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)
Migalastat reassessment of an orphan drug after exceeding the EUR 30 million turnover limit (Fabry disease, ≥ 12 years)

of 15 February 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 active ingredient migalastat (Galafold) was listed for the first time on 1 June 2016 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices. Migalastat was approved on 26 May 2016 for the long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) 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. At its session on 1 December 2016, the G-BA decided on the benefit assessment of migalastat in the therapeutic indication "Galafold is indicated for long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation" in accordance with Section 35a SGB V.

On 23 July 2021, migalastat 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, p. 7).
At its session on 17 February 2022, the G-BA decided on the benefit assessment of migalastat in the therapeutic indication "Galafold is indicated for the long-term treatment of adolescents aged 12 to < 16 years with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation" in accordance with Section 35a SGB V.

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

By letter dated 1 December 2022, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 1 August 2023, due to exceeding the € 30 million turnover limit within the period from December 2021 to November 2022. The pharmaceutical company has submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 6 VerfO on 15 August 2023.

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

The G-BA came to a resolution on whether an additional benefit of migalastat 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 migalastat.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

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

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Migalastat (Galafold) in accordance with the product information

Galafold 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.

Therapeutic indication of the resolution (resolution of 15.02.2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for migalastat:

- Agalsidase alfa or agalsidase beta

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

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

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

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

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal

product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

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

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

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

on 1. In addition to the active substance to be assessed, the active ingredients agalsidase alfa and agalsidase beta and the active ingredient pegunigalsidase alfa are approved for the treatment of Fabry disease.

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

on 3. In the therapeutic indication "Fabry disease", there are resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for migalastat of 1 December 2016 and 17 February 2022, which are replaced by the present resolution.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic 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 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, 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 to be assessed may represent a further therapy option for patients with an amenable mutation.

The active ingredient pegunigalsidase alfa is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved for the treatment of adult patients with Fabry disease (marketing authorisation on 4 May 2023). Based on the generally accepted state of medical knowledge, pegunigalsidase alfa is not determined to be an appropriate comparator therapy for the present resolution.

For the active ingredient migalastat to be assessed, treatment with agalsidase alfa or agalsidase beta is determined as an appropriate comparator therapy on the basis of the available evidence for 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. Both active ingredients are equally appropriate therapy options.

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 migalastat is assessed as follows:

For 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, an additional benefit has not been proven.

Justification:

The ATTRACT study (AT1001-012) is an open-label RCT in which migalastat was compared with treatment with enzyme replacement therapy (ERT). A total of 60 patients aged 16 to 74 years were randomised in a 1.5:1 ratio to the migalastat or ERT group with stratification according to sex and urine protein (< 100 mg/ 24 h; ≥ 100 mg/ 24 h). For enrolment in the study, patients had to have a migalastat-sensitive mutation of the gene coding for α-galactosidase A (GLA gene), confirmed by genotyping, and a glomerular filtration rate ≥ 30 ml/ min/ 1.73m². In addition, treatment with enzyme replacement therapy had to have been initiated at least 12 months prior to the start of study. In the comparator arm, patients continued their enzyme replacement therapy with agalsidase alfa or agalsidase beta - existing at the start of study - during the study, while patients in the intervention arm had to discontinue their existing enzyme replacement therapy prior to initiating treatment with migalastat. According to the information provided by the pharmaceutical company in the written statement procedure, an antibody determination and the testing of a change of preparation in the event of a drop in efficacy during enzyme replacement therapy was not planned within the study.

Treatment with migalastat or enzyme replacement therapy was given for 18 months. After the randomised, comparator treatment phase, patients could optionally participate in a 12-month extension phase in which migalastat was administered in an unblinded study arm. The primary endpoints of the study are the change in the measured glomerular filtration rate with lohexol (mGFR) per year after 18 months and the change in the estimated glomerular filtration rate (eGFR) per year after 18 months.

The study was conducted between 2011 and 2015 in 25 study sites in 10 countries (Austria, Australia, Belgium, Brazil, Denmark, France, Italy, Japan, UK and USA). This was followed by the opportunity to take part in a 12-month open-label extension phase.

Only patients aged 16 years and older were enrolled in the ATTRACT study; data on adolescents aged 12 years and older were not presented for the present benefit assessment.

Extent and probability of the additional benefit

Mortality

There were no deaths in the course of the study.

Morbidity

In the ATTRACT study, a composite endpoint on clinical morbidity was recorded with the components renal morbidity, cardiac morbidity, cerebrovascular morbidity and death. For a composite endpoint to be considered in the benefit assessment, the individual components of the endpoint must be patient-relevant and of similar severity. As the present operationalisation of the composite endpoint is unsuitable, only the individual components of this endpoint, the evaluation of which was also planned according to the study design, are considered for the benefit assessment.

Renal morbidity

Renal morbidity was operationalised via a decrease in the estimated glomerular filtration rate (eGFR) ≥ 15 ml/ min/ 1.73 m² (with the decreased eGFR < 90 ml/ min/ 1.73 m² relative to the start of study) and an increase in 24-hour urine protein ≥ 33% (with the increased protein ≥ 300 mg relative to the start of study)

A decrease in eGFR ≥ 15 ml/ min/ 1.73 m² and an increase in 24-hour urine protein ≥ 33% are not per se patient-relevant. Taking into account the high mean mGFR baseline values (approx. 82 ml/ min/ 1.73 m²) and the mean 24-hour urine protein baseline values (approx. 260 mg/ mmol and approx. 417 mg/ mmol), it cannot be assumed that these changes represent a noticeable deterioration in renal function for the majority of affected patients. The renal morbidity endpoint is therefore not used for the benefit assessment in the present operationalisation.

Cardiac morbidity

The cardiac morbidity endpoint was operationalised via the patient-relevant individual components myocardial infarction, unstable angina pectoris, new symptomatic arrhythmia

and heart failure. Myocardial infarction and unstable angina pectoris did not occur in the study.

For the endpoint of cardiac morbidity, no statistically significant difference was detected between the treatment groups.

Cerebrovascular morbidity

The cerebrovascular morbidity endpoint was operationalised via the patient-relevant individual components stroke and transient ischaemic attack (TIA). However, no strokes occurred in the study. As the pharmaceutical company did not submit any results on the individual components for the present procedure, the corresponding information from the benefit assessment procedure for the active ingredient migalastat (resolution of 1 December 2016) is used.

For the endpoint of cerebrovascular morbidity, no statistically significant difference was detected between the treatment groups.

Pain

In the ATTRACT study, the pain endpoint was collected using the Brief Pain Inventory - Short Form (BPI-SF). The pharmaceutical company submits responder analyses as well as evaluations of continuous data for this endpoint. For the responder analyses, the percentage of patients with an improvement or deterioration of ≥ 15% (≥ 1.5 points) of the scale range (scale range 0 to 10) was evaluated. A change of ≥ 1.5 points is considered a clinically relevant change. In the analyses presented, patients are classified as responders if they show a deterioration or improvement at any time during the evaluation period up to month 18. However, the responder analyses submitted with the dossier are not considered since the consideration of the endpoints at the latest possible time point, i.e. at the end of study at month 18 would be relevant in the present indication of a chronic, progressive disease. In the written statement procedure, the pharmaceutical company submitted responder analyses for the pain endpoint collected using BPI-SF at the time of evaluation at month 18. In the ATTRACT study, items 3-6 of the BPI-SF (worst, least, average and current pain) were to be surveyed. In this therapeutic indication, pain relief, i.e. improvement of the endpoint, is considered. The endpoint of worst pain (item 3) is used for the benefit assessment; pain intensity (items 3 to 6) is presented additionally.

For the endpoint of worst pain (BPI-SF), no statistically significant difference was detected between the treatment arms.

As adequate responder analyses for the benefit assessment are available for the endpoint, the evaluations of continuous data (change compared to the start of study) are not considered.

<u>Health-related quality of life</u>

Health-related quality of life was assessed in the ATTRACT study using the Short Form-36 Health Survey version 2 (SF-36v2). The pharmaceutical company submits responder analyses as well as evaluations of continuous data for this endpoint. For the responder analyses, the percentage of patients with a deterioration or improvement of ≥ 9.4 (physical component

summary score) or ≥ 9.6 points (mental component summary score) was evaluated. This corresponds to 15% of the scale range in each case and is regarded as a clinically relevant improvement or deterioration. An increase in the values compared to the start of study corresponds to an improvement. As the responder analyses for the SF-36v2 submitted with the dossier were not evaluated at the longest possible evaluation time point at month 18, they cannot be considered for the benefit assessment (*see pain endpoint*). In the written statement procedure, the pharmaceutical company subsequently submitted responder analyses for the quality of life endpoint assessed using SF-36v2 at the time of evaluation at month 18. In this therapeutic indication, the improvement in quality of life, i.e. the improvement in the endpoint, is considered.

The responder analyses at the time of evaluation at month 18 does not show any statistically significant difference between the treatment arms for the physical component summary (PCS) score and the mental component summary (MCS) score of the SF-36v2.

As adequate responder analyses for the benefit assessment are available for the endpoint, the evaluations of continuous data (change compared to the start of study) are not considered.

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. Since the underlying disease manifests itself in various symptoms due to the failure of different organs, it is not possible to clearly differentiate between side effects of the therapy and events of the underlying disease.

Serious adverse events (SAEs)

For the endpoint of SAEs, no statistically significant difference was detected between the treatment groups.

Discontinuation due to AEs

There were no discontinuations due to AEs in the course of the study.

Infusion-related reactions

Infusion-related reactions are a relevant side effect for the present benefit assessment, as the administration of the active ingredients agalsidase alfa and agalsidase beta frequently leads to infusion-related reactions according to the product information. However, this endpoint was not assessed in the ATTRACT study. In the written statement procedure, the pharmaceutical company submits post hoc operationalised evaluations of infusion-related reactions. For the evaluation, the pharmaceutical company selects the preferred terms it considers relevant (including "nausea associated with a procedure") in the system organ class (SOC) "Injury, poisoning and procedural complications". However, due to the selective consideration of exclusively procedural events, which can only occur in the comparator arm, no comparator data is available. The benefit assessment would require comparator data based on an aggregated analysis of all potentially relevant symptomatic adverse events for infusion-related reactions. Specific adverse events that represent infusion-related reactions should either be predefined or refer to substantially justified compositions based on

publications or compositions of the MedDRA system. The evaluations subsequently submitted by the pharmaceutical company on the endpoint "infusion-related reactions" are therefore unsuitable for the benefit assessment.

Overall assessment

For the assessment of the additional benefit of migalastat compared to the appropriate comparator therapy, an enzyme replacement therapy with agalsidase alfa or agalsidase beta, results of the ATTRACT RCT study were presented.
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 cardiac morbidity, cerebrovascular morbidity and pain were taken into account. However, there was no statistically significant difference between the treatment groups for these endpoints. An additional benefit of migalastat is therefore not proven in the morbidity category.
In the category of health-related quality of life, there were no statistically significant differences between the treatment groups in the responder analyses at the time of evaluation at month 18. An additional benefit can therefore also not be derived for the category of health-related quality of life.
In the side effects category, an additional benefit is also not proven due to a lack of statistically significant differences between the treatment groups.

Overall, an additional benefit of migalastat compared to the appropriate comparator therapy is therefore not proven.

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient migalastat (Galafold) due to the exceeding of the € 30 million turnover limit. Galafold was approved as an orphan drug 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.

For 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, treatment with agalsidase alfa or agalsidase beta was determined to be an appropriate comparator therapy.
The results of the ATTRACT RCT study were presented for the assessment of the additional benefit of migalastat. 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 cardiac morbidity, cerebrovascular morbidity and pain were taken into account. However, there was no statistically significant difference between the treatment groups for these endpoints. An additional benefit of migalastat is therefore not proven in the morbidity category.
In the category of health-related quality of life, there were no statistically significant differences between the treatment groups in the responder analyses at the time of evaluation at month 18. An additional benefit can therefore also not be derived for the category of health-related quality of life.

In the side effects category, an additional benefit is also not proven due to a lack of statistically significant differences between the treatment groups.

Overall, an additional benefit of migalastat 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 uncertainty, in particular due to the source used to determine the percentage of patients with an underlying mutation of the α galactosidase A gene, which is supported by an expert statement based on data from a university hospital and relies on an uncertain definition.

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 Galafold (active ingredient: migalastat) at the following publicly accessible link (last access: 23 November 2023):

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

Treatment with migalastat should only be initiated and monitored by specialists who are experienced in the treatment of patients with Fabry disease. Galafold is not indicated for concomitant use with enzyme replacement therapy (ERT).

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 January 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 2017 – body measurements of the population" as well

as "Microcensus 2021 – body measurements of the population" were applied (average body weight of children aged 12 years: 47.1 kg[2], average body weight of adults: 77.7 kg[3]).

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.

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

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					
Migalastat	123 mg	1 x 123 mg	1 x 123 mg	182.5	182.5 x 123 mg
Appropriate comparator therapy					
Agalsidase alfa or agalsidase beta					

[2] Federal Health Reporting. Average body measurements of the population (2017, both sexes, 1 year and older), www.gbe-bund.de

[3] 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
Agalsidase alfa	12 years and older: 0.2 mg/ kg = 9.4 mg – 15.5 mg	9.4 mg – 15.5 mg	3 x 3.5 mg – 5 x 3.5 mg	26.1	78.3 x 3.5 mg – 130.5 x 3.5 mg
Agalsidase beta	12 years and older: 1 mg/ kg = 47.1 mg – 77.7 mg	47.1 mg – 77.7 mg	1 x 35 mg + 3 x 5 mg – 2 x 35 mg + 2 x 5 mg	26.1	26.1 x 35 mg + 78.3 x 5 mg – 52.2 x 35 mg + 52.2 x 5 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					
Migalastat 123 mg	14 HC	€ 18,768.88	€ 2.00	€ 0.00	€ 18,766.88
Appropriate comparator therapy					
Agalsidase alfa 3.5 mg	10 CIS	€ 28,586.41	€ 2.00	€ 1,629.28	€ 26,955.13
Agalsidase beta 5 mg	5 PCI	€ 4,076.08	€ 2.00	€ 232.19	€ 3,841.89
Agalsidase beta 35 mg	10 PCI	€ 56,929.96	€ 2.00	€ 3,250.69	€ 53,677.27
Abbreviations: HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; Pci = powder for a concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 15 January 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.

Concomitant active ingredient:

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

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

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

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

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic

indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

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

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

Designation

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

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

Exception to the designation

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

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

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the

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

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

Justification for the findings on designation in the present resolution:

Adults and adolescents aged 12 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation

- 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 of migalastat (Galafold); Galafold 123 mg hard capsules; last revised: April 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 24 November 2015, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 29 August 2023.

On 15 August 2023, the pharmaceutical company submitted a dossier for the benefit assessment of migalastat to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 6 VerfO.

By letter dated 15 August 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient migalastat.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 November 2023, and the written statement procedure was initiated with publication on the G-BA website on 15 November 2023. The deadline for submitting statements was 6 December 2023.

The oral hearing was held on 8 January 2024.

By letter dated 16 January 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 26 January 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 6 February 2024, and the proposed resolution was approved.

At its session on 15 February 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	24 November 2015	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	29 August 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	19 December 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	8 January 2024	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	16 January 2024 30 January 2024	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	6 February 2024	Concluding discussion of the draft resolution
Plenum	15 February 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 15 February 2024

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

Prof. Hecken