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)
Vadadustat (symptomatic anaemia in dialysis-dependent chronic kidney disease)

of 22 November 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 relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient vadadustat on 1 June 2024 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 29 May 2024.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 September 2024 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 vadadustat compared with the appropriate comparator therapy could be determined on the basis of the dossier of the

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

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 Vadadustat (Vafseo) in accordance with the product information

Vafseo is indicated for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis.

Therapeutic indication of the resolution (resolution of 22.11.2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with symptomatic anaemia associated with chronic kidney disease (CKD) on chronic maintenance dialysis

Appropriate comparator therapy for vadadustat:

Darbepoetin alfa or epoetin alfa or epoetin beta or epoetin theta or epoetin zeta or methoxy polyethylene glycol epoetin beta

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.

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

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

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

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

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

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

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

On 1. In addition to vadadustat, the HIF prolyl hydroxylase inhibitor roxadustat and the following erythropoiesis-stimulating agents (ESA) are approved for adults with symptomatic anaemia associated with chronic kidney disease: Darbepoetin alfa, epoetin alfa, epoetin beta, epoetin theta, epoetin zeta, methoxy PEG epoetin beta.

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.

On 2. Red blood cell transfusion is considered a non-medicinal treatment option that can be covered by the statutory health insurance in Germany.

On 3. There are several resolutions of the G-BA on the therapeutic indication and the active ingredients used for it. Annex I to the Medicinal Products Guideline (AM-RL) regulates the prescribability of iron (II) compounds as well as water-soluble vitamins in parts of the therapeutic indication under numbers 17, 43 and 44. In Annex III to the AM-RL, number 8 excludes the prescription of antianaemic combinations. Annex IV contains relevant therapeutic information on erythropoiesis-stimulating agents for the treatment of symptomatic renal anaemia.

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.

For the therapeutic indication of symptomatic anaemia associated with chronic kidney disease, a resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient roxadustat is available (resolution of 3 March 2022).

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

The guidelines unanimously recommend treatment with an erythropoiesis-stimulating agent in the present treatment setting. Within this product class, all approved options (darbepoetin alfa, epoetin alfa, epoetin beta, epoetin theta, epoetin zeta, methoxy PEG epoetin beta) are considered equally appropriate. In contrast, treatment with red blood cell transfusions is only recommended as a secondary option due to possible alloimmunisation and the resulting potential complications in the event of a subsequent kidney transplant.

No additional benefit was identified by the G-BA for the active ingredient roxadustat in adult patients with symptomatic anaemia associated with chronic kidney disease, as no suitable data were available for a comparison with the appropriate comparator therapy. In addition, roxadustat is a comparatively new therapy option whose significance cannot yet be conclusively assessed. Therefore, the active ingredient roxadustat is not determined to be appropriate comparator therapy for the present patient group.

In the overall assessment, the G-BA comes to the conclusion that an erythropoiesis-stimulating agent (darbepoetin alfa or epoetin alfa or epoetin beta or epoetin theta or epoetin zeta or methoxy PEG epoetin beta) represents the appropriate comparator therapy in the present therapeutic indication.

The use of an erythropoiesis-stimulating agent requires that other causes of anaemia (in particular iron deficiency) have been ruled out. Depending on the individual clinical

symptomatology, treatment should be considered from a haemoglobin value ≤ 10.0 g/dl.[2]

Overall, it is assumed that the treatment of deficiencies that could trigger specific anaemia (e.g. iron deficiency, water-soluble vitamins) is ensured in accordance with the guidelines and marketing authorisation.

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 vadadustat is assessed as follows:

An additional benefit is not proven.

Justification:

The pharmaceutical company presented the CI-0016 and CI-0017 studies for the assessment of the additional benefit of vadadustat. In addition, the pharmaceutical company identified two further studies (MT-6548-J03 and CI-0036), but excluded them from the study pool.

CI-0016 and CI-0017 studies

Both studies are unblinded, multicentre, parallel RCTs comparing vadadustat with darbepoetin alfa. Patients with end-stage chronic kidney disease on maintenance dialysis were enrolled. Other causes of anaemia – in particular a lack of iron and water-soluble vitamins – had to be ruled out prior to enrolment in the study. Patients with pre-existing cardiovascular conditions such as severe heart failure or acute coronary syndrome were excluded from both studies.

In the CI-0016 study, patients with anaemia were examined after newly initiated maintenance dialysis that had been in place for a maximum of 16 weeks. Originally, only patients without permanent prior ESA therapy were enrolled in the CI-0016 study; following a protocol change, the enrolment of patients with long-term prior ESA therapy was also permitted. In contrast, the CI-0017 study examined patients with a long history of dialysis (more than 12 weeks) and exclusively with permanent prior ESA therapy.

In the CI-0016 study, 369 patients were randomised in a 1:1 ratio to treatment with vadadustat (N = 181) or darbepoetin alfa (N = 188). It was stratified according to the geographical region (USA, Europe, rest of the world), New York Heart Association (NYHA) heart failure class (0 or I vs II or III) and haemoglobin (Hb) value at the start of the study (< 9.5 g/dl; ≥ 9.5 g/dl).

In the CI-0017 study, 3,554 patients were randomised in a 1:1 ratio into the intervention arm with vadadustat (N = 1,777) and the comparator arm with darbepoetin alfa (N = 1,777).

[2] Therapeutic information in accordance with Section 92, paragraph 2, sentence 7 SGB V in conjunction with Section 17 Pharmaceuticals Directive on the economic prescription of medicinal products, erythropoiesis-stimulating agents (for the treatment of symptomatic renal anaemia), resolution of 23 June 2011

Treatment was also stratified according to the geographical region (USA, Europe, rest of the world), NYHA heart failure class (0 or I vs II or III) and Hb value at the start of the study, but with a higher cut-off value (< 10.0 g/dl; ≥ 10.0 g/dl) than in the CI-0016 study.

The primary endpoints of the CI-0016 and CI-0017 studies were the efficacy endpoint "change in Hb value from the start of the study to the period between week 24-36" and the harm endpoint MACE with the components death from any cause, non-fatal myocardial infarction and non-fatal stroke.

MT-6548-J03 and CI-0036 studies

The MT-6548-J03 study is a double-blind randomised study comparing vadadustat with darbepoetin alfa conducted in Japan. There is uncertainty in the study as to the extent to which the presence of iron deficiency as the cause of symptomatic anaemia can be ruled out prior to the start of treatment. In addition, with 323 patients, the study comprises less than 10% of the study population of the two CI-0016 and CI-0017 studies included, which is why it can be assumed that the influence on the results of the present benefit assessment is low. The study is therefore not used for the benefit assessment.

The CI-0036 study is an open-label, 3-arm, 1:1:1 randomised study comparing vadadustat administered once daily with vadadustat administered 3 times weekly with darbepoetin alfa. There is uncertainty regarding the maximum on-label dose of vadadustat during the course of the study. In addition, with 165 patients, the potentially relevant sub-population of the study comprises only about 4% of the study population of the two CI-0016 and CI-0017 studies included, which is why it can be assumed that the influence on the results of the present benefit assessment is low. The study is therefore not used for the benefit assessment.

Extent and probability of the additional benefit

Mortality

For the "overall mortality" endpoint, there was no statistically significant difference between the treatment arms in the meta-analysis of the CI-0016 and CI-0017 studies.

Morbidity

Transfusion independence

In its dossier, the pharmaceutical company presented evaluations of the transfusion independence at week 52. However, these evaluations do not take into account surveys after therapy discontinuation by the patients. This means that patients who received a transfusion after therapy discontinuation are still counted as transfusion-independent, although a connection between discontinuation and subsequent transfusion cannot be ruled out. In addition, information on the duration of observation per study arm is missing and it is unclear to what extent different durations of observation exist. These evaluations are therefore considered inappropriate.

As part of the written statement procedure, the pharmaceutical company subsequently submitted evaluations on the percentage of patients without red blood cell transfusion from the start of the study to the end of the study. These evaluations also take into account red

blood cell transfusions that were given after premature therapy discontinuation. In addition, the pharmaceutical company presented time-to-event analyses for the time up to the first red blood cell transfusion. The subsequently submitted data on the percentage of patients without red blood cell transfusions covers the entire study period. Thus, the same observation period is considered for both treatment arms in these evaluations.

As previously stated, red blood cell transfusions are only recommended as a secondary option for the treatment of symptomatic anaemia associated with chronic kidney disease, particularly due to possible alloimmunisation and the resulting potential complications in the event of a subsequent kidney transplant. The clinicians also stated during the written statement procedure that transfusions are of minor importance in this therapeutic indication. Against this background, the transfusion independence endpoint is not used for deriving an additional benefit.

However, long-term or sustained avoidance of transfusions is a therapeutic goal that must be taken into account due to the long-term secondary complications of transfusions, such as the formation of alloantibodies and chronic iron overload. Therefore, the results for the transfusion independence endpoint are presented additionally here.

Quality of life

No endpoints on health-related quality of life were collected in the CI-0016 and CI-0017 studies.

Side effects

Serious adverse events (SAE)

For the SAE endpoint, the meta-analysis of the CI-0016 and CI-0017 studies showed a statistically significant advantage of vadadustat over darbepoetin alfa.

It should be noted here that there is uncertainty regarding the on-label dosage of darbepoetin alfa in the comparator arm, which could not be ruled out by the information subsequently submitted by the pharmaceutical company.

Therapy discontinuation due to adverse events (AEs)

For the endpoint of therapy discontinuation due to AEs, the meta-analysis of the CI-0016 and CI-0017 studies showed a statistically significant disadvantage of vadadustat over darbepoetin alfa.

Major adverse cardiovascular events (MACE), hospitalisation due to heart failure and thromboembolic events

For the endpoints MACE (consisting of the individual components cardiovascular death, non-fatal myocardial infarction or non-fatal stroke), hospitalisation due to heart failure, thromboembolic events (consisting of the individual components arterial thrombosis, deep vein thrombosis, pulmonary embolism and vascular access thrombosis), the meta-analysis of the CI-0016 and CI-0017 studies showed no statistically significant difference between the treatment arms.

Liver toxicity

For the endpoint of liver toxicity, the meta-analysis of the CI-0016 and CI-0017 studies showed no statistically significant difference between the treatment arms.

Specific AEs

In *detail*, the meta-analysis of the CI-0016 and CI-0017 studies each showed a statistically significant advantage of vadadustat over darbepoetin alfa for the specific AEs "Cardiac disorders (SOC, SAE)", "Benign, malignant and unspecified neoplasms (SOC, SAE)", "Urinary tract infection (PT, SAE)" and "Mood altered(PT, SAE)".

Overall assessment

For the benefit assessment, the open-label, randomised CI-0016 and CI-0017 studies are available, in which vadadustat was compared with darbepoetin alfa in adult patients with symptomatic anaemia associated with chronic kidney disease (CKD) on chronic maintenance dialysis.
In the mortality category, the meta-analysis of the CI-0016 and CI-0017 studies showed no statistically significant difference between the treatment groups for the overall mortality endpoint.
In the side effects category, the meta-analysis of the CI-0016 and CI-0017 studies showed statistically significant advantages of vadadustat for the SAE endpoint as well as for several specific AEs in detail. In contrast, for the endpoint of therapy discontinuation due to AEs, the meta-analysis of the CI-0016 and CI-0017 studies showed a statistically significant disadvantage of vadadustat.

The overall assessment of the results therefore only showed statistically significant differences between the treatment arms for the side effects. No additional benefit of vadadustat compared with darbepoetin alfa was identified in the overall assessment as both positive and negative effects for the active ingredient vadadustat occur in this endpoint category.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Vafseo with the active ingredient vadadustat. Vadadustat is approved for the treatment of adults with symptomatic anaemia associated with chronic kidney disease (CKD) on chronic maintenance dialysis.
The G-BA determined the erythropoiesis-stimulating agents darbepoetin alfa or epoetin alfa or epoetin beta or epoetin theta or epoetin zeta or methoxy PEG epoetin beta as the appropriate comparator therapy.
For the assessment of the additional benefit, the pharmaceutical company presented the RCTs CI-0016 and CI-0017, in which vadadustat was compared with darbepoetin alfa.
For the endpoint of overall mortality, the meta-analysis of both studies showed no statistically significant difference between the treatment groups. In the side effects category, the meta-analysis showed statistically significant advantages of vadadustat for the SAE endpoint and for several specific AEs in detail, with such advantages being offset by a statistically significant disadvantage for the endpoint of therapy discontinuation due to AEs. Therefore, in the overall assessment, no additional benefit of vadadustat compared with darbepoetin alfa was identified.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier, which are, however, subject to uncertainty due to various methodological aspects. Uncertainties arise from the omission of additional EBM codes as an inclusion criterion for dialysis-dependent patients and from differing observation periods between the publications used in which patients received an ESA prescription. Overall, the patient numbers are in a plausible range despite the uncertainties.

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 Vafseo (active ingredient: vadadustat) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 6 September 2024):

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

Treatment with vadadustat should only be initiated and monitored by doctors experienced in anaemia treatment.

Treatment should not be continued beyond 24 weeks if no clinically significant increase in haemoglobin levels is achieved.

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: 1 November 2024).

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.

For dosages depending on body weight (BW), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were used as a basis (average body height: 1.72 m; average body weight: 77.7 kg)[3].

The dosage is given individually to achieve a haemoglobin level of 10 to 12 g/dl. The calculation of the annual treatment costs is based on the dosage data of the initial and maximum dosages in the product information. For the active ingredients methoxy PEG epoetin beta and

[3] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

darbepoetin alfa, no maximum dosage can be taken from the product information as a basis for calculation.

From the substance class of erythropoiesis-stimulating agents, the following active ingredients are available for the treatment of symptomatic anaemia associated with chronic kidney disease: Darbepoetin alfa, epoetin alfa, epoetin beta, epoetin theta, epoetin zeta, methoxy-PEG-epoetin beta. 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 symptomatic anaemia associated with chronic kidney disease (CKD) on chronic maintenance dialysis

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Vadadustat	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				
Erythropoiesis-stimulating agent				
Epoetin alfa/ epoetin zeta	Continuously, 2 x within 7 days	52.1	2	104.2
	Continuously, 3 x within 7 days	52.1	3	156.3
Epoetin beta	Continuously, 1 x within 7 days	52.1	1	52.1
	Continuously, 3 x within 7 days	52.1	3	156.3
Epoetin theta	Continuously, 2 x within 7 days	52.1	2	104.2
	Continuously, 3 x within 7 days	52.1	3	156.3
Darbepoetin alfa	Continuously, 1 x every 7 days	52.1	1	52.1
	Continuously, 1 x every 28 days	13.0	1	13.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Methoxy PEG epoetin beta	Continuously, 1 x every 7 days	52.1	1	52.1
	Continuously, 1 x every 28 days	13.0	1	13.0

Consumption:

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					
Vadadustat	150 mg – 300 mg	150 mg – 600 mg	1 x 150 mg – 2 x 300 mg	365.0	365 x 150 mg – 730 x 300 mg
Appropriate comparator therapy					
Erythropoiesis-stimulating agent					
Epoetin alfa/ epoetin zeta	25 I.U./ kg BW = 1,942.5 I.U. -	1,942.5 I.U. -	1 x 2,000 I.U. -	104.2 -	104.2 x 2,000 I.U. -
	100 I.U./ kg BW = 7,770 I.U.	7,770 I.U.	1 x 8,000 I.U.	156.3	156.3 x 8,000 I.U.
Epoetin beta	20 I.U./ kg BW = 1,554 I.U.	1,554 I.U.	1 x 2,000 I.U.	156.3	156.3 x 2,000 I.U.
	720 I.U./ kg BW = 55,944 I.U.	55,944 I.U.	2 x 30,000 I.U.	52.1	104.2 x 30,000 I.U.
Epoetin theta	20 I.U./ kg BW = 1,554 I.U.	1,554 I.U.	1 x 2,000 I.U.	156.3	156.3 x 2,000 I.U.
	350 I.U./kg BW = 27,195 I.U.	27,195 I.U.	1 x 30,000 I.U.	104.2	104.2 x 30,000 I.U.
Darbepoetin alfa	Not calculable				
Methoxy PEG epoetin beta	Not calculable				

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 Sections 130 and 130 a 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					
Vadadustat 150 mg	98 FCT	€ 852.97	€ 2.00	€ 46.60	€ 804.37
Vadadustat 300 mg	98 FCT	€ 1,689.55	€ 2.00	€ 93.20	€ 1,594.35
Appropriate comparator therapy					
Darbepoetin alfa	Not calculable				
Epoetin alfa 2,000 I.U.[4]	6 SPF	€ 96.81	€ 2.00	€ 6.76	€ 88.05
Epoetin alfa 8,000 I.U.[4]	6 PS	€ 372.96	€ 2.00	€ 28.60	€ 342.36
Epoetin beta 2,000 I.U.[4]	6 SFI	€ 96.81	€ 2.00	€ 0.00	€ 94.81
Epoetin beta 30,000 I.U.[4]	4 SFI	€ 960.20	€ 2.00	€ 0.00	€ 958.20
Epoetin theta 2,000 I.U.[4]	6 PS	€ 96.81	€ 2.00	€ 0.00	€ 94.81
Epoetin theta 30,000 I.U.[4]	4 PS	€ 960.20	€ 2.00	€ 0.00	€ 958.20
Epoetin beta 2,000 I.U.[4]	6 PS	€ 96.81	€ 2.00	€ 6.76	€ 88.05
Epoetin beta 8,000 I.U.[4]	6 PS	€ 372.96	€ 2.00	€ 28.60	€ 342.36
Methoxy PEG epoetin beta	Not calculable				
Abbreviations: PS = prefilled syringes; FCT = film-coated tablets; SPF = solution for injection in a pre-filled syringe; SFI = 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

[4] Fixed reimbursement rate

(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.

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:

Adults with symptomatic anaemia associated with chronic kidney disease (CKD) on chronic maintenance dialysis

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 vadadustat (Vafseo); Vafseo 150/300/450 mg film-coated tablets; last revised: June 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 8 January 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

The appropriate comparator therapy was adjusted once the positive opinion was issued.

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

By letter dated 30 May 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 vadadustat.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 August 2024, and the written statement procedure was initiated with publication on the G-BA website on 2 September 2024. The deadline for submitting statements was 23 September 2024.

The oral hearing was held on 7 October 2024.

By letter dated 8 October 2024, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 31 October 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 12 November 2024, and the proposed draft resolution was approved.

At its session on 22 November 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	8 January 2019	Determination of the appropriate comparator therapy
Working group Section 35a	15 March 2023	Implementation of the appropriate comparator therapy
Working group Section 35a	1 October 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	7 October 2024	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	16 October 2024 6 November 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	12 November 2024	Concluding discussion of the draft resolution
Plenum	22 November 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 22 November 2024

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

Prof. Hecken