-units in Weeks 13–24 compared with the screening phase. Furthermore, endpoints of the categories morbidity (transfusion-free period-free period,

hospitalisation, further endpoints on transfusion burden), health-related quality of life, and adverse events, among others, will be surveyed in the study. In the dossier, the pharmaceutical company submitted evaluations of unstratified relative risks (i.e. without taking the stratification variable region into account). These evaluations are not considered adequate because of the stratification performed in the randomised study. 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

In the BELIEVE study, deaths are recorded as safety events. At the time of the relevant data cut-off, one death occurred in each of the two treatment arms.

Thus, there is no relevant difference for overall survival for the benefit assessment.

Morbidity

Transfusion burden

In the BELIEVE study, the transfusion burden is defined as the number of EC-units transfused per defined time interval. In the BELIEVE study, in the case of low Hb values, symptoms associated with anaemia, or comorbidities, EC transfusions are administered at the discretion of the investigator. A pre-transfusion threshold was set individually for each person based on the burden of transfusion 24 weeks prior to randomisation. A reduction in transfusion burden ≥ 33% and with a reduction of at least two EC units within the period of Week 13–24 is the primary endpoint in the BELIEVE study.

Transfusion-dependent β-thalassaemia is the result of anaemia caused by significantly reduced production of functional β-globin. This anaemia requires frequent and lifelong transfusions with erythrocyte concentrates. Despite iron chelation therapy, the required transfusions can lead to increasing organ iron overload and subsequent long-term complications in patients.

The reduction in transfusion frequency alone is not considered relevant to patients *per se* because it does not allow any statements to be made about the long-term avoidance of transfusions in the sense of transfusion-free periods. The advantages of having fewer transfusions should also be reflected in the endpoint categories of morbidity and quality of life. The pharmaceutical company also did not submit a validation of the transfusion burden as a surrogate parameter for a patient-relevant endpoint. The endpoint transfusion burden is assessed neither as a directly patient-relevant endpoint nor as a validated surrogate endpoint and is therefore not used for the present assessment.

Transfusion-free period

The endpoint transfusion-free period is defined as a period without receiving EC transfusions over a certain duration within the course of the study. Evaluations were submitted by the pharmaceutical company on different transfusion-free periods between study week 1 to 48.

Transfusion-dependent β-thalassaemia is the result of anaemia caused by significantly reduced production of functional β-globin. This anaemia requires frequent and lifelong transfusions with erythrocyte concentrates. Despite iron chelation therapy, the required transfusions can lead to increasing organ iron overload and subsequent long-term complications in patients.

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 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 (transfusion-free period). Thus, a

transfusion-free period ≥ 24 weeks may represent a patient-relevant endpoint in the present therapeutic indication.

A transfusion-free period ≥ 24 weeks was observed in five patients in the intervention arm and in none in the control arm. Data on transfusion-free periods over the entire study period are not available.

Based on the results for a transfusion-free period ≥ 24 weeks, no statistically robust difference can be determined with regard to long-term avoidance of transfusions (transfusion-free period).

Hospitalisation

In the BELIEVE study, the endpoint hospitalisation is surveyed as the number of patients with hospitalisations of any cause. There are statistically significant differences in hospitalisations for any cause to the disadvantage of luspatercept + BSC compared with placebo + BSC.

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. It is questionable whether this bias can be fully compensated for by stratified randomisation by geographic region and not at the study centre or country level. The pharmaceutical company does not provide any further information on this. 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 view, a disadvantage of luspatercept + BSC compared with placebo + BSC is shown for the endpoint category morbidity with regard to hospitalisations.

Quality of life

In the BELIEVE study, health-related quality of life is surveyed using the disease-specific questionnaire TranQoL (transfusion-dependent quality of life questionnaire) and the generic SF-36 (Short Form-36 Health Survey) questionnaire.

TranQoL

The TranQoL is a disease-specific questionnaire to measure the quality of life in individuals with transfusion-dependent thalassaemia; it consists of five domains and a total of 36 questions. The total score of the questionnaire can take values from 0 to 100; a higher score reflects a better quality of life.

The pharmaceutical company submitted evaluations of responder analyses in the dossier; however, these are not used for the present assessment because of the lack of a validated MID.

Furthermore, the pharmaceutical company submitted evaluations on the mean change for which the pre-specified ANCOVA analyses are used in the present assessment. Usable evaluations with sufficiently high return rates are available for Week 48 (78.6% in both treatment arms). Overall, based on the mean difference, there is no statistically significant difference between the treatment arms.

SF-36

The SF-36 questionnaire is a generic instrument for measuring health-related quality of life. It consists of eight domains and a total of 36 questions. The assessment was based on the physical component score (PCS) as well as the mental component score (MCS) of the generic quality-of-life questionnaire SF-36 Version 2. A higher value reflects a better quality of life.

In the dossier, the pharmaceutical company submitted evaluations on the improvement of the two sum scales of the SF-36. Furthermore, evaluations on deterioration were submitted as part of the written statement procedure. The responder analyses submitted by the pharmaceutical

company on the basis of a relevance threshold of ≥ 5 points for improvement and deterioration are used for the present assessment.

There are no statistically significant differences between the treatment groups; neither for the improvement nor for the deterioration of the PCS and the MCS.

In the overall view, there were no statistically significant differences in health-related quality of life between the treatment arms. Overall, neither an advantage nor a disadvantage for luspatercept + BSC compared with placebo + BSC can be determined.

Side effects

Total adverse events (AE)

Almost all study participants experienced an adverse event. The results are presented additionally.

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

With regard to SAE, severe AE (CTCAE grade ≥ 3), and therapy discontinuations because of adverse events, there is a statistically significant difference to the disadvantage of luspatercept + BSC compared with placebo + BSC in each case.

AE of special interest of other relevant safety events

Regarding AE of special interest (malignancies and pre-malignant diseases [SMQ]), at the time of the relevant data cut-off, two events occurred in the intervention arm and none in the control arm. Because of the low number of events, no comparative analyses were carried out.

For the other relevant safety events, there is a statistically significant difference to the disadvantage of luspatercept + BSC compared with placebo + BSC for bone pain (PT).

In the overall view of the results for adverse events, there are disadvantages for luspatercept + BSC compared with placebo + BSC for serious and severe adverse events (CTCAE grade ≥ 3) as well as therapy discontinuations because of adverse events, thereby resulting in an overall relevant disadvantage for luspatercept + BSC compared with placebo + BSC in the endpoint category side effects.

Overall assessment

For the assessment of the additional benefit of luspatercept for the treatment of adult patients with transfusion-dependent anaemia associated with beta-thalassaemia, results on the endpoint categories mortality, morbidity, quality of life, and side effects from the BELIEVE study are available.

In the ongoing study luspatercept + best supportive care (BSC) is compared with placebo + BSC. The BSC includes erythrocyte concentrate transfusions and iron chelation therapies as well as antibiotic therapies, antiviral and antifungal therapies, and/or nutritional support as needed.

For overall survival, neither an advantage nor a disadvantage of treatment with luspatercept + BSC compared with placebo + BSC can be established.

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).

Based on the results for transfusion-free period ≥ 24 weeks, no statistically robust difference can be determined with regard to long-term avoidance of transfusions (transfusion-free period).

Furthermore, results regarding hospitalisation are available for the endpoint category morbidity. This shows a disadvantage of luspatercept + BSC compared with placebo + BSC.

For health-related quality of life, measured by the TranQoL and the SF-36, neither an advantage nor a disadvantage can be found for luspatercept + BSC compared with placebo + BSC.

With respect to the endpoint category side effects, there was a relevant disadvantage for luspatercept + BSC compared with placebo + BSC for serious and severe adverse events (CTCAE grade ≥ 3) and therapy discontinuations because of adverse events.

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 associated with beta-thalassaemia 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 BELIEVE Phase III study.

The results from the BELIEVE 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. Reblozyl was approved as an orphan drug. Luspatercept is indicated for the treatment of adult patients with transfusion-dependent anaemia associated with beta-thalassaemia.

The pharmaceutical company presents the double-blind, randomised, controlled Phase-III BELIEVE study in which luspatercept + best supportive care (BSC) was compared with placebo + BSC.

For overall survival, neither an advantage nor a disadvantage of treatment with luspatercept + BSC compared with placebo + BSC can be established.

For the endpoint category morbidity, there is a disadvantage of luspatercept + BSC compared with placebo + BSC with regard to hospitalisations.

Based on the results for a transfusion-free period ≥ 24 weeks, no statistically robust difference can be determined with regard to long-term avoidance of transfusions (transfusion-free period).

Neither an advantage nor a disadvantage can be determined for health-related quality of life.

For the endpoint category side effects, there is an overall relevant disadvantage 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 associated with beta-thalassaemia 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. Overall, the number of patients stated by the pharmaceutical company is plausible based on the data presented.

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 January 2021).

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	Consumption 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 × 1.25 mg/kg = 96.3 mg	61.6 g – 96.3 g	1 × 75 mg – (1 × 75 mg + 1 × 25 mg)	17.4	17.4 × 75 mg – 17.4 × (75 mg + 25 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.

[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 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 25 mg	1 PIJ	€ 1,868.97	€ 1.77	€ 103.46	€ 1,763.74
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

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