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 (reassessment of an orphan drug after exceeding the EUR 30 million turnover limit: β-thalassaemia, transfusion-dependent anaemia)

of 2 November 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

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. Reblozyl for the treatment of transfusion-dependent anaemia associated with β-thalassaemia is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

At its session on 21 January 2021, the G-BA decided on the benefit assessment of luspatercept in the therapeutic indication "Treatment of adults with transfusion-dependent anaemia associated with β-thalassaemia" in accordance with Section 35a SGB V.

If the sales of the orphan drug through the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including value-added tax, exceed an amount of € 30 million in the last twelve calendar months, the pharmaceutical company must submit evidence in accordance with Section 5, paragraphs 1 to 6 within three months of being requested to do so by the Federal Joint Committee, and in this evidence must demonstrate the additional benefit compared to the appropriate comparator therapy.

In a letter dated 1 December 2022, the pharmaceutical company was informed that the EUR 30 million turnover limit for luspatercept had been exceeded within the period from December 2021 to November 2022. By resolution of 2 February 2023 the procedure was suspended till 16 October 2023. By letter dated 2 February 2023, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 16 October 2023, due to exceeding the € 30 million turnover limit. By resolution of 6 April 2023, the relevant date for the submission of the dossier was brought forward to 15 May 2023 in order to enable a discussion on the new therapeutic indication of non-transfusion-dependent β-thalassaemia (resolution of the G-BA of 21 September 2023) in a short period of time. The pharmaceutical company has 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, paragraph1, number 6 VerfO on 11 May 2022.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 15 August 2023 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of luspatercept compared to 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. 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 7.0 from 19.09.2023. 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 02.11.2023):

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with transfusion-dependent anaemia associated with 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, deferiprone and deferoxamine as well as various red blood cell concentrates are approved in the present therapeutic indication.

on 2. Allogeneic stem cell transplantation is basically considered 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 therapeutic indication, the following resolutions from the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available:

- Betibeglogene autotemcel[2]: Resolution of 14 May 2020

[2] The marketing authorisation was withdrawn by the pharmaceutical company and Zynteglo has no longer been approved in the EU since 24 March 2022.

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 therapeutic indication according to Section 35a, paragraph 7 SGB V. There is a joint written statement of the German Society for Haematology and Medical Oncology (DGHO) and the Society for Paediatric Oncology and Haematology (GPOH).

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

According to the limited evidence available, red blood cell transfusions are used to treat anaemia associated with transfusion-dependent β-thalassaemia. Overall, the evidence for the administration of red blood cell concentrates is limited and neither an explicit threshold value (e.g. based on the haemoglobin (Hb) value) for use nor a recommended frequency can be derived on the basis of the available evidence.

Based on the available evidence, it should also be noted that patients with transfusion-dependent anaemia due to β-thalassaemia regularly receive chelation therapy in order to avoid a threatening iron overload of the organism as a result of transfusion therapy. Chelation therapy is preferably used as monotherapy.

According to the scientific-medical societies, if patients are ineligible for allogeneic stem cell transplantation, medicinal options such as luspatercept and hydroxycarbamide are a treatment option in addition to transfusion therapy.

For the benefit assessment according to Section 35a SGB V, a comparison with the active ingredient itself, specifically a comparison of identical therapies, is ruled out regarding the question of the benefit assessment. The present dossier procedure concerns the active ingredient luspatercept, which is therefore excluded for the appropriate comparator therapy.

The cytostatic agent hydroxycarbamide has no marketing authorisation for the treatment of β-thalassaemia. It cannot be deduced from the available evidence that the off-label use of hydroxycarbamide is generally preferable to the medicinal products previously approved in the therapeutic indication according to the generally recognised state of medical knowledge. Hydroxycarbamide is therefore not considered an appropriate comparator therapy.

The gene therapy betibeglogene autotemcel (Zynteglo) named by the scientific-medical societies has no longer been approved in the EU since 24 March 2022 and is therefore not considered as an appropriate comparator therapy.

In the overall assessment, a transfusion therapy on demand with red blood cell concentrates in combination with chelation therapy according to the marketing authorisation, preferably as monotherapy, is determined to be an 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:

Adults with transfusion-dependent anaemia associated with β-thalassaemia

An additional benefit is not proven.

Justification:

For the benefit assessment of the active ingredient luspatercept, the pharmaceutical company is presenting the results of the completed pivotal phase III BELIEVE study (ACE-536- B-THAL-001). It is a double-blind, randomised, controlled, multi-centre study that was conducted in 15 countries and 65 study sites (including Europe, Australia, the Middle East, North America and South East Asia). Study sites from Germany were not involved in the study. The BELIEVE study on which the benefit assessment was based enrolled adults with β-thalassaemia or haemoglobin E/ β-thalassaemia who receive regular transfusions (defined as 6-20 red blood cell concentrate [RBC] units and no transfusion-free period of > 35 days within the 24 weeks prior to randomisation).

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

There are uncertainties regarding the administration of luspatercept in the BELIEVE study in accordance with the product information. According to the product information, treatment with luspatercept should be discontinued if there is no reduction in the transfusion burden after 9 weeks (3 doses) with the highest dosage. A corresponding discontinuation criterion was not defined in the study. The dossier of the pharmaceutical company did not contain any information on how many patients who did not show a reduction in the transfusion burden after 9 weeks (3 doses) with the highest dose of luspatercept were treated further. The

pharmaceutical company did not submit any information in this regard during the written statement procedure either. The interpretability of the present study results is therefore fraught with uncertainties.

The patients had a mean age of approx. 32 years at the time of enrolment in the study and had received an average of approx. 15 RBC units within the last 24 weeks. The BELIEVE study comprised a 12-week screening phase, a 48-week treatment phase and a long-term treatment phase in which patients were treated at the doctor's discretion according to their initial allocation. The long-term treatment phase ended after all patients had completed the 48-week treatment phase. The study was then unblinded. In the subsequent open-label extension phase, adults from both study arms continued to be treated with luspatercept + BSC.

The primary endpoint of the BELIEVE study is the reduction of the transfusion burden by ≥ 33% RBC units with at least two RBC units in weeks 13-24 compared to the screening phase. Furthermore, endpoints of the categories morbidity, health-related quality of life and adverse events were collected in the study.

A total of four data cut-offs are available for the study (11 May 2018, 7 January 2019, 1 July 2019, 5 January 2021). The pre-specified final data cut-off from 5 January 2021 is used for the present benefit assessment. This contains data on two evaluation time points: Evaluations at week 48, which are used for the patient-reported outcomes (PROs), and analyses up to unblinding, which are taken into account for the assessment of all other patient-relevant endpoints. Later evaluation time points are based on non-comparator data and are not used for the present assessment.

Extent and probability of the additional benefit

Mortality

Deaths were recorded as safety events in the BELIEVE study. At the time of the relevant data cut-off, one death occurred in each of the two treatment arms. Thus, there is no statistically significant difference for the benefit assessment in terms of overall survival.

Morbidity

Transfusion avoidance (transfusion independence)

The endpoint of transfusion avoidance (transfusion independence) was defined as a period without receipt of RBC transfusions over a certain duration during the course of the study. The pharmaceutical company submitted evaluations of various periods of transfusion avoidance between study weeks 1 and 48.

Transfusion-dependent β-thalassaemia is based on anaemia caused by the significantly reduced production of functional β-globin, which requires frequent and lifelong RBC transfusions. The required transfusions can lead to increasing iron overload of the organs and subsequent long-term complications in the patients despite iron elimination therapy.

A long-term or sustainable avoidance of transfusions (transfusion independence) while maintaining a defined minimum value of haemoglobin represents a therapeutic goal of higher priority in the present therapeutic indication, with which a control of anaemia and anaemia-related symptoms is achieved, while avoiding RBC transfusions.

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

The endpoint of transfusion avoidance (transfusion independence) presented by the pharmaceutical company, operationalised as the percentage of patients who did not require a transfusion of a red blood cell concentrate for ≥ 24 weeks until unblinding of the study, is assessed as patient-relevant and used for the present benefit assessment.

Transfusion independence of ≥ 24 weeks was observed in five subjects in the intervention arm and in none in the control arm until the study was unblinded. There is no statistically significant difference between the treatment arms.

Transfusion burden

In the BELIEVE study, the transfusion burden was defined as the number of transfused RBC units per defined time interval. In the BELIEVE study, RBC transfusions were administered at the discretion of the investigator in cases of low Hb levels, anaemia-associated symptoms or comorbidities. A pre-transfusion value was determined individually for each subject based on the transfusion burden, 24 weeks prior to randomisation.

The reduction in transfusion frequency alone is not considered patient-relevant *per se* as it does not allow any conclusions to be drawn about the long-term avoidance of transfusions in the sense of transfusion independence. The advantages resulting from a lower number of transfusions should also be reflected in the patient-relevant endpoints of the morbidity and health-related quality of life endpoint categories.

Overall, however, it is unclear what kind of change or reduction in the transfusion burden represents a relevant and noticeable improvement for the patients – particularly in view of the fact that no symptomatology was collected in the BELIEVE study. The pharmaceutical company also provides no information on how a partial reduction of the transfusion burden affects the improvement of symptomatology and the avoidance of secondary complications of transfusion therapy or whether threshold values can be derived for this. In addition, there are no statistically significant differences between the treatment arms in the health-related quality of life endpoint category (see below).

According to the statements made by the scientific-medical society at the oral hearing, a reduction in the transfusion burden is relevant for patients, particularly to avoid long-term complications due to secondary iron overload and due to an improvement in quality of life,

particularly by prolongation of the transfusion interval. Conclusions regarding the potential prevention of long-term transfusion-related secondary complications based on the data of the BELIEVE study are not possible.

A validation of the transfusion burden as a surrogate parameter for a patient-relevant endpoint was not submitted by the pharmaceutical company.

The endpoint of transfusion burden is neither assessed as a directly patient-relevant endpoint nor as a validated surrogate endpoint and is therefore only presented additionally in the present assessment.

Total hospitalisation

In the BELIEVE study, the endpoint of total hospitalisation was collected as the number of adults with hospitalisations for any cause. There is a statistically significant difference to the disadvantage of luspatercept. It cannot be conclusively assessed to what extent events of the endpoint were also collected in the context of serious adverse events and thus considered twice.

Quality of life

Health-related quality of life was assessed in the BELIEVE study using the disease-specific questionnaire TranQoL (Transfusion-dependent quality of life questionnaire) and the generic questionnaire SF-36v2 (Short Form-36 Health Survey version 2).

In the dossier, the pharmaceutical company presents responder analyses on both improvement and deterioration in quality of life. The therapy of β-thalassaemia is primarily intended to improve the quality of life, so that the evaluations on the improvement of the quality of life at week 48 are used for the present benefit assessment.

TranQoL

The TranQoL is a disease-specific questionnaire to assess the quality of life of subjects with transfusion-dependent thalassaemia, consisting of five domains and a total of 36 questions. The total score of the questionnaire can range from 0 to 100, with a higher score reflecting a better quality of life.

The responder analyses presented by the pharmaceutical company on the basis of a relevance threshold of 15 points (corresponding to 15% of the scale range) are used for the present assessment.

Overall, there are no statistically significant differences between the treatment arms based on the responder analyses.

SF-36v2

SF-36v2 questionnaire 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) scale and the mental component summary (MCS) scale were used in the assessment. A higher value reflects a better quality of life.

The responder analyses submitted by the pharmaceutical company based on a relevance threshold of ≥ 9.4 (PCS) or ≥ 9.6 (MCS) points for improvement are used for the present assessment.

There were no statistically significant differences between the treatment groups for the improvement in PCS and MCS.

Conclusion on health-related quality of life

In the overall assessment, there are no statistically significant differences between the treatment arms for the health-related quality of life as measured by TranQoL and SF-36v2.

Side effects

Adverse events (AEs) in total

Nearly all study participants experienced an adverse event. The results were only presented additionally.

Serious AEs (SAE) and severe AEs (CTCAE grade ≥ 3)

With regard to SAEs and severe AEs (CTCAE grade ≥ 3), there is a statistically significant difference in each case to the disadvantage of luspatercept compared to placebo.

Therapy discontinuations due to AEs

With regard to therapy discontinuation due to AEs, there is no statistically significant difference between the study arms.

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

The overall assessment of the results on side effects shows statistically significant differences to the disadvantage of luspatercept in the endpoints of serious and severe adverse events (CTCAE grade ≥ 3) as well as in detail for the specific AE of bone pain.

Overall assessment

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

The completed phase III study compares luspatercept + best supportive care (BSC) versus placebo + BSC. The BSC includes, among others, red blood cell concentrate transfusions, iron

chelation therapies as well as antibiotic therapies, antiviral and antifungal therapies and/or nutritional support as required.

For overall survival, there is no statistically significant difference.

Results on transfusion avoidance and total hospitalisation are available for the morbidity endpoint category. For the present assessment, transfusion avoidance of ≥ 24 weeks is regarded as the relevant period in order to be able to assume long-term avoidance of transfusions (transfusion independence). Based on the results for transfusion avoidance of ≥ 24 weeks, no statistically reliable difference between the treatment groups can be determined. For the endpoint of total hospitalisation, there is a statistically significant disadvantage of luspatercept.

No statistically significant differences were found between the study arms for health-related quality of life, measured using the TranQoL and the SF-36v2.

With regard to the endpoint category of side effects, there was a statistically significant disadvantage of luspatercept for serious and severe AEs (CTCAE grade ≥ 3) and in detail, for bone pain. For the endpoint of therapy discontinuation due to AEs, there are no statistically significant differences.

The interpretation of the study results is associated with uncertainties due to the lack of clarity regarding the use of luspatercept in the BELIEVE study in accordance with the product information. With regard to the luspatercept arm in particular, it cannot be ruled out that some of the adverse events that occurred during treatment could have been avoided if treatment had been discontinued earlier in accordance with the product information.

Taking these uncertainties into account, the existing disadvantages in the endpoints of total hospitalisation, severe AEs and serious AEs are considered insufficient to derive an overall lower benefit of luspatercept in the overall assessment compared to a transfusion therapy on demand with red blood cell concentrates in combination with chelation therapy according to the marketing authorisation, preferably as monotherapy. It is therefore concluded that there is no proven additional benefit of luspatercept compared with a transfusion therapy on demand with red blood cell concentrates in combination with chelation therapy in accordance with the marketing authorisation, preferably as monotherapy.

In the present therapeutic indication, luspatercept may represent a relevant treatment option for individual patients.

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the medicinal product Reblozyl with the active ingredient luspatercept due to the exceeding of the € 30 million turnover limit. Reblozyl was approved as an orphan drug. Luspatercept is indicated in adults for the treatment of anaemia associated with transfusion-dependent and non-transfusion-

dependent β-thalassaemia. The present assessment refers exclusively to the 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.

The pharmaceutical company is presenting the double-blind, randomised phase-III BELIEVE study, in which luspatercept + best supportive care (BSC) was compared with placebo + BSC. Under BSC, a transfusion therapy on demand with red blood cell concentrates could also be used in accordance with the appropriate comparator therapy determined by the G-BA.

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

For the morbidity endpoint category, there is a disadvantage of luspatercept with regard to total hospitalisation.

Based on the results of transfusion independence of ≥ 24 weeks, no statistically reliable difference can be identified with regard to long-term avoidance of transfusions (transfusion independence).

For health-related quality of life, neither an advantage nor a disadvantage can be identified.

For the endpoint category of side effects, there is an overall disadvantage of luspatercept in the endpoints of severe and serious AEs and in detail, for bone pain. For the endpoint of discontinuation due to AEs, there is no statistically significant difference.

Uncertainties remain regarding the administration of luspatercept in accordance with the product information, which are reflected in particular in the interpretation of the study results on side effects.

Taking these uncertainties into account, it is concluded overall that there is no proven additional benefit for luspatercept compared with transfusion therapy on demand with red blood cell concentrates in combination with chelation therapy in accordance with the marketing authorisation, preferably as monotherapy.

In the present therapeutic indication, luspatercept may represent a relevant treatment option for individual patients.

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. 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: 24 August 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 any 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 comorbidities) or whenever unacceptable toxicity occurs.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 October 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.

For deferiprone, a combination therapy with another chelating agent is considered for thalassaemia major. The cost calculation is based on the assumption that deferiprone is generally used as monotherapy. In line with the appropriate comparator therapy, monotherapy is therefore shown in the costs.

Treatment period:

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 varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for 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 x every 21 days	17.4	1	17.4
Appropriate comparator therapy				
A transfusion therapy on demand with red blood cell concentrates in combination with a chelation therapy according to the marketing authorisation, preferably as monotherapy				
Transfusion therapy on demand with red blood cell concentrates	Different from patient to patient			
Chelation therapy				
Deferasirox	Different from patient to patient			
Deferiprone	Different from patient to patient			
Deferoxamine	Different from patient to patient			

Consumption:

The (daily) doses recommended in the product information were used as the calculation basis.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

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.

The active ingredient luspatercept is administered according to body weight. For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.0 kg).[3]

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

As it is not always possible to achieve the exact calculated dose per day with the commercially available dose potencies, in these cases rounding up to the next higher or lower available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

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	0.8 – 1.25 mg/kg	61.6 – 96.25 mg	1 x 75 mg – 1 x 25 mg + 1 x 75 mg	17.4	17.4 x 75 mg – 17.4 x 25 mg + 17.4 x 75 mg
Appropriate comparator therapy					
Transfusion therapy on demand with red blood cell concentrates	Different from patient to patient				
Chelation therapy					
Deferasirox	7 – 28 mg/kg/day	539 – 2,156 mg	3 x 180 mg – 2 x 900 mg + 1 x 360 mg	Different from patient to patient	

[3] 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
Deferiprone	25 mg/kg	3 x 1,925 mg	6 x 1,000 mg	Different from patient to patient	
Deferoxamine	20 – 60 mg/kg	1,540 – 4,620 mg	1 x 2,000 mg – 2 x 2,000 mg + 2 x 500 mg	Different from patient to patient	

Costs:

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

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

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	€ 1,358.00	€ 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
Deferasirox 360 mg	90 FCT	€ 130.16	€ 2.00	€ 5.64	€ 122.52

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
Deferasirox 900 mg	30 FCT	€ 450.03	€ 2.00	€ 20.82	€ 427.21
Deferiprone 1,000 mg	50 FCT	€ 273.58	€ 2.00	€ 24.89	€ 246.69
Deferoxamine 2,000 mg	10 PII	€ 588.86	€ 2.00	€ 27.41	€ 559.45
Deferoxamine 500 mg	10 PII	€ 155.71	€ 2.00	€ 6.85	€ 146.86
Abbreviations: PSI = powder for solution for injection; FCT = film-coated tablets; PII = powder for the preparation of a solution for injection or infusion					

LAUER-TAXE® last revised: 15 October 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 need 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.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d

SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient:

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults with transfusion-dependent anaemia associated with β-thalassaemia

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:

Product information for luspatercept (Reblozyl); Reblozyl 25 mg/ 75 mg powder for solution for injection; last revised: June 2023

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 7 March 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 11 May 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 6 VerfO.

By letter dated 15 May 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 11 August 2023, and the written statement procedure was initiated with publication on the G-BA website on 15 August 2023. The deadline for submitting statements was 5 September 2023.

The oral hearing was held on 25 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 24 October 2023, and the proposed resolution was approved.

At its session on 2 November 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	7 March 2023	Determination of the appropriate comparator therapy
Working group Section 35a	20 September 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	25 September 2023	Conduct of the oral hearing
Working group Section 35a	5 October 2023 18 October 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	24 October 2023	Concluding discussion of the draft resolution
Plenum	2 November 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 2 November 2023

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

Prof. Hecken