Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) 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: β-thalassaemia, non-transfusion-dependent anaemia)

of 21 September 2023

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. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient luspatercept (Reblozyl) was listed for the first time on 1 August 2020 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

Luspatercept is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999. Within the previously approved therapeutic indications, the sales volume of luspatercept with the statutory health insurance at pharmacy sales prices, including value-added tax exceeded € 30 million. Evidence must therefore be provided for luspatercept in

accordance with Section 5, paragraph 1 through 6 VerfO, and the additional benefit compared with the appropriate comparator therapy must be demonstrated.

On 27 February 2023, luspatercept received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 23 March 2023, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient luspatercept with the new therapeutic indication (treatment of anaemia associated with non-transfusion-dependent beta-thalassaemia) in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on the G-BA website (www.g-ba.de) on 3 July 2023, thus initiating the written statement procedure. An oral hearing was also held.

The G-BA came to a resolution on whether an additional benefit of luspatercept compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, as well of the addendum drawn up by the IQWiG on the benefit assessment. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods 1 was not used in the benefit assessment of luspatercept.

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

[1] General Methods, version 6.1 of 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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

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

Reblozyl is indicated in adults for the treatment of anaemia associated with transfusion-dependent and non-transfusion-dependent beta-thalassaemia.

Therapeutic indication of the resolution (resolution of 21.09.2023):

Reblozyl is indicated in adults for the treatment of anaemia associated with non-transfusion-dependent beta-thalassaemia.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with non-transfusion-dependent anaemia due to β-thalassaemia

Appropriate comparator therapy for luspatercept:

Transfusion therapy on demand with red blood cell concentrates in combination with a chelation therapy according to the marketing authorisation, preferably as monotherapy

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:</u>

on 1. In addition to luspatercept, the active ingredients deferasirox, deferoxamine and various erythrocyte concentrates are approved in the present therapeutic indication.

on 2. Allogeneic stem cell transplantation is basically available as a non-medicinal therapy in the present therapeutic indication. However, it is assumed that patients are ineligible for an allogeneic stem cell transplantation at the time of therapy with luspatercept. Non-medicinal treatment is therefore not considered.

on 3. In the specific therapeutic indication of non-transfusion-dependent anaemia in patients with β-thalassaemia, no resolutions of the G-BA are available.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a, paragraph 7 SGB V. However, no written comments were received from the scientific-medical societies and the AkdÄ.

For the determination of the appropriate comparator therapy, it is assumed that the patients are in need of treatment.

The limited evidence available for the treatment of non-transfusion-dependent anaemia in patients with β-thalassaemia shows that transfusion therapy with erythrocyte concentrates is used for therapy on demand. The decision for a transfusion therapy is made in particular depending on the clinical symptomatology. In addition, chelation therapies are used to treat iron overload, usually as monotherapy.

Therefore, transfusion therapy with red blood cell concentrates in combination with chelation therapy according to the marketing authorisation, preferably as monotherapy, is defined as appropriate comparator therapy.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

Indication of a minor additional benefit

Justification:

For the benefit assessment, the results of the completed, randomised, double-blind phase III BEYOND study comparing luspatercept + best supportive care (BSC) with placebo + BSC in adult patients with non-transfusion-dependent β-thalassaemia are available.

Patients with β-thalassaemia or haemoglobin E / β-thalassaemia were enrolled in the study. The mean haemoglobin (Hb) value had to be below 10 g/dl over the last four weeks before randomisation. Patients were allowed to have received a maximum of 5 red blood cell concentrate units 24 weeks prior to randomisation and no transfusion of a red blood cell concentrate eight weeks prior to randomisation and had to have an ECOG status of 0 to 1.

A total of 145 patients were randomised in a 2:1 ratio to the two study arms (luspatercept + BSC: N = 96; placebo + BSC: N = 49). Randomisation was stratified by Hb concentration (≥ 8.5 g/dl vs < 8.5 g/dl) and the Non-Transfusion-Dependent Thalassemia-Patient Reported Outcomes (NTDT-PRO) total score in the fatigue/ weakness domain at baseline (< 3 points vs

≥ 3 points). In both treatment arms, withing the framework of BSC, transfusions of red blood cell concentrates were allowed at the doctor's discretion for the treatment of low Hb levels, anaemia-related symptoms or comorbidities. Chelation therapies could be administered as needed. In both study arms, about 40% of the patients received iron chelation therapy.

Patients were on average 40 years old, and had a median Hb value of approximately 8 g/dl. About one third of the patients had no or only minor symptomatology of fatigue/ weakness at the start of the study (NTDT-PRO value for the fatigue/ weakness domain < 3). The percentage of patients with previous splenectomy was unbalanced between the study arms at 35% versus 53%. On the part of the scientific-medical society, it was pointed out during the oral hearing in the present benefit assessment procedure that the percentage of patients with splenectomy is significantly lower in the current healthcare context.

The BEYOND study includes a 4-week screening phase, a 48-week double-blind treatment phase, a 24-month open-label treatment phase and a follow-up phase. The study was unblinded after the last enrolled patient completed the 48-week, double-blinded treatment phase or discontinued therapy prematurely. Patients who had completed the 48-week treatment phase before this point remained blinded in the study and continued to receive treatment, so that the study endpoints continued to be collected for this group of patients after week 48. After the study was unblinded, patients in both study arms were able to receive luspatercept in the open-label treatment phase.

The study was conducted between 2018 and 2022 in 12 study sites in Europe, Asia and the Americas. The pharmaceutical company submits the results of the pre-specified data cut-off of 14.09.2020 for the benefit assessment. Data cut-off occurred at the time when all patients had completed the 48-week double-blind study phase. Based on this data cut-off, the pharmaceutical company submits evaluations at week 24, at week 48 and/or over the entire observation period up to the data cut-off, depending on the respective endpoint category.

The primary endpoint of the BEYOND study was the increase in haemoglobin concentration, operationalised as the percentage of patients with an increase in mean haemoglobin concentration compared to baseline by ≥ 1 g/dL in the absence of transfusions over a continuous 12-week period between week 13 and week 24. In addition, patient-relevant endpoints on morbidity, health-related quality of life and side effects were assessed.

For the benefit assessment, the results of the BEYOND study presented are used, based on the data cut-off of 14.09.2020, whereby, depending on the respective endpoint to be considered, the evaluations for week 24, week 48 or the entire observation period up to the data cut-off are used as a basis.

Mortality

Deaths were recorded in the BEYOND study as part of the assessment of adverse events. No deaths occurred in either study arm during the entire observation period until the data cut-off of 14.09.2020.

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

Morbidity

Total hospitalisation

In the BEYOND study, all documented inpatient hospitalisations during the study were counted as hospitalisations, regardless of their cause.

With regard to total hospitalisation, there is no statistically significant difference between the study arms.

Symptomatology

In the BEYOND study, patient-reported symptomatology was assessed using the NTDT-PRO questionnaire and the Patient Global Impression of Change (PGI-C) and Patient Global Impression of Severity (PGI-S) scales.

In the dossier, the pharmaceutical company submits both responder analyses at week 24 and week 48 for improvement and deterioration of symptomatology, respectively, and responder analyses for time to first improvement and deterioration, respectively. The therapy of β-thalassaemia is primarily intended to improve the symptomatology, so that the evaluations on the improvement of the symptomatology are used for the present benefit assessment. In addition, the responder analyses at week 24 and week 48 have more significance than the responder analyses for the first-time improvement, as they can show a continuous improvement in symptomatology over the respective period. Therefore, the responder analyses at week 24 or week 48 are considered, depending on the respective return rates of the questionnaires.

With regard to the results on improvement of symptomatology, it should be taken into account that some of the patients enrolled in the BEYOND study showed only mild symptomatology at baseline and thus, had only little potential for improvement or none in the corresponding endpoints.

NTDT-PRO

The NTDT-PRO is a validated questionnaire developed for patients with non-transfusion-dependent β-thalassaemia to assess the anaemia-related symptoms of fatigue/ weakness and shortness of breath. The questionnaire includes 6 items grouped into the domains of fatigue/ weakness (4 items) and shortness of breath (2 items), each with a scale range of 0 to 10. Lower values mean an improvement of symptomatology.

The pharmaceutical company submits responder analyses with an improvement by 1.5 points. As the return rates at week 48 were significantly below 70%, the results on the percentage of patients with an improvement of 1.5 points at week 24 are used for the benefit assessment.

For the NTDT-PRO, there is a statistically significant advantage in favour of luspatercept in both the fatigue/ weakness and shortness of breath domains.

PGIS

The PGIS consists of a single question in which the patient rates the severity of β-thalassaemia-related symptomatology on a 10-point scale. Lower values mean lower symptomatology. The pharmaceutical company submits responder analyses with an improvement by 1.5 points. As the return rates at week 48 were significantly below 70%, the results on the percentage of patients with an improvement of 1.5 points at week 24 are used for the benefit assessment.

For the PGIS, there is a statistically significant difference to the advantage of luspatercept between the treatment arms.

PGIC

The PGIC consists of a single question in which the patient assesses the overall change in her/his β-thalassaemia-related symptomatology since the start of the study. The pharmaceutical company submits a responder analysis in which the change "much better" and "very much better" is considered a relevant improvement. The responder analysis at week 48 is used for the benefit assessment.

For the PGIC, there is a statistically significant difference to the advantage of luspatercept between the treatment arms.

Transfusion avoidance

The pharmaceutical company presents in its dossier an evaluation of the avoidance of transfusions at week 24 and week 48. In the BEYOND study, transfusions should also be documented up to week 48 in patients who have discontinued therapy.

The pharmaceutical company's evaluation in the dossier only takes into account red blood cell transfusions that were performed up to 20 days after therapy discontinuation. This evaluation is considered unsuitable because patients who discontinued therapy before week 48 are not taken into account. In addition, patients who did not receive a transfusion within 20 days of therapy discontinuation were not included in the analysis and counted as "missing".

In the course of the written statement procedure, the pharmaceutical company submits an evaluation for the endpoint of transfusion avoidance, which also includes the complete duration of observation after therapy discontinuation.

In the present therapeutic indication of non-transfusion-dependent β-thalassaemia, patients are not dependent on regular transfusion therapy with red blood cell concentrates, but receive irregular or occasional red blood cell transfusions, for example in connection with infections, surgical interventions or anaemia-related symptoms. Thus, in contrast to patients with transfusion-dependent β-thalassaemia, there is no chronic need for transfusion. Instead, periods of higher and lower transfusion requirements alternate. Against the background of a

comparatively lower transfusion burden in the present therapeutic indication, the endpoint of (complete) transfusion avoidance is not considered as patient-relevant per se.

However, patients with non-transfusion-dependent β-thalassaemia may also develop secondary haemochromatosis requiring therapy due to increased intestinal iron resorption during the course of the disease and may be more frequently dependent on red blood cell transfusions due to aggravating anaemia. Necessary transfusions can lead to increasing iron overload of the organs and subsequent long-term complications despite iron elimination therapy. According to the available patient characteristics, 29% and 33% of the patients in the BEYOND study received iron chelation therapy in the 24 weeks before the start of the study and approximately 40% of the patients within the study.

Although the statement of the scientific-medical society in the present benefit assessment procedure shows that a long-term or sustainable avoidance of transfusions while maintaining a defined minimum haemoglobin value can also represent a primary therapeutic goal in patients with non-transfusion-dependent β-thalassaemia, among other things, in order to prevent relevant secondary complications due to iron overload, conclusions regarding the potential avoidance of long-term transfusion-related secondary complications are not possible based on the data of the BEYOND study.

According to the inclusion criteria of the BEYOND study, patients were allowed to have received a maximum of 5 red blood cell concentrate units 24 weeks before randomisation and no transfusion of a red blood cell concentrate eight weeks before randomisation. From the information provided by the pharmaceutical company in the dossier, it can be seen that the majority of patients in both study arms did not require transfusions in the 24 weeks prior to the start of the study (approx. 86%). No one received more than 4 transfusions in the 24 weeks prior to enrolment in the study.

Based on the low number of necessary transfusions at baseline in the BEYOND study, the present magnitude of the effect shown is only classified as a minor improvement of the therapy-relevant benefit. The results of the evaluation submitted subsequently in the written statement procedure are only presented additionally.

Conclusion on morbidity

For the endpoint category of morbidity, there are statistically significant differences overall in patient-reported symptomatology (NTDT-PRO, PGIS, PGIC) to the advantage of luspatercept.

Quality of life

Health-related quality of life was assessed in the BEYOND study using the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue and the Short Form-36 Health Survey Version 2 (SF-36v2).

In accordance with the above explanations on the symptomatology, the therapy of β-thalassaemia is primarily intended to achieve an improvement in health-related quality of life,

so that the evaluations of the improvement are considered for the present benefit assessment.

In addition, for the endpoints on health-related quality of life, taking into account the above comments on the significance of the respective responder analyses available in the dossier, the responder analyses for week 48 are used due to sufficiently high return rates.

FACIT-F

The FACIT-F consists of 13 items that assess the intensity of fatigue as well as the weakness and difficulty in performing daily activities due to fatigue within the last 7 days. The items are answered on a 5-point numerical scale, with higher scores indicating an improvement in health-related quality of life.

For the FACIT-F, there are no statistically significant differences between the study arms with regard to both the total score and the individual subscales.

SF-36v2

SF-36 is a generic instrument for measuring health-related quality of life, consisting of eight domains and a total of 36 questions. The physical component summary (PCS) score and the mental component summary (MCS) score were used in the assessment. A higher value reflects a better quality of life.

For the SF-36v2, there are no statistically significant differences between the study arms.

Conclusion on health-related quality of life

For the endpoint category of health-related quality of life, there are no statistically significant differences between the treatment arms.

Side effects

For the side effects, evaluations are available in the dossier, based on the entire duration of observation up to the data cut-off.

Adverse events (AEs) in total

AEs occurred in almost all study participants. The results were only presented additionally.

Serious adverse events (SAE)

For the endpoint of serious AEs (SAEs), there is a statistically significant difference between the treatment arms to the advantage of luspatercept.

There is an effect modification due to the "previous splenectomy" characteristic. Patients with a previous splenectomy showed a statistically significant difference to the advantage of luspatercept (HR = 0.08 [0.02;0.37]; < 0.001). For patients without prior splenectomy, there is no statistically significant difference between treatment arms (HR = 1.18 [0.25;5.62]; 0.832).

This effect modification is not evident in other endpoints of the BEYOND study. According to the comments of the scientific-medical society during the oral hearing, no clear medical rationale can be derived for the present effect modification. Overall, the significance of the subgroup results is considered insufficient to derive separate statements on the additional benefit of luspatercept based on the overall assessment.

Severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs

There is no statistically significant difference between the study arms for the endpoints of severe AEs and therapy discontinuation due to AEs.

Specific AEs - bone pain

For the endpoint of bone pain (preferred term), there was a statistically significant difference to the disadvantage of luspatercept.

Conclusion on side effects

In the overall assessment, there is an advantage of luspatercept in the endpoint of SAE, driven by the subgroup of patients with prior splenectomy. In detail, there is a disadvantage of luspatercept for the specific AE of bone pain.

Overall assessment

For the assessment of the additional benefit of luspatercept for the treatment of adults with anaemia associated with non-transfusion-dependent β-thalassaemia, results are available for the endpoint categories of mortality, morbidity, health-related quality of life and side effects from the completed, double-blind phase III BEYOND study. The study compared luspatercept + best supportive care (BSC) versus placebo + BSC. Red blood cell transfusions and chelation therapy could be used as needed in the BSC.

Neither an advantage nor a disadvantage of luspatercept can be determined for overall survival.

For the endpoint category of morbidity, results are available for the endpoints of total hospitalisation and patient-reported symptomatology assessed using the questionnaires NTDT-PRO, PGI-S and PGI-C.

For the endpoint of total hospitalisation, there are no statistically significant differences between the treatment arms. For patient-reported symptomatology, all questionnaires used in the study showed a statistically significant advantage of luspatercept.

For health-related quality of life measured by the FACIT-F and SF-36v2 questionnaires, neither an advantage nor a disadvantage of treatment with luspatercept can be determined.

Regarding the endpoint category of side effects, there are no statistically significant differences in the endpoints of severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due

to AEs. For the endpoint of serious AEs, there is an advantage of luspatercept, driven by the subgroup of patients with prior splenectomy. In detail, one disadvantage of luspatercept is the specific AE of bone pain.

Based on the advantages of luspatercept in the endpoint category of morbidity, a moderate and not only minor improvement of the therapy-relevant benefit was found in the endpoints on patient-reported symptomatology. The G-BA therefore concludes that there is a minor additional benefit of luspatercept for the treatment of adults with anaemia due to non-transfusion-dependent β-thalassaemia compared to transfusion therapy on demand with red blood cell concentrates in combination with chelation therapy.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the completed double-blind phase III BEYOND study.

The risk of bias at the study level is rated as low.

Since the benefit assessment is based on the results of only one study, only indications of an additional benefit can be derived with regard to the reliability of data of the results.

The risk of bias for the endpoint of overall survival is rated as low.

For the endpoints on patient-reported symptomatology and health-related quality of life, there are uncertainties due to decreasing return rates of the respective questionnaires in both treatment arms.

The endpoint-specific risk of bias for the endpoint of side effects is estimated to be low. With regard to the endpoint of serious AEs, uncertainties arise due to the relatively high percentage of patients with previous splenectomy, which is not representative for the current German healthcare context, and for which there are also imbalances between the study arms of the BEYOND study.

In the overall assessment, the reliability of data for the additional benefit determined is classified in the "indication" category.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient luspatercept. Luspatercept was approved as an orphan drug.

Luspatercept is indicated in adults for the treatment of anaemia associated with transfusion-dependent and non-transfusion-dependent beta-thalassaemia. The therapeutic indication assessed here refers exclusively to patients with non-transfusion-dependent β-thalassaemia.

The G-BA determined transfusion therapy with red blood cell concentrates in combination with chelation therapy according to the marketing authorisation, preferably as monotherapy, to be an appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company submits the completed, double-blind phase III BEYOND study, in which luspatercept + BSC was compared with placebo + BSC.

There is no statistically significant difference for the overall survival.

For the endpoint category of morbidity, no statistically significant difference can be found in relation to total hospitalisation. In terms of patient-reported symptomatology, there are advantages of luspatercept.

For health-related quality of life, there was neither an advantage nor a disadvantage of luspatercept.

Regarding the endpoint category of side effects, there are no statistically significant differences in the endpoints of severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs. For the endpoint of serious AEs, there is an advantage of luspatercept, driven by the subgroup of patients with prior splenectomy. In detail, one disadvantage of luspatercept is the specific AE of bone pain.

In the overall assessment, based on the advantages in the endpoints on patient-reported symptomatology, an indication of a minor additional benefit is identified.

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 is based on the information from the dossier of the pharmaceutical company. The patient numbers are subject to uncertainties.

The pharmaceutical company operationalises non-transfusion-dependent β-thalassaemia requiring treatment via at least one transfusion with red blood cell concentrates in the period from 2015 to 2019, but not in 2020, or via one to five transfusions with red blood cell concentrates in 2020. It remains unclear how many patients were excluded who were not transfusion-dependent for the entire year under consideration, but for part of the year under consideration, and who are also part of the target population for this period. Furthermore, it is uncertain whether a single transfusion with red blood cell concentrates within several years can still be assumed to require therapy in a single year under consideration.

According to the pharmaceutical company's comments, there is also uncertainty due to possible coding errors and the generally limited data available on the patient group in question.

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: 26 April 2023):

https://www.ema.europa.eu/en/documents/product-information/reblozyl-epar-product-information_en.pdf

Treatment with luspatercept should only be initiated and monitored by doctors experienced in treating patients with haematological diseases.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients including patient identification card (only for women of reproductive age). The training material includes, among other things, a checklist for healthcare professionals to use before starting any treatment, at each administration and then at regular intervals during follow-up visits. The patient identification card must be given to women of reproductive age at the time of 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 an increase in Hb from baseline after nine weeks of treatment (three doses) with the highest dose, without transfusions, unless other explanations for the lack of response are found (e.g. bleeding, surgery, other comorbidities) 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 September 2023).

As part of the appropriate comparator therapy, transfusions with red blood cell concentrates, as well as the associated chelation therapy, are administered as needed. Thus, the treatment mode, the number of treatments/ patient/ year, the treatment duration/ number of treatments (days) and the treatment days/ patient are different from patient to patient.

Treatment period:

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 x every 21 days	17.4	1	17.4
Appropriate comparator therapy				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Transfusion therapy on demand with red blood cell concentrates	Different from patient to patient			
Chelation therapy				
Deferasirox	Different from patient to patient			
Deferoxamine	Different from patient to patient			

Consumption:

As part of the appropriate comparator therapy, transfusions with red blood cell concentrates, as well as the associated chelation therapy, are administered as needed. For transfusion therapy with red blood cell concentrates, the dosage/ application, the dose/ patient/ treatment day, the consumption by potency/ treatment day, the treatment days/ patient/ year and the average annual consumption by potency are therefore different from patient to patient. For chelation therapy, the treatment days/ patient/ year and the average annual consumption by potency are different from patient to patient.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements of the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[2].

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Luspatercept	1 x 0.6 mg/kg = 46.2 mg – 1 x 1.25 mg/kg = 96.3 mg	46.2 mg - 96.3 mg	2 x 25 mg - 1 x 75 mg + 1 x 25 mg	17.4	34.8 x 25 mg - 17.4 x 75 mg + 17.4 x 25 mg
Appropriate comparator therapy					
Transfusion therapy on demand	Different from patient to patient				

[2] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
with red blood cell concentrates					
Chelation therapy					
Deferasirox	7 – 14 mg/kg/day	539 mg - 1,078 mg	3 x 180 mg - 6 x 180 mg	Different from patient to patient	
Deferoxamine	20 – 60 mg/kg/day	1,540 mg - 4,620 mg	1 x 2,000 mg - 2 x 500 mg + 2 x 2,000 mg	Different from patient to patient	

Costs:

Costs of the medicinal products:

There are no proprietary medicinal products listed in the LAUER-TAXE® for transfusion therapy on demand with red cell concentrates. The costs of transfusion therapy on demand with red blood cell concentrates are therefore non-quantifiable.

Designation of the therapy	Packaging 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 PSI	€ 1,358	€ 2.00	€ 127.82	€ 1,228.18
Luspatercept 75 mg	1 PSI	€ 3,974.34	€ 2.00	€ 383.46	€ 3,588.88
Appropriate comparator therapy					
Transfusion therapy on demand with red blood cell concentrates	Incalculable				
Chelation therapy					
Deferasirox 180 mg	90 FCT	€ 49.88	€ 2.00	€ 1.83	€ 46.05
Deferoxamine 500 mg	10 PSII	€ 155.71	€ 2.00	€ 6.85	€ 146.86
Deferoxamine 2000 mg	10 PSII	€ 588.86	€ 2.00	€ 27.41	€ 559.45
Abbreviations: FCT: film-coated tablets; PSI: powder for solution for injection; PSII: powder and solvent for the preparation of injection or infusion solution					

LAUER-TAXE® last revised: 1 September 2023

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 evaluated and the appropriate comparator therapy 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 the standard expenditure in the course of the treatment are not shown.

Because there are no 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 evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate 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 currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail 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 purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

For the preparation of other parenteral solutions including deferoxamine, a surcharge of € 54 per ready-to-use unit is billable in accordance with Annex 3, Part 7, Item 6. According to Annex 3, Part 7b, a surcharge of € 81 is billable for the preparation of solutions containing Reblozyl, in deviation from Annex 3, Part 7, Item 7, per ready-to-apply unit.

2.5 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

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed

medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

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

At its session on 9 November 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 23 March 2023, 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, paragraph 1, number 2, sentence 2 VerfO.

By letter dated 27 March 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient luspatercept.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 June 2023, and the written statement procedure was initiated with publication on the G-BA website on 3 July 2023. The deadline for submitting statements was 24 July 2023.

The oral hearing was held on 7 August 2023.

By letter dated 8 August 2023, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 1 September 2023.

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 was discussed at the session of the subcommittee on 12 September 2023, and the proposed resolution was approved.

At its session on 21 September 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	9 November 2021	Determination of the appropriate comparator therapy
Working group Section 35a	1 August 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	7 August 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	16 August 2023 23 August 2023 6 September 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	12 September 2023	Concluding discussion of the draft resolution
Plenum	21 September 2023	Adoption of the resolution on the amendment of the AM-RL

Berlin, 21 September 2023

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

Prof. Hecken