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)
Pegunigalsidase alfa (Fabry disease)

of 21 March 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 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 pegunigalsidase alfa on 1 October 2023 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 20 September 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 2 January 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 pegunigalsidase alfa 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 pegunigalsidase alfa.

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 Pegunigalsidase alfa (Elfabrio) according to the product information

Elfabrio is indicated for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase).

Therapeutic indication of the resolution (resolution of 21.03.2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with a confirmed diagnosis of Fabry disease (alpha-galactosidase A deficiency)

Appropriate comparator therapy for pegunigalsidase alfa:

- Agalsidase alfa or agalsidase beta or migalastat (only for patients with an amenable mutation)

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

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

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. The active ingredients agalsidase alfa, agalsidase beta and migalastat are currently approved for the treatment of Fabry disease. According to the product information, the active ingredient migalastat is indicated for long-term treatment of adults and adolescents aged 12 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation

on 2. A non-medicinal treatment cannot be considered as appropriate comparator therapy in this therapeutic indication.

on 3. There is a resolution of the G-BA on the early benefit assessment according to Section 35a SGB V in the therapeutic indication "Fabry disease" for the active ingredient migalastat (date of resolution: 15 February 2024).

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

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

The current evidence for the treatment of Fabry disease in adults is limited overall. Due to the lack of higher-quality evidence, only one Spanish guideline (Calderón Sandubete EJ et al., 2019) could be additionally considered in the evidence search. Based on the evidence currently available and taking into account the statements of the scientific-medical societies, an enzyme replacement therapy (agalsidase alfa or agalsidase beta) is recommended for the treatment of Fabry disease. As an alternative to enzyme replacement therapy, the active ingredient migalastat may represent a further therapy option for patients with an amenable mutation.

For the active ingredient pegunigalsidase alfa to be assessed, taking into account the available evidence and the statements of the scientific-medical societies, a treatment with agalsidase alfa or agalsidase beta or migalastat (only for patients with an amenable mutation) is therefore determined as the appropriate comparator therapy for adults with a confirmed diagnosis of Fabry disease (alpha-galactosidase A deficiency). The active ingredients of the appropriate comparator therapy represent equally appropriate therapy options, taking into account the respective marketing authorisations.

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 pegunigalsidase alfa is assessed as follows:

For adults with a confirmed diagnosis of Fabry disease (deficiency of α-galactosidase), an additional benefit is not proven.

Justification:

The BALANCE study is a randomised, double-blind, controlled phase III study in which treatment with pegunigalsidase alfa was compared with treatment with agalsidase beta. 78 adult patients aged 18 - 60 years with a confirmed diagnosis of Fabry disease who had been treated with agalsidase beta for at least 1 year prior to the start of study and had a linear decrease in the estimated glomerular filtration rate (eGFR) of at least 2 ml/min/1.73 m²/year were enrolled in the study. Patients with an eGFR below 40 ml/min/1.73 m² and treatment-naive patients were excluded from participation in the study. Patients were randomised in a 2:1 ratio to treatment with pegunigalsidase alfa (N = 53) or continuation of therapy with agalsidase beta (N = 25), stratified according to the urine protein/ creatinine ratio category at baseline (< 1 g/g vs ≥ 1 g/g). The percentage of patients with antibodies against the respective active ingredient administered was comparable in both arms at the start of study (pegunigalsidase alfa: 34.6% vs agalsidase beta: 32.0%). No information is available on whether a change of preparation was tested in the event of a decrease in the efficacy of enzyme replacement therapy.
Following a screening phase of 1 month, the patients were treated for 24 months. The primary endpoint of the study was the annual change in renal function (eGFR slope). Patient-relevant secondary endpoints were assessed in the categories of mortality, morbidity and side effects.

The study was conducted in Europe and the USA between August 2016 and October 2021.

The population referred to by the pharmaceutical company as the intention to treat (ITT) population differs from the population of randomised patients (pegunigalsidase alfa N = 53 vs agalsidase beta N = 25) and comprises those patients who received at least one dose of the study medication (pegunigalsidase alfa N = 52 vs agalsidase beta N = 25).

Uncertainties of the study

The percentage of patients in the BALANCE study who were on premedication at the previous therapy with agalsidase beta at baseline was 39% in the intervention arm and 60% in the comparator arm. After the first administration of the study medication, the existing premedication was gradually reduced for all patients within the first 3 months. The product information for pegunigalsidase alfa contains the recommendation for patients switching from treatment with agalsidase alfa or beta to pegunigalsidase alfa that the pretreatment should be maintained for the first 3 months (6 infusions) of treatment with pegunigalsidase alfa, whereby this can be gradually discontinued depending on the patient's tolerability.

In its statement, the pharmaceutical company explains that the reduction of premedication in the BALANCE study was carried out with ongoing consideration of patient-individual tolerability and that it was possible to continue or resume premedication that had already been discontinued. However, it is not clear from the documents and the information provided in the written statement procedure that the decision to initiate a reduction in the BALANCE study was assessed on a patient-individual basis after appropriate tolerability. It is therefore still unclear whether infusion-related reactions have already occurred in a relevant percentage of patients as a result of the reduction in premedication during the 2nd infusion.

Extent and probability of the additional benefit

Mortality

There were no deaths in the course of the study.

Morbidity

Change in renal function (eGFR slope)

A change in renal function based on the glomerular filtration rate is not per se patient-relevant. Taking into account the high median eGFR baseline values of 73.45 ml/min/1.73m² in the intervention arm and 74.85 ml/min/1.73m² in the comparator arm and the small change in renal function measured in the study (median change per year of approx. -2.5 and -2.2 ml/min/1.73m² respectively), it cannot be assumed that the endpoint represents a noticeable deterioration in renal function for the majority of patients affected. The endpoint of change in renal function (eGFR slope) is therefore not used for the benefit assessment in the present case.

Composite endpoint on clinical morbidity of Fabry disease

The composite endpoint on clinical morbidity includes the following components: renal morbidity, cardiac morbidity, cerebrovascular morbidity and death without cardiac cause.
Events that were categorised as relevant by a clinical monitor either as part of the AE assessment or from the clinical information stored in the database were recorded under the respective components. The operationalisation of the components is not fully comprehensible; moreover, individual events of the respective components do not directly include patient-relevant events. The composite endpoint on clinical morbidity of Fabry disease and its individual components are therefore not used in the present benefit assessment.

Symptomatology assessed using the Mainz Severity Score Index (MSSI)

The disease-specific instrument MSSI comprises the 4 domains of general symptoms, renal symptoms, neurological symptoms and cardiovascular symptoms. Doctors check for the presence of certain symptoms which are assigned a defined point value if they are present. The total score is calculated from the sum of the point scores and ranges from 0 to 76, with higher scores indicating more severe symptomatology. Categorisation into the different severity grades - mild (0 to 19 points), moderate (20 to 40 points) and severe (> 40 points) - is based on the point values achieved.
In the present operationalisation, the events in which the symptom is considered to be present is not clear for each symptom. Furthermore, it remains unclear whether the variable scoring of the individual symptoms based on expert assessments is adequate. In addition, the MSSI contains some components, such as abnormalities in the electrocardiogram which are not directly patient-relevant. Validation is available for the total score, but not for the individual domains.
Due to the uncertainties described above, the results for the endpoint of symptomatology, collected via the MSSI, are not used for the benefit assessment.

Pain

The endpoint of pain was collected using the Brief Pain Inventory – Short Form (BPI-SF). The worst pain experienced by patients (item 3), which is of particular significance to patients, and the impairment due to pain (BPI-SF item 9a-g) are taken into account. The average pain severity (BPI-SF items 3-6) is only presented additionally here; otherwise, the results of item 3 would be considered twice. For these endpoints, the pharmaceutical company presents responder analyses for the percentage of patients with an improvement ≥ 15% of the scale range (0 to 10) at week 104. A change of ≥ 1.5 points is considered a clinically relevant change.

For the endpoints of worst pain and impairment due to pain, there is no statistically significant difference between the treatment groups.

Health status (EQ-5D, visual analogue scale)

The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. The VAS of the EQ-5D is a visual analogue scale from 0 to 100 on which patients rate their health status. A value of 0 corresponds to the worst possible health status and a value of 100 to the best possible health status. For the endpoint, the pharmaceutical company presents responder analyses for the percentage of patients with an improvement ≥ 15% of the scale range at week 104 (scale range 0 to 100).
For the endpoint of health status, collected using VAS of the EQ-5D, there is no statistically significant difference between the treatment groups.

Quality of life

No data on health-related quality of life are available.

Side effects

The pharmaceutical company submits evaluations of the side effects, which include all adverse events (AEs), regardless of the symptoms of the disease or side effects of the study medication as well as evaluations of side effects without disease-related events. For the benefit assessment, the evaluations of the side effects, which include all adverse events (AEs), are taken into account.

For the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs, there are no statistically significant differences between the treatment groups in each case.

Infusion-related reactions

Due to the described uncertainties in the reduction of the premedication in place prior to study participation to avoid infusion-related reactions, it cannot be ruled out that the occurred events were significantly influenced by the attempt to gradually reduce the premedication in place prior to enrolment in the study in accordance with the study protocol.

Irrespective of this uncertainty, the evaluations used by the pharmaceutical company to derive the additional benefit are unsuitable for other reasons. The interpretation of the results is already limited in principle, as no specific criteria were specified in the BALANCE study for the investigators' assessment of whether an AE was to be classified as an infusion-related AE. The evaluations of the number of patients with at least 1 infusion-related reaction, which are

fundamentally relevant for the benefit assessment, can therefore not be taken into account due to the uncertainties mentioned.
The pharmaceutical company also primarily uses evaluations of the number and rate of infusion-related reactions to derive the additional benefit. As part of the written statement procedure, the pharmaceutical company also submitted evaluations of the rate of infusion-related reactions for sub-populations and evaluations of the cumulative numbers of infusion-related reactions. However, the evaluations mentioned, which take recurrent events into account, are only selectively available for the AE of infusion-related reactions. In addition, patients who had more than one infusion-related reaction are included more than once in these evaluations, so that individual patients with frequently recurring reactions could account for a relevant percentage of the events. The evaluations of the number and rate of infusion-related reactions are therefore also unsuitable for the benefit assessment.

No suitable data are therefore available for the endpoint of infusion-related reactions.

Chest pain (SAEs), respiratory, thoracic and mediastinal disorders (severe AEs)

For the endpoints of chest pain (SAEs) and respiratory, thoracic and mediastinal disorders (severe AEs), there is a statistically significant difference between the treatment groups to the advantage of pegunigalsidase alfa. However, due to the low number of events (2 events in the endpoint of chest pain and 3 events in the endpoint of respiratory, thoracic and mediastinal disorders) and the existing uncertainties of the BALANCE study, these effects are considered inadequate to derive an overall additional benefit of pegunigalsidase alfa over agalsidase beta.

Overall assessment

For the assessment of the additional benefit of pegunigalsidase alfa compared with the appropriate comparator therapy, results of the RCT study BALANCE (comparison with treatment with agalsidase beta) were presented for the endpoint categories of mortality, morbidity and side effects. No deaths occurred during the course of the study, so no statements on the additional benefit can be derived for the mortality category. In the morbidity category, the endpoints of pain and health status were taken into account using the EQ-5D visual analogue scale. However, there was no statistically significant difference between the treatment groups for these endpoints. An additional benefit of pegunigalsidase alfa is therefore not proven in the morbidity category. Additional benefit cannot be derived as no data were presented for the category of health-related quality of life. No additional benefit can be derived in the side effects category either.
Overall, an additional benefit of pegunigalsidase alfa compared to the appropriate comparator therapy is therefore not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Elfabrio with the active ingredient pegunigalsidase alfa. Pegunigalsidase alfa is approved for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of α-galactosidase).

Treatment with agalsidase alfa or agalsidase beta or migalastat (only for patients with an amenable mutation) was determined by the G-BA as an appropriate comparator therapy.
For the assessment of the additional benefit of pegunigalsidase alfa compared with the appropriate comparator therapy, results of the RCT study BALANCE (comparison with treatment with agalsidase beta) were presented for the endpoint categories of mortality, morbidity and side effects. No deaths occurred during the course of the study, so no statements on the additional benefit can be derived for the mortality category. In the morbidity category, the endpoints of pain and health status were taken into account using the EQ-5D visual analogue scale. However, there was no statistically significant difference between the treatment groups for these endpoints. An additional benefit of pegunigalsidase alfa is therefore not proven in the morbidity category. Additional benefit cannot be derived as no data were presented for the category of health-related quality of life. No additional benefit can be derived in the side effects category either.
Overall, an additional benefit of pegunigalsidase alfa compared to the appropriate comparator therapy is therefore 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 information provided by the pharmaceutical company in the dossier.

The patient numbers are subject to uncertainties, as the studies on which the lower and upper limits were based are very limited timeliness (data from 1981 to 2011) and the transferability of the calculated birth prevalence to Germany is questionable in view of the variance in the international publications used.

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 Elfabrio (active ingredient: pegunigalsidase alfa) at the following publicly accessible link (last access: 22 November 2023):

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

Treatment with pegunigalsidase alfa should only be initiated and monitored by doctors experienced in treating patients with Fabry disease.

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 March 2024).

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

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

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body weight of adults 77.7 kg). [2]

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				
Pegunigalsidase alfa	Continuously, 1 x every 14 days	26.1	1	26.1
Appropriate comparator therapy				
Agalsidase alfa or agalsidase beta or migalastat				
Agalsidase alfa	Continuously, 1 x every 14 days	26.1	1	26.1
Agalsidase beta	Continuously, 1 x every 14 days	26.1	1	26.1
Migalastat	Continuously, 1 x every 2 days	182.5	1	182.5

Consumption:

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.

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

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					
Pegunigalsidase alfa	1 mg / kg = 77.7 mg	77.7 mg	4 x 20 mg	26.1	104.4 x 20 mg
Appropriate comparator therapy					
Agalsidase alfa or agalsidase beta or migalastat					
Agalsidase alfa	0.2 mg / kg = 15.5 mg	15.5 mg	5 x 3.5 mg	26.1	130.5 x 3.5 mg
Agalsidase beta	1 mg / kg = 77.7 mg	77.7 mg	2 x 35 mg + 2 x 5 mg	26.1	52.2 x 35 mg + 52.2 x 5 mg
Migalastat	123 mg	1 x 123 mg	1 x 123 mg	182.5	182.5 x 123 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 fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Pegunigalsidase alfa 20 mg	10 CII	€ 36,287.47	€ 2.00	€ 2,071.79	€ 34,213.68
Appropriate comparator therapy					
Agalsidase alfa 3.5 mg	10 CIS	€ 28,586.41	€ 2.00	€ 1,629.28	€ 26,955.13

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
Agalsidase beta 35 mg	10 PCI	€ 56,929.96	€ 2.00	€ 3,250.69	€ 53,677.27
Agalsidase beta 5 mg	5 PCI	€ 4,076.08	€ 2.00	€ 232.19	€ 3,841.89
Migalastat hydrochloride 123 mg	14 HC	€ 18,768.88	€ 2.00	€ 0.00	€ 18,766.88
Abbreviations: HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; CII = concentrate for injection or infusion solution; PCI = powder for a concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 1 March 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.

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.

<u>Concomitant active ingredient</u>

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

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

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

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

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

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

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

Designation

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

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

Exception to the designation

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

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

Legal effects of the designation

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

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

Justification for the findings on designation in the present resolution:

Adults with a confirmed diagnosis of Fabry disease (alpha-galactosidase A deficiency)

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 pegunigalsidase alfa (Elfabrio); Elfabrio 2 mg/ml concentrate for the preparation of an infusion solution; last revised: May 2023

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 11 October 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 20 September 2023, the pharmaceutical company submitted a dossier for the benefit assessment of pegunigalsidase alfa to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 29 September 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 pegunigalsidase alfa.

The dossier assessment by the IQWiG was submitted to the G-BA on 22 December 2023, and the written statement procedure was initiated with publication on the G-BA website on 2 January 2024. The deadline for submitting statements was 23 January 2024.

The oral hearing was held on 5 February 2024.

By letter dated 5 February 2024, the IQWiG was commissioned with a supplementary assessment, taking into account data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 1 March 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 March 2024, and the proposed resolution was approved.

At its session on 21 March 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	11 October 2022	Determination of the appropriate comparator therapy

Working group Section 35a	30 January 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	5 February 2024	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	13 February 2024; 5 March 2024	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	12 March 2024	Concluding discussion of the draft resolution
Plenum	21 March 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 21 March 2024

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

Prof. Hecken