Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V) Luspatercept (new therapeutic indication: myelodysplastic syndromes with transfusion-dependent anaemia, non-pretreated, and without ring sideroblasts, pretreated)

of 17 October 2024

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

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

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

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

2. Key points of the resolution

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

Reblozyl is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

Within the previously approved therapeutic indication, the sales volume of luspatercept with the statutory health insurance at pharmacy sales prices, including value-added tax exceeded € 30 million. Evidence must therefore be provided for luspatercept in accordance with Section 5, paragraph 1 through 6 VerfO, and the additional benefit compared with the appropriate comparator therapy must be demonstrated.

A benefit assessment of luspatercept has already been conducted according to Section 35 a SGB V in the therapeutic indication: "Adults [...] with ring sideroblasts [...] who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy" and in this regard an amendment to Annex XII was made by resolution of 2 November 2023 (benefit assessment procedure for the active ingredient luspatercept (reassessment of orphan drug > EUR 30 million: myelodysplastic syndrome with transfusion-dependent anaemia, pretreated)). This therapeutic indication is not covered by the present benefit assessment. The present benefit assessment refers exclusively to those indications that have been added as a result of the marketing authorisation of the new therapeutic indication.

On 27 March 2024, luspatercept received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 29 April 2024, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, No.2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient luspatercept with the new therapeutic indications "Reblozyl is indicated in adults for the treatment of transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS)[1], who have not received previous erythropoietin (EPO)-based therapy and are eligible for it as well as in adults for the treatment of transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) without ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin (EPO)-based therapy." in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 August 2024 on the G-BA website (www.g-ba.de), therefore initiating the written statement procedure. In addition, an oral hearing was held.

Based on 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, the G-BA decided on the question on whether an additional benefit of luspatercept compared with the appropriate comparator therapy could be determined – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V. In order to determine the extent of the additional benefit, the G-BA has evaluated

1 Referred to as "myelodysplastic neoplasms" according to the WHO classification 2022, abbreviated also as MDS. In ICD-10 coding, the term "myelodysplastic syndromes" is also used, which is to be regarded as a synonym for "myelodysplastic neoplasms".

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 IQWiG[2] according to the General Methods was not used in the benefit assessment of luspatercept – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V.

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 in adults for the treatment of transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS)

Therapeutic indication of the resolution (resolution of 17.10.2024):

Reblozyl is indicated in adults for the treatment of transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), who have not received previous erythropoietin (EPO)-based therapy and are eligible for it.

Reblozyl is indicated in adult patients for the treatment of transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) without ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin -based therapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), who have not yet received any erythropoiesis-stimulating agents (ESA)-based therapy and are eligible for it; and adults with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS without ring sideroblasts, who had an unsatisfactory response to or are ineligible for ESA-based therapy.

Appropriate comparator therapy for luspatercept:

Patient-individual therapy with selection of:

2 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

- Erythropoiesis-stimulating agents (erythropoietin alfa/ erythropoietin zeta; only in patients with an erythropoietin serum level of < 200 U/L)
- A transfusion therapy on demand with red blood cell (RBC) concentrates in combination with chelation therapy
- Lenalidomide (only for patients with an isolated 5q deletion if other treatment options are insufficient or inappropriate)

taking into account the erythropoietin serum level, cytogenetics and previous therapy

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 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 principle, the erythropoiesis-stimulating agents epoetin alfa and zeta, red blood cell concentrates as well as imatinib, azacitidine and lenalidomide are approved for the therapy of myelodysplastic syndrome or anaemia due to very low, low and intermediate-risk myelodysplastic syndrome (MDS). The marketing authorisations are limited to specific treatment settings. The iron chelators deferasirox and deferoxamine are approved for the treatment of transfusion-related iron overload.

on 2. Allogeneic stem cell transplantation is considered as non-medicinal treatment in the indication of MDS. However, for the present treatment setting, it is assumed that the patients are ineligible for an allogeneic stem cell transplantation at the time of therapy.

on 3. There is a resolution on luspatercept dated 2 November 2023 with the therapeutic indication: "Luspatercept 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.".

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"). A written statement from the German Society for Haematology and Medical Oncology (DGHO) is available.

The guidelines identified for this therapeutic indication as well as the written statement of the DGHO provide various therapy recommendations, depending on the subtype of MDS.

In the present guidelines and the written statement of the DGHO, therapy with erythropoiesis-stimulating agents is recommended for patients with a serum epoetin level (sEPO) < 200 U/L. At the same time, a possible response in patients with a sEPO of up to 500 U/L is mentioned. However, epoetin alfa/ epoetin zeta are only approved for the treatment of patients with a sEPO < 200 U/L in this therapeutic indication.

The pivotal study on epoetin alfa, which enrolled patients with a sEPO of up to 500 U/L, showed that all patients with a response had a sEPO < 200 U/L[3]. It can therefore not be concluded that the off-label use of epoetin alfa in patients with sEPO between 200 and 500 U/L according to the generally recognised state of medical knowledge is to be generally preferred to the medicinal products previously approved in the therapeutic indication or, for relevant patient groups or indication areas, to the medicinal products previously approved in the therapeutic indication. From the G-BA's point of view, the statements in the guidelines for use in patients with sEPO between 200 and 500 U/L do not represent a clear recommendation, but merely describe the possibility of a response. Therefore, erythropoiesis-stimulating agents are only determined as appropriate comparator therapy for patients with a sEPO < 200 U/L as part of the patient-individual therapy in accordance with the marketing authorisation.

According to the Pharmaceuticals Directive (Annex VIIa: biologics and biosimilars, last revised 17 February 2023), medicinal products with the active ingredient variant epoetin zeta are designated as bioengineered biological medicinal products essentially identical to the original/reference medicinal product with the active ingredient variant epoetin alfa.

Furthermore, the present guidelines and the written statement of the DGHO recommend lenalidomide for patients with a del(5q) mutation (MDS del(5q)). Patients with MDS with a del(5q) mutation represent a distinct subentity of MDS according to the WHO classification[4] and can be clearly differentiated diagnostically. This patient group is formally covered by the planned therapeutic indication, which is generally aimed at the treatment of transfusion-dependent anaemia in MDS. Therefore, lenalidomide is determined as a component of a patient-individual therapy for the appropriate comparator therapy. According to the available evidence, only patients who show an isolated 5q deletion and for whom other treatment options are insufficient or inappropriate should be treated with lenalidomide.

3 Fenaux et al., A phase 3 randomised, placebo-controlled study assessing the efficacy and safety of epoetin-α in anaemic patients with low-risk MDS. Leukaemia. 2018 Dec;32(12):2648-2658.

4 Arber et al.; International Consensus Classification of Myeloid Neoplasms and Acute Leukaemias: integrating morphologic, clinical, and genomic data; *Blood* (2022) 140 (11): 1200–1228.

In addition to systemic therapy with erythropoiesis-stimulating agents or lenalidomide, transfusion therapy on demand with red blood cell concentrates in combination with chelation therapy may be indicated as part of patient-individual therapy due to transfusion dependence. Chelation therapy is used to prevent a threatening iron overload of the organism. In doing so, deferasirox is used for the treatment of chronic, transfusion-related iron overload in adults, children and adolescents aged 2 years and older when deferoxamine therapy is contraindicated or inappropriate.

It is assumed that the transfusion of red blood cell concentrates, if necessary in combination with iron chelation therapy and other supportive measures (including platelet concentrates, infection management) may be carried out on demand in both study arms.

In addition, it should be possible to adjust the study medication/ concomitant medication to the respective needs of the patient in both study arms. In the process, therapy adjustment can include both dosage adjustments and change of therapy in the case of deterioration of existing symptoms.

This means that patients have various treatment options available to them. The therapy option is selected on the basis of various patient-individual factors, including in particular the erythropoietin serum level, cytogenetics and previous therapy.

The G-BA therefore determines a patient-individual therapy with selection of erythropoiesis-stimulating agents, transfusion therapy on demand with red blood cell concentrates in combination with chelation therapy and lenalidomide, taking into account the erythropoietin serum level, cytogenetics and previous therapy.

For patients who show an inadequate response to epoetin after 16 weeks, the use of epoetin in combination with granulocyte-colony stimulating factor (G-CSF) is mentioned as an additional therapy option in the present indication according to the available evidence. G-CSF is not approved for this therapeutic indication. It cannot be inferred from the available evidence that the off-label use of G-CSF according to the generally recognised state of medical knowledge would generally have to be preferred to the medicinal products previously approved in the therapeutic indication or, for relevant patient groups or indication areas, to the medicinal products previously approved in the therapeutic indication. G-CSF is therefore not determined as an appropriate comparator therapy.

For the active ingredient imatinib, which is approved for adults with myelodysplastic/ myeloproliferative diseases (MDS/MPD) in conjunction with gene rearrangements of the PDGF receptor (platelet-derived growth factor), the present guidelines and the written statement of the DGHO do not contain any therapy recommendations. Azacitidine is approved only for adults with intermediate risk 2 and high risk according to the International Prognostic Scoring System (IPSS), thus not representing a suitable

therapy option for the present patient population. Therefore, the active ingredients imatinib and azacitidine are not considered to be part of the patient-individual therapy.

Information on the implementation of patient-individual therapy:

With regard to the implementation of patient-individual therapy in a direct comparator study, it is expected that investigators will have a choice of several treatment options that will allow a patient-individual treatment decision to be made, taking into account the criteria mentioned (multi-comparator study). The selection and, if necessary, limitation of treatment options must be justified. The patient-individual treatment decision with regard to the comparator therapy should be made before group allocation (e.g. randomisation). This does not include necessary therapy adjustments during the course of the study (e.g. due to the onset of symptomatology or similar). The choice of the comparator used must be justified in the dossier.

If only a single comparator study is presented, the extent to which conclusions can be drawn about a sub-population will be examined as part of the benefit assessment.

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:

a) Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), who have not yet received any erythropoiesis-stimulating agents (ESA)-based therapy and are eligible for it; and adults with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS without ring sideroblasts, who had an unsatisfactory response to or are ineligible for ESA-based therapy.

   a1) Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), who have not yet received any erythropoiesis-stimulating agents (ESA)-based therapy and are eligible for it

   Hint for a minor additional benefit

   a2) Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS without ring sideroblasts, who had an unsatisfactory response to or are ineligible for ESA-based therapy

   An additional benefit is not proven.

Justification:

For the benefit assessment of the active ingredient luspatercept, the pharmaceutical company submitted results of the pivotal COMMANDS study. This is an open-label, randomised, controlled, multicentre phase III study.

The COMMANDS study on which the benefit assessment was based enrolled patients with transfusion-dependent anaemia due to very low, low or intermediate risk MDS according to IPSS-R (International Prognostic Scoring System - revised) and serum erythropoietin levels (sEPO) < 500 U/L who were therapy naive to erythropoietin-based therapies. Transfusion dependence was defined as a requirement of 2 to 6 red blood cell concentrate units/ 8 weeks, confirmed over a period of at least 8 weeks immediately prior to randomisation. Patients with MDS del(5q) (deletion of the q-arm of chromosome 5) were excluded.

363 patients were enrolled in a 1:1 randomisation, stratified according to the number of transfusions at baseline (≥ 4 red blood cell concentrate units/ 8 weeks vs < 4 red blood cell concentrate units/ 8 weeks), the ring sideroblast status and the sEPO level (≤ 200 U/L vs > 200 U/L) at the start of the study.

In the annex to the dossier, the pharmaceutical company presented evaluations of the sub-population with sEPO < 200 U/L, which is used as the relevant sub-population for the present benefit assessment, with 145 patients in the luspatercept arm and 144 patients in the epoetin alfa arm (see comments below on the *relevant subpopulation*).

The patients in the relevant sub-population had a mean age of 74 years. Patients who reached the endpoint of transfusion independence received a median of two red blood cell transfusions within the last eight weeks at baseline. In both study arms, red blood cell transfusions were permitted at the doctor's discretion in the event of low haemoglobin (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 COMMANDS study is divided into a screening phase, treatment phase (primary and further treatment phase) and long-term follow-up phase. The primary treatment phase lasted 24 weeks, the further treatment phase began from week 25, provided there was a clinical benefit (reduction in the transfusion burden) and no disease progression. If no clinical benefit was observed after week 24, the MDS progressed or treatment was discontinued during the further treatment phase, the administration of the study medication was terminated and the patients were transferred to the long-term follow-up study. The long-term follow-up study was conducted for up to 3 years after the last administration of study medication or 5 years after the first dose of study medication (whichever occurred last). Switching from epoetin alfa to luspatercept was not permitted during the treatment phase.

Transfusion independence for 12 weeks (weeks 1 to 24) with a simultaneous mean increase in Hb values by ≥ 1.5 g/dL compared to the start of the study was the primary endpoint of the COMMANDS study. In addition, overall survival and endpoints in the categories of morbidity

(symptomatology, other endpoints for transfusion independence), health-related quality of life and adverse events were collected.

The ongoing COMMANDS study launched in January 2019 is being conducted in a total of 144 study sites in Europe, Asia, Australia and North America. The pharmaceutical company submitted evaluations of the primary data cut-off from 31.03.2023 and the follow-up analysis of 22.09.2023 (fourth data cut-off).

For the endpoints of symptomatology, health-related quality of life and side effects, the primary data cut-off after the primary treatment phase (weeks 1 – 24) for the relevant sub-population was used for the benefit assessment. For the endpoints of overall survival and transfusion independence for 24 weeks, the fourth data cut-off for the relevant sub-population was used for the benefit assessment.

Relevant sub-population:

In the dossier, the pharmaceutical company presented evaluations of the total COMMANDS study population, which had sEPO < 500 U/L at the start of the study. In addition, the pharmaceutical company demonstrated an effect modification by ring sideroblast status for the endpoint of transfusion independence for 24 weeks in the total population. In the annex to the dossier, the pharmaceutical company presented results for the sub-population with sEPO levels < 200 U/L.

In the present benefit assessment, the sub-population with sEPO levels < 200 U/L is considered relevant, as epoetin alfa is approved up to sEPO < 200 U/L and a unanimous recommendation for off-label use is not evident from the available evidence (see comments on the appropriate comparator therapy). In the relevant sub-population, there was no significant effect modification by ring sideroblast status, so there is no further subdivision of the patient population.

Extent and probability of the additional benefit

Analysis across endpoints

The relevant sub-population with sEPO < 200 U/L was used in the present benefit assessment. As only ESA-therapy naive patients were enrolled in the study presented, the following comments refer to this patient group:

a1) Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), who have not yet received any erythropoiesis-stimulating agents (ESA)-based therapy and are eligible for it

Mortality

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

There was no statistically significant difference between the treatment arms.

Morbidity

Transfusion independence

The endpoint of transfusion independence is defined as the period without red blood cell concentrate (RBC) transfusions over a certain duration during the course of the study. Transfusion independence for 12 weeks is the primary endpoint of the COMMANDS study, with a mean increase in Hb value by ≥ 1.5 g/dL. The pharmaceutical company submitted evaluations of various periods of transfusion independence, including transfusion independence until the end of the primary treatment phase (up to week 24).

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.

A long-term or sustainable avoidance of transfusions 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 independence, a transfusion independence for 24 weeks is used as the relevant period for assuming long-term avoidance of transfusions. Thus, transfusion independence for 24 weeks may represent a patient-relevant endpoint in the present therapeutic indication.

No valid interpretation of evaluation periods beyond the primary treatment phase (weeks 1 – 24) is possible, as the treatment and observation periods differ.

With regard to the percentage of patients with transfusion independence for 24 weeks, there is a statistically significant difference between the treatment arms to the advantage of luspatercept compared to epoetin alfa. A transfusion independence for 24 weeks was observed in 79 subjects (54.5%) in the intervention arm and in 55 subjects (38.2%) in the control arm (relative risk = 1.41; 95% confidence interval = [1.10; 1.80]; p value = 0.007; absolute difference = +16.3%).

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

EORTC QLQ-C30 - symptom scales

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

The pharmaceutical company submitted continuous analyses using a mixed model for repeated measures (MMRM) for the change in mean values over the course of the study for the primary treatment phase (weeks 1-24).

For symptomatology, there was no statistically significant difference between the study arms.

Quality of life

EORTC QLQ-C30 - functional scales

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.

The pharmaceutical company submitted continuous analyses using a mixed model for repeated measures (MMRM) for the change in mean values over the course of the study for the primary treatment phase (weeks 1-24).

There was no statistically significant difference between the study arms for each one of the scales of health-related quality of life of the EORTC QLQ-C30.

FACT-An

Furthermore, health-related quality of life was assessed using the FACT-An (Functional Assessment of Cancer Therapy - Anaemia) questionnaire, which is specific to cancer patients with anaemia and fatigue.

The pharmaceutical company submitted continuous analyses using a mixed model for repeated measures (MMRM) for the change in mean values over the course of the study for the primary treatment phase (weeks 1-24).

There were no statistically significant differences between the study arms.

Side effects

Adverse events (AEs) in total

AEs occurred in 90.3% of study participants in the luspatercept arm and 81.8% in the epoetin alfa arm. The results were only presented additionally.

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

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

Eye disorders (SOC, AEs)

For the specific AE of the system organ class (SOC) eye disorders, there was a 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 identified for luspatercept compared to epoetin alfa.

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), who have not yet received any erythropoiesis-stimulating agents (ESA)-based therapy and are eligible for it, results are available for the endpoint categories of mortality, morbidity, quality of life and side effects from the COMMANDS study comparing luspatercept versus epoetin alfa.

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

Results on transfusion independence 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 independence for 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 independence for 24 weeks, there was a statistically significant advantage of luspatercept compared to epoetin alfa.

In the endpoints on symptomatology (EORTC QLQ-C30), there was neither an advantage nor a disadvantage of luspatercept overall.

There were no significant differences between the study arms in the endpoints on health-related quality of life (EORTC QLQ-C30 and FACT-An).

In terms of side effects, neither an advantage nor a disadvantage of luspatercept compared to epoetin alfa was found in the overall assessment.

In detail, there was a disadvantage in the AEs of the system organ class "eye disorders".

In the overall assessment of the available results on the patient-relevant endpoints, a minor additional benefit of luspatercept compared with epoetin alfa was found due to the advantage in the "transfusion independence" endpoint.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomised, open-label, controlled phase III COMMANDS study.

At the study level, the risk of bias is considered low.

The risk of bias at endpoint level is classified as low for overall survival, SAEs, severe AEs and thromboembolic events (severe AEs) and as high for the other endpoints. In the endpoint categories of morbidity and health-related quality of life as well as in some endpoints on side effects, the lack of blinding leads to a high risk of bias. For the endpoint of transfusion independence for 24 weeks, the risk of bias is classified as high due to the lack of blinding and the subjective decision on discontinuation (subjective decision to perform a transfusion).

In summary, the G-BA deduces a hint for the identified additional benefit with regard to the reliability of data (probability of additional benefit).

a2) Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS without ring sideroblasts, who had an unsatisfactory response to or are ineligible for ESA-based therapy

An additional benefit is not proven.

Justification:

The COMMANDS study is unsuitable for deriving the additional benefit, as only ESA-therapy-naive patients were enrolled in this study. Thus, an additional benefit for adults who had an unsatisfactory response to or are ineligible for ESA-based therapy is not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the medicinal product Reblozyl with the active ingredient luspatercept. Reblozyl was approved as an orphan drug. Because of exceeding the EUR 30 million turnover limit for luspatercept in accordance with Section 35a, para. 1, sentence 12 SGB V, a regular assessment for the new therapeutic indication is carried out accordingly. Reblozyl is indicated in adults for the treatment of transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS). The present benefit assessment relates exclusively to the two patient groups a1) and a2) of the resolution and not to the entire therapeutic indication according to the marketing authorisation, as an assessment already exists for a patient group covered by the marketing authorisation (resolution of 2 November 2023).

Due to the fact that no data were available for a relevant sub-population in the present therapeutic indication, the assessment is performed separately for two patient groups, according to the pretreatment with erythropoiesis-stimulating agents (ESA) or the suitability of the patients for ESA:

a1) Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), who have not yet received any erythropoiesis-stimulating agents (ESA)-based therapy and are eligible for it

a2) Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS without ring sideroblasts, who had an unsatisfactory response to or are ineligible for ESA-based therapy

The appropriate comparator therapy comprises a patient-individual therapy with selection of several therapy options, including erythropoietin alfa (only for patients with an erythropoietin serum level < 200 U/L), taking into account the erythropoietin serum level, cytogenetics and previous therapy.

On patient group a1)

The results of the open-label, randomised, controlled phase III COMMANDS study, in which luspatercept was compared with epoetin alfa, are available for the benefit assessment. In accordance with the determination of the appropriate comparator therapy, evaluations of the relevant sub-population with sEPO < 200 U/L were used for the benefit assessment.

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

In the endpoint category of morbidity, the symptom scales of the EORTC QLQ-C30 showed neither an advantage nor a disadvantage of luspatercept.

For the results on transfusion independence for 24 weeks on which the assessment is based, a difference to the advantage of treatment with luspatercept can be identified with regard to long-term avoidance of transfusions.

There were no differences between the study arms in terms of health-related quality of life, measured using the EORTC QLQ-C30 functional scales and the FACT-An.

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

In summary, a minor additional benefit of luspatercept was identified. The lack of blinding of the study results in uncertainties in the reliability of data, which is why a hint results.

Overall, this results in a hint for a minor additional benefit of luspatercept.

On patient group a2)

Since no data were presented for adults with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS without ring sideroblasts, who had an unsatisfactory response to or are ineligible for ESA-based therapy, an additional benefit for patient group a2) 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. For calculating the number of patients, the pharmaceutical company uses percentages of adults with < 5% blasts in the bone marrow and adults without unclassifiable MDS (MDS-U) and without MDS with isolated deletion on chromosome 5q (MDS del(5q)), as these subjects were excluded from the COMMANDS study. The G-BA considered this procedure to be inappropriate as these subjects are covered by the therapeutic indication according to the marketing authorisation.

In the derivation for this resolution, patients with ≥ 5% blasts in the bone marrow, MDS-U and MDS del(5q) are therefore included in the patient population number.

The following percentages are assumed for a best possible estimate of the target population:

- 5-year prevalence in 2018: 14,030 – 20,014
- Percentage of adults: 100%
- Percentage of subjects with low-risk MDS (very low, low or intermediate risk according to IPSS-R): 56.4%
- Percentage of subjects with ring sideroblasts 23.2%
- Percentage of subjects without ring sideroblasts 76.8%
- Percentage of subjects with ring sideroblasts and transfusion-dependent anaemia: 88.0%, of which ESA-naive or eligible: 58.9%
- Percentage of subjects without ring sideroblasts and transfusion-dependent anaemia: 77.3%, of which ESA-naive or eligible: 76.2%
- Percentage of subjects without ring sideroblasts and transfusion-dependent anaemia: 77.3%, of which ESA-pretreated with unsatisfactory response or ineligible: 23.8%
- Percentage of SHI-insured subjects: 87.8%

This results in around 3,980 to 5,680 subjects for sub-population a1) and around 980 to 1,400 subjects for sub-population a2).

The number of patients in the SHI target population is subject to uncertainty due to the following aspects:

- Subjects who fell ill before 2013 and were still alive in 2018 were not taken into account in the determination of prevalence.
- In the German MDS registry used, information on risk stratification according to IPSS-R was available for less than half of the adults with MDS. In addition, the transfer of the risk distribution for low-risk MDS from prevalence to incidence leads to uncertainties, as a low risk according to IPSS-R is associated with a more favourable prognosis for survival. Thus, a reference to incidence could result in a percentage of patients at low risk according to the IPSS-R different from a reference to prevalence.
- When determining the upper limit based on a care structure data analysis, it is unclear whether patients were assessed more than once.
- The 5-year prevalence was derived for 2018. No extrapolation was made for 2024. In their written statement, the pharmaceutical company argued that the transfer of the incidence increase rate from myeloid leukaemia to MDS already leads to uncertainty and therefore no extrapolation to 2024 was made. This reasoning is followed, which is why it is not extrapolated to 2024 here.

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: 12 June 2024):

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.

Patients with an isolated deletion on chromosome 5q (MDS del(5q)) were excluded from the COMMANDS study. Accordingly, luspatercept was not investigated in this patient group.

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, including no increase in initial haemoglobin value, 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 September 2024).

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.

From the substance class of erythropoiesis-stimulating agents (ESA), the following active ingredients are available for the treatment of transfusion-dependent anaemia due to

myelodysplastic syndromes (MDS): epoetin alfa and epoetin zeta. The erythropoiesis-stimulating agents are grouped together in the reference price group "Anti-anaemic preparations, other, group 1" in level 2. By resolution of the G-BA on Annex VIIa (biologics and biosimilars) - first version of 19 November 2021, medicinal products with the active ingredient variant epoetin zeta are designated as essentially identical bioengineered biological medicinal products to the original/reference medicinal product with the active ingredient variant epoetin alfa.

Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), who have not yet received any ESA-based therapy and are eligible for it; and adults with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS without ring sideroblasts, who had an unsatisfactory response to or are ineligible for ESA-based therapy.

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	Continuously, every 21 days	17.4	1	17.4
Appropriate comparator therapy				
Erythropoiesis-stimulating agents[5]				
Erythropoietin alfa	Continuously, 1 x every 7 days	52.1	1	52.1
Transfusion therapy with red blood cell (RBC) concentrates in combination with chelation therapy				
Transfusion therapy on demand with red blood cell concentrates	Different from patient to patient			
Deferasirox	Different from patient to patient			
Deferoxamine	Different from patient to patient			

5 Erythropoietin alfa is shown as a representative

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Lenalidomide				
Lenalidomide	Day 1 to 21: 28-day cycle	13.0	21	273.0

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 co-morbidities) 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.

For dosages depending on body weight (BW), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population"[6] were used as a basis (average body weight: 77.7 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 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 mg/kg BW = 62.2 mg – 1.75 mg/kg BW = 136 mg	62.2 mg – 136 mg	1 x 75 mg – 2 x 75 mg	17.4	17.4 x 75 mg – 34.8 x 75 mg

6 Federal health reporting. Average body measurements of the population (2021, both sexes, 15 years and older), 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
Appropriate comparator therapy					
Erythropoiesis-stimulating agents					
Erythropoietin alfa	450 I.U./kg BW = 34,395 I.U. – 80,000 I.U.	34,395 I.U. – 80,000 I.U.	1 x 40,000 I.U. – 2 x 40,000 I.U.	52.1	52.1 x 40,000 I.U. – 104.2 x 40,000 I.U.
Transfusion therapy with red blood cell (RBC) concentrates in combination with chelation therapy					
Transfusion therapy on demand with red blood cell concentrates	Different from patient to patient				
Deferasirox	7 mg/kg BW = 543.9 mg - 28 mg/kg BW = 2175.6 mg	543 mg – 2,175 mg	3 x 180 mg – 2 x 900 mg + 1 x 360 mg	Different from patient to patient	
Deferoxamine	20 mg/kg BW = 1,554 mg – 60 mg/kg BW = 4,662 mg	1,554 mg – 4,662 mg	3 x 500 mg – 2 x 2 g + 1 x 500 mg	Different from patient to patient	
Lenalidomide					
Lenalidomide	10 mg	10 mg	1 x 10 mg	273.0	273.0 x 10 mg

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 reference prices 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 75 mg	1 PSI	€ 2,865.76	€ 2.00	€ 160.37	€ 2,703.39
Medicinal product to be assessed					
Erythropoiesis-stimulating agents					
Epoetin alfa 40,000 I.U.[7]	6 PS	€ 1,962.14	€ 2.00	€ 155.38	€ 1,804.76
Transfusion therapy with red blood cell (RBC) concentrates in combination with chelation therapy					
Transfusion therapy on demand with red blood cell (RBC) concentrates	Not calculable				
Deferasirox 180 mg	90 FCT	€ 47.97	€ 2.00	€ 1.74	€ 44.23
Deferasirox 360 mg	90 FCT	€ 123.83	€ 2.00	€ 5.34	€ 116.49
Deferasirox 900 mg	30 FCT	€ 450.03	€ 2.00	€ 20.82	€ 427.21
Deferoxamine 500 mg	10 PII	€ 155.71	€ 2.00	€ 6.85	€ 146.86
Deferoxamine 2 g	10 PII	€ 588.86	€ 2.00	€ 27.41	€ 559.45
Lenalidomide					
Lenalidomide 10 mg[7]	63 HC	€ 117.32	€ 2.00	€ 8.38	€ 106.94
Abbreviations: PS = prefilled syringes; FCT = film-coated tablets; HC = hard capsules; PSI = powder for solution for injection; PSS = powder and solvent for solution for injection; PII = powder for the preparation of a solution for injection or infusion					

LAUER-TAXE® last revised: 15 September 2024

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.

[7] Fixed reimbursement rate

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 1.10.2009 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 Hilfstaxe in its currently valid version, surcharges for the production of parenteral preparations containing cytostatic agents amount to a maximum of € 100 per ready-to-apply preparation. 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 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 requirements 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:

a) Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), who have not yet received any erythropoiesis-stimulating agents (ESA)-based therapy and are eligible for it; and adults with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS without ring sideroblasts, who had an unsatisfactory response to or are ineligible for ESA-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: March 2024

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 9 January 2024, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 29 April 2024, the pharmaceutical company submitted a dossier for the benefit assessment of luspatercept to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 30 April 2024 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 30 July 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 August 2024. The deadline for submitting statements was 22 August 2024.

The oral hearing was held on 9 September 2024.

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 8 October 2024, and the proposed draft resolution was approved.

At its session on 17 October 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	9 January 2024	Determination of the appropriate comparator therapy
Working group Section 35a	3 September 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	9 September 2024	Conduct of the oral hearing
Working group Section 35a	17 September 2024 30 September 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	8 October 2024	Concluding discussion of the draft resolution
Plenum	17 October 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 17 October 2024

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

Prof. Hecken