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: myelodysplastic syndromes with transfusion-dependent anaemia, pretreated)

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 due to myelodysplastic syndromes (MDS) is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) number 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 adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy" in 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 2023.

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:

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 for the treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.

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

Therapeutic indication of the resolution (resolution of 02.11.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy

Appropriate comparator therapy for luspatercept:

- A transfusion therapy on demand with red blood cell concentrates in combination with chelation therapy in accordance with the marketing authorisation

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.

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

on 1 In addition to luspatercept, the active ingredients azacitidine, deferasirox, deferoxamine, epoetin alfa, epoetin zeta, imatinib, lenalidomide as well as red blood cell concentrates are approved for the treatment of transfusion-dependent anaemia due to myelodysplastic syndromes (MDS).

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 present therapeutic indication, there are no resolutions approved by the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V or non-medicinal treatments.

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 (see "Information on Appropriate Comparator Therapy").

Among the approved active ingredients listed under 1.), only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

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

According to the present guidelines, various treatment options are mentioned for the treatment setting defined in this way. These include in particular lenalidomide, hypomethylating agents (such as azacitidine and decitabine) and immunosuppressive therapy with antithymocyte globulin in combination with ciclosporin A. Lenalidomide is specifically recommended for patients with a single deletion on chromosome 5. Treatment with antithymocyte globulin in combination with ciclosporin A, in contrast, is specifically recommended for patients with hypocellular bone marrow. In addition

to these limitations, the above-mentioned treatment options have the development of further haematological disorders (e.g. thrombocytopenia or neutropenia) as a frequent side effect or are not approved for the present treatment setting and are therefore not designated as appropriate comparator therapy.

For patients with transfusion-dependent anaemia due to myelodysplastic syndromes, red blood cell transfusions are regularly used to treat the anaemia. Overall, the evidence for the administration of red blood cell concentrates is very limited and neither an explicit threshold value (e.g. haemoglobin (Hb) value) for use nor a recommended frequency can be derived.

The decision in favour of a red blood cell transfusion is made by the treating doctor based on the patient's clinical picture. Patients are treated with a red blood cell transfusion therapy on demand in combination with chelation therapy to prevent iron overload of the organism, which is used in accordance with the marketing authorisation.

According to the scientific-medical societies, the therapy standard in the treatment of patients in this therapeutic indication is the administration of luspatercept.

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.

Overall, a transfusion therapy on demand with red blood cell concentrates in combination with chelation therapy according to the marketing authorisation is determined to be the appropriate comparator therapy in the present therapeutic indication.

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:

An additional benefit is not proven.

Justification:

For the benefit assessment of the active ingredient luspatercept, the pharmaceutical company submitted results of the pivotal MEDALIST study (ACE-536-MDS-001). This is a double-blind, randomised, controlled, multicentre phase III study.

The MEDALIST study on which the benefit assessment was based enrolled patients with anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS)

according to IPSS-R (International Prognostic Scoring System - revised), with ring sideroblasts and transfusion dependence.

In a 2:1 randomisation, 229 patients were assigned to treatment with luspatercept + best supportive care (BSC) (153 patients) or the control arm with placebo + BSC (76 patients). Randomisation was stratified according to the number of transfusions at baseline (≥ 6 red blood cell concentrate units/ 8 weeks vs < 6 red blood cell concentrate units/ 8 weeks) and the IPSS-R risk score (very low or low vs intermediate) at baseline.

The patients had a mean age of 71 years and had received a median of 6 red blood cell transfusions within the last 8 weeks at baseline.

In both study arms, red blood cell transfusions were permitted at the doctor's discretion in the event of low Hb levels, anaemia-related symptoms or comorbidities. In combination with the administration of red blood cell concentrates, chelation therapy could be used at the doctor's discretion in accordance with the marketing authorisation.

The MEDALIST study is divided into a screening phase, treatment phase (primary and extension phase) and follow-up phase. The primary treatment phase lasted up to 24 weeks, the extension phase of treatment began from week 25 and continued until treatment was discontinued. Long-term follow-up was carried out for up to 3 years after the last administration of the study medication. Following the primary treatment phase (week 25), the clinical benefit of treatment with luspatercept was assessed by the medical staff. If there was no clinical benefit or if the MDS progressed, the administration of the study medication was terminated and the patients were transferred to long-term follow-up. If there was a clinical benefit and no progression of the MDS was detected, the patients entered the extension phase, in which the randomised assignment to treatment and blinding were maintained.

After reviewing the clinical benefit after study week 24, a large number of patients discontinued treatment with the study medication. This occurred more frequently in the placebo arm than in the luspatercept arm. Switching between the treatment arms (cross-over) was not permitted during the course of the study.

Transfusion avoidance (transfusion independence) ≥ 8 weeks (weeks 1 to 24) was the primary endpoint of the MEDALIST study. In addition, overall survival and endpoints in the categories of morbidity (symptomatology, hospitalisation, other endpoints for transfusion avoidance), health-related quality of life and adverse events were collected.

The MEDALIST study was conducted in a total of 65 study sites in Europe and North America between February 2016 and November 2020.

The pharmaceutical company submitted analyses of the final data cut-off of the MEDALIST study from 26.11.2020.

For all endpoints whose duration of observation was linked to the end of treatment (concerns the endpoint categories of morbidity, health-related quality of life and side effects), evaluations up to and including week 24 or week 25 were used for the benefit assessment due to a relevant number of treatment discontinuations after study week 24 in both study arms.

For the mortality endpoint category, overall survival is used on the basis of an time-to-event analysis for the final data cut-off.

Extent and probability of the additional benefit

Mortality

Overall survival

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

There is no statistically significant difference between the treatment arms.

Morbidity

Transfusion avoidance (transfusion independence)

The endpoint of transfusion avoidance is defined as the period without red blood cell concentrate (RBC) transfusions over a certain duration during the course of the study. The pharmaceutical company submitted evaluations on various periods of transfusion avoidance, including transfusion avoidance until the end of the study. Transfusion avoidance ≥ 8 weeks is the primary endpoint of the MEDALIST study.

Patients in the present therapeutic indication require frequent and lifelong RBC transfusions. The required transfusions can lead to increasing iron overload of the organs and subsequent long-term complications despite iron elimination therapy.

In the MEDALIST study, RBC transfusions will be administered at the discretion of the investigator in cases of low Hb levels, symptoms associated with anaemia or comorbidities.

A long-term or sustainable avoidance of transfusions 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 with simultaneous independence from RBC transfusions.

With regard to the evaluations of the different periods of transfusion avoidance, transfusion avoidance over the entire study period would generally be preferable. However, due to the relevant number of treatment discontinuations after the end of the primary treatment phase (week 24), transfusion avoidance of 24 weeks is used as the relevant period in order to be able to assume long-term avoidance of transfusions. Thus, transfusion avoidance ≥ 24 weeks may represent a patient-relevant endpoint in the present therapeutic indication.

With regard to the percentage of patients with transfusion avoidance of ≥ 24 weeks, there is a statistically significant difference between the treatment arms to the advantage of treatment with luspatercept + BSC compared to placebo + BSC. Transfusion avoidance of ≥ 24 weeks was observed in 20 subjects (13.1%) in the intervention arm and in one subject (1.3%) in the control arm.

However, this advantage is not reflected in other endpoints that may in principle be associated with transfusion avoidance. In particular, there was a negative effect on the "physical functioning" subscale of the EORTC QLQ-C30.

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

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

Other endpoints related to the avoidance of transfusions (e.g. reduction in transfusion burden) are not presented in the resolution as these are not patient-relevant per se and the data do not provide any information beyond the data on the endpoint of transfusion avoidance ≥ 24 weeks.

Symptomatology

Disease symptomatology was assessed using the symptom scales of the cancer-specific questionnaire EORTC QLQ-C30.

The pharmaceutical company submitted responder analyses based on a minimum important difference (MID) of 10 points for the percentage of patients with an improvement or deterioration of symptomatology for the primary treatment phase (week 1-24).

For the improvement of symptomatology, there is no statistically significant difference between the study arms.

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

Hospitalisation

The endpoint of hospitalisation was defined as the percentage of patients who were hospitalised due to any cause (total hospitalisation) from randomisation to the time of data analysis.

For the hospitalisation due to any cause, there is no statistically significant difference between the treatment arms.

As this is a multicentre study, it remains unclear whether there are regional differences that could lead to a bias in the number of hospitalisations. The pharmaceutical company does not provide any further information on this. Stratified randomisation at study site or country level was not planned in the MEDALIST study. There are uncertainties regarding the operationalisation of the endpoint due to the absence of information on when admission to a hospital was classified as hospitalisation (e.g. with regard to outpatient, semi-inpatient admission). Furthermore, it cannot be conclusively assessed to what extent events of the endpoint are also collected in the context of serious adverse events and would therefore be considered twice.

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

Quality of life

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

Among other things, the pharmaceutical company submitted responder analyses based on an MID of 10 points on the percentage of patients with an improvement or deterioration in health-related quality of life for the primary treatment phase (week 1 to 24).

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

However, this disadvantage is not reflected in any other subscale of the EORTC QLQ-C30. In the overall assessment, neither an advantage nor a disadvantage of luspatercept + BSC compared to placebo + BSC in the "quality of life" category is derived.

Side effects

Adverse events (AEs) in total

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

Serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3), therapy discontinuation due to AEs

There were no statistically significant differences between the treatment arms for the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs.

Nervous system disorders (severe AEs)

In the system organ class of nervous system disorders, events occurred in eight subjects in the intervention arm (5.2%) compared to none in the control arm. There is a statistically significant difference to the disadvantage of luspatercept.

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

Overall assessment

For the assessment of the additional benefit of luspatercept for the treatment of adults with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy, results are available for the endpoint categories of mortality, morbidity, quality of life and side effects from the MEDALIST study comparing luspatercept + best supportive care (BSC) versus placebo + BSC.

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

In the morbidity endpoint category, luspatercept + BSC showed an advantage in terms of deterioration of symptomatology in the insomnia endpoint and a disadvantage in the fatigue endpoint.

Results on transfusion avoidance are available for the morbidity endpoint category. For patients in the therapeutic indication, long-term or sustainable avoidance of transfusions is a therapeutic goal of high priority, with which anaemia and anaemia-related symptoms can be controlled with simultaneous independence from red blood cell concentrate transfusions. For the present assessment, transfusion avoidance of ≥ 24 weeks is regarded as the relevant period in order to be able to assume a long-term avoidance of transfusions.

With regard to the percentage of patients with transfusion avoidance of ≥ 24 weeks, there was a statistically significant difference to the advantage of treatment with luspatercept + BSC compared to placebo + BSC. However, this advantage is not reflected in other endpoints that may in principle be associated with transfusion avoidance. In particular, there was a negative effect on the "physical functioning" subscale of the EORTC QLQ-C30. Overall, based on these results for transfusion avoidance of ≥ 24 weeks, a statistically significant difference to the advantage of treatment with luspatercept + BSC can therefore be determined with regard to long-term avoidance of transfusions.

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

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

In detail, there is a disadvantage in the severe AEs (CTCAE grade ≥ 3) of the system organ class "nervous system disorders".

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

In the overall assessment of the available results on the patient-relevant endpoints, an additional benefit of luspatercept over the appropriate comparator therapy is not proven.

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the new 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 approved for the treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.

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

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

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

For the results on transfusion avoidance of ≥ 24 weeks on which the assessment is based, a difference to the advantage of treatment with luspatercept + BSC can be identified with regard to long-term avoidance of transfusions. However, this advantage is not reflected in other endpoints that may in principle be associated with transfusion avoidance. In particular, there is a negative effect on physical functioning. However, taking into account the results on the other endpoints, the extent of this difference is assessed as too small in the present case for this result to justify the derivation of an additional benefit at endpoint level in the overall assessment.

In terms of the side effects, there is no relevant difference for the benefit assessment between the treatment arms.

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

In the overall assessment of the available results on the patient-relevant endpoints, an additional benefit of luspatercept over the appropriate comparator therapy is not proven.

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 information is subject to uncertainty. However, it is preferable to the information provided in the previous benefit assessment of luspatercept in the same therapeutic indication due to updates and corrections.

Corrections relate in particular to the calculation of the 5-year prevalence of MDS, taking into account the incidence of 4,090 patients with MDS and a correct linking of survival probabilities with predicted incidences for patients with very low risk.

Irrespective of this, the uncertainties identified in the previous procedure continue to exist.

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: 29 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 specialists in internal medicine, haematology and oncology experienced in the treatment of patients with myelodysplastic syndromes with transfusion-dependent anaemia.

In accordance with the requirements of the EMA regarding additional risk minimisation measures, the pharmaceutical company must provide all healthcare professionals who may use luspatercept with an information package. The information package contains information on where to get the current product information as well as a checklist for healthcare professionals to use before starting any treatment, at each administration and then at regular intervals during follow-up visits. The information package also contains a patient card, which healthcare professionals must hand over to women in reproductive age at the start of treatment. Treatment with luspatercept must not be started if a woman is pregnant. Luspatercept is contraindicated during pregnancy. Patients must use highly effective contraceptives during treatment with luspatercept. If a patient becomes pregnant, luspatercept should be discontinued. Treatment with luspatercept should be discontinued if patients do not 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.

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				
Transfusion therapy 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:

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

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.

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.

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).

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	1 x 0.8 mg/kg – 1 x 1.75 mg/kg	61.6 mg – 134.8 mg	1 x 75 mg – 2 x 75 mg	17.4	17.4 x 75 mg – 34.8 x 75 mg
Appropriate comparator therapy					
Transfusion therapy on demand with red blood cell concentrates		Different from patient to patient			
Chelation therapy					
Deferasirox	7 mg/kg – 28 mg/kg	539 mg – 2,156 mg	3 x 180 mg – 2 x 900 mg + 1 x 360 mg	365.0	Different from patient to patient
Deferoxamine	20 mg/kg – 60 mg/kg	1540 mg – 4620 mg	1 x 2.0 mg – 2 x 2.0 g + 2 x 0.5 g	365.0	Different from patient to patient

Costs:

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.

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.

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, 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
Deferasirox 900 mg	30 FCT	€ 450.03	€ 2.00	€ 20.82	€ 427.21
Deferoxamine 2.0 g	10 PII	€ 588.86	€ 2.00	€ 27.41	€ 559.45
Deferoxamine 0.5 g	10 PII	€ 155.71	€ 2.00	€ 6.85	€ 146.86
Abbreviations: FCT = film-coated tablets; PII = powder for the preparation of a solution for injection or infusion; PSI = powder for solution for injection					

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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.

In the case of information on "determined" or "undetermined" combinations, the assessed medicinal product can be used in a combination therapy according to this information on the basis of the marketing authorisation under Medicinal Products Act. For the designation, the G-BA, within the scope of its legislative discretion, uses the constellation of a "determined" or an "undetermined" combination as a justifiable interpretation variant.

If a designation as a so-called determined or as a so-called undetermined combination is omitted due to the lack of information on a combination therapy in the product information of the assessed medicinal product, the non-designation in the resolution according to Section 35a, paragraph 3, sentence 1 SGB V does not affect the possibility that the assessed medicinal product can be used in an open-label combination under marketing authorisation regulations.

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 SGBV.

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 due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy

No medicinal product with new active ingredients that can be used in a combination therapy and 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: August 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 the AM-RL

Berlin, 2 November 2023

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

Prof. Hecken