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
(new therapeutic indication: Fabry disease, 12 to < 16 years)

of 17 February 2022

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.

For medicinal products for the treatment of a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a paragraph 1 sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the marketing authorisation studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). According to Section 35a paragraph 2 SGB V, the assessment by the G-BA 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.

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).

On 19 August 2021, i.e. at the latest within four weeks after the notification of the pharmaceutical company of the approval of a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient migalastat with the new therapeutic indication (long-term treatment of adults and adolescents 12 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) who have an amenable mutation).

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

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the marketing authorisation studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 1 December 2021 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G21-25) and the statements made in the written statement and oral hearing procedure, as well as the amendment to the benefit assessment drawn up by the G-BA.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for the marketing authorisation considering their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1,

numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of migalastat.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of migalastat (Galafold) according to 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 17 February 2022):

Galafold is indicated for 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.

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of migalastat is assessed as follows:

Adolescents aged 12 to < 16 years with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Justification:

The AT1001-020 study is a completed, single-arm, open-label phase IIIb study in which 22 adolescents aged 12 to < 18 years and weighing ≥ 45 kg with diagnosis of Fabry disease and amenable (= migalastat-sensitive) GLA mutation were treated with migalastat. The study consists of two consecutive phases with a total study duration of 12 months. The study is divided into the following phases: Screening from day -30 to -14, phase 1 from month 0 to 1 (examination of safety and pharmacokinetics), phase 2 from month 1 to 12 (examination of pharmacodynamics, safety and efficacy) and a safety follow-up of 30 days.
Patients who have completed the AT1001-020 study can then participate in a long-term extension study (AT1001-036). The extension study is still ongoing.
The AT1001-020 study was conducted from August 2018 to February 2021 at one study site in the United Kingdom and 7 study sites in the United States.

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

For the benefit assessment, only the relevant study population of subjects aged 12 to < 16 years at the time of enrolment in the study is considered (mITT population: N = 15).

Mortality

There were no deaths in the AT1001-020 study. No statement can be made on the extent of the additional benefit as there is no control group.

Morbidity

Short Fabry Disease Patient Reported Outcome – Gastrointestinal (FABPRO-GI) and Pain Questionnaire for Clinical Trials (24h Version)

The FABPRO-GI was developed specifically for assessing gastrointestinal signs and symptoms in patients with Fabry disease. According to the study protocol, the short version of the FABPRO-GI and Pain Questionnaire for Clinical Trials (24h version) includes 4 questions on gastrointestinal signs and symptoms and 2 questions on pain, each referring to the last 24 hours. Patients record the frequency and consistency of their bowel movements using the Bristol Stool Scale. Patients also record the severity of their worst diarrhoea, constipation, abdominal pain and overall pain on a scale from 0 (none) to 10 (worst). No validation studies were provided for the questionnaire.

The FABPRO-GI and Pain Questionnaire for Clinical Trials (24h version) is not considered in the benefit assessment due to unproven validity.

Patient Global Impression of Change (PGI-C)

Using the PGI-C, patients assessed the perceived change in their symptomatology in the last 7 days compared to the reference time at the start of the study using a 7-point scale (from "very much better" to "very much worse"). The PGI-C in the AT1001-020 study consisted of 4 questions related to the symptoms "diarrhoea", "abdominal pain", "overall pain" and "activities of daily living" (e.g.: eating, sleeping, going to school, playing).

It was classified into subjects with "improvement", "deterioration" or "no change". For an "improvement", the categories "very much better", "better" and "a little better" were grouped, and for a "deterioration", the categories "very much worse", "worse" and "a little worse" were grouped. "No change" was categorised separately.

In month 12 or premature discontinuation, 6 subjects (50.0%) reported improvement in the PGI-C for "diarrhoea", "overall pain" and "activities of daily living" and 5 subjects (41.7%) reported improvement in the PGI-C for "abdominal pain" compared to the start of the study. Deterioration was reported by 1 subject each (8.3%) in the PGI-C for "abdominal pain", "overall pain" and "activities of daily living" in month 12 or with premature discontinuation.

Fabry-specific Paediatric Health and Pain Questionnaire (FPHPQ)

The FPHPQ measures Fabry disease-specific symptoms in children with Fabry disease and consists of 27 items (23 symptom-related and 4 outcome-related items). Symptom-related items include questions about pain, a burning sensation, fatigue, diarrhoea and flatulence.

These are grouped into 3 subscales ("pain associated with heat or exertion", "pain associated with cold" and "abdominal pain and fatigue"). Outcome-related items include items that assess whether children enjoy doing sports, participate in sports, get tired while doing sports, and get more tired compared to friends. The AT1001-020 study used 2 age-specific self-reported versions (8-12 or 13-18 years). Only the results on the three subscales of the FPHPQ are used. The ambiguities regarding the operationalisation of the FPHPQ could be clarified with the written statement of the pharmaceutical company.

The results of the a priori planned continuous evaluation are used for the benefit assessment. These are considered more significant than the responder analyses, since the measured values fluctuate over the course of the study and, in addition, a response was only detected for a few subjects during the study period. The return rate in relation to the entire relevant population (N = 15) was < 70% in month 9 and in month 12 or in the case of premature discontinuation, therefore the data in month 6 are presented in the resolution.

In summary, only the abdominal pain and fatigue subscales in both age-specific versions of the FPHPQ show a slight improvement in scores in month 6 compared to baseline.

Quality of life

Paediatric Quality of Life Inventory (PedsQL)

The PedsQL measures the general health-related quality of life in children and adolescents. It consists of four multi-dimensional scales (physical functioning, emotional functioning, social functioning and school functioning) and 3 summative scores (total score, physical health summative score, psychosocial health summative score). In the AT1001-020 study, both parents or a legally authorised person and the patient completed the age-appropriate version (version 8-12 or version 13-18 years) of the PedsQL independently.

The return rate in relation to the entire relevant population (N = 15) was < 70% in month 9 and in month 12 or in the case of premature discontinuation, therefore the data in month 6 are presented in the resolution. In summary, the PedsQL total score and the two summated scales show a slight improvement in the health-related quality of life up to month 6 compared to the baseline value.

Summary assessment of the endpoints examining symptomatology and the health-related quality of life:

The symptomatology of patients with Fabry disease are different from patient to patient, as it is a multi-system disease in which different organs can be in the foreground. In the present AT1001-020 study, among other things, disease-specific symptoms and patient-reported changes in symptomatology, as well as the health-related quality of life were assessed in adolescent patients with Fabry disease. The assessment of appropriate endpoints is of great importance in the benefit assessment and is expressly advocated by the G-BA. However, in the present assessment, no valid interpretation and assessment of the results on the present endpoints can be made due to the missing control group. Therefore, no statements on the additional benefit can be derived on the basis of these endpoints.

Side effects

Serious adverse events (SAEs) were observed in 1 of 14 subjects in the AT1001-020 study, and serious adverse events (SAEs CTCAE grade ≥ 3) occurred in 2 of 14 subjects during treatment with migalastat. In the AT1001-020 study, no subject discontinued the therapy with migalastat due to AEs.

AEs of any severity grade that occurred in ≥ 10% of the subjects in the study occurred most frequently (approx. 64% of patients) in the system organ class "infections and infestations". AEs in the system organ class "upper respiratory tract infections" were reported by 35.7% and "nervous system disorders" by 28.6% of the study participants. In slightly more than one fifth (n = 3) of the patients, AEs occurred in the system organ classes "musculoskeletal and connective tissue disorders", "respiratory, thoracic and mediastinal disorders" and "skin and subcutaneous tissue disorders". AEs of special interest were not defined.

In the overall analysis of the results on side effects, no statements on the extent of the additional benefit can be derived due to the absence of a control group.

Overall assessment / conclusion

The benefit assessment of migalastat for the treatment of adolescents aged 12 to < 16 years with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) who have an amenable mutation was based on the single-arm, uncontrolled AT1001-020 study. Results from the AT1001-020 study are available on patient-relevant endpoints in the categories of mortality, morbidity, quality of life and side effects.

There were no deaths in the AT1001-020 study. No statement can be made on the extent of the additional benefit as there is no control group.

The study also assessed endpoints on disease-specific symptoms and patient-reported change in symptomatology. Health-related quality of life was assessed with a measurement instrument suitable for the paediatric patient population. However, in the present assessment, no valid interpretation and assessment of the results can be made due to the absence of a control group. For the category of morbidity and quality of life, no statements can therefore be derived on the extent of the additional benefit.

In the category of side effects, no comparative assessment is possible on the basis of the results presented. No statement on the extent of the additional benefit can be derived.

In conclusion, the G-BA classifies the extent of the additional benefit of migalastat for the treatment of adolescents aged 12 to < 16 years with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) who have an amenable mutation as non-quantifiable due to the limited data based on the criteria in Section 5 paragraph 7 of the AM-NutzenV. There is an additional benefit in accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SBG V, but it is non-quantifiable since the scientific data does not allow a quantification.

Significance of the evidence

The benefit assessment is based on the single-arm, uncontrolled AT1001-020 study, which has a high risk of bias. No comparator studies were presented.
In the overall assessment, the result is a hint for a non-quantifiable additional benefit concerning the significance of the evidence.

2.1.3 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient migalastat (Galafold). Galafold was approved as an orphan drug. The therapeutic indication assessed here is as follows: "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) who have an amenable mutation."
For the benefit assessment, the pharmaceutical company submits the single-arm, uncontrolled AT1001-020 study with results on patient-relevant endpoints of the categories of mortality, morbidity, quality of life and side effects. The results have a high risk of bias due to the study design.

There were no deaths in the AT1001-020 study. No statement can be made on the extent of the additional benefit as there is no control group.

The study also assessed endpoints on disease-specific symptoms and patient-reported change in symptomatology. Health-related quality of life was assessed with a measurement instrument suitable for the paediatric patient population. However, in the present assessment, no valid interpretation and assessment of the results can be made due to the absence of a control group. For the category of morbidity and quality of life, no statements can therefore be derived on the extent of the additional benefit.

In the category of side effects, no comparative assessment is possible on the basis of the results presented. No statement on the extent of the additional benefit can be derived.

In the overall assessment, a hint for a non-quantifiable additional benefit is identified since the scientific data basis does not allow quantification.

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

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

The G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier. However, the number of patients in the SHI target population is subject to uncertainty. The considerable variation in the prevalence data used is taken into account by specifying a range. However, there is further uncertainty due to the calculation of the percentage of patients with underlying mutation of the GLA gene based on expert statement without information on age distribution.

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: 8 December 2021):
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 (EET).

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 January 2022).

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 hydrochloride	continuously, every 2 days	182.5	1	182.5

Consumption:

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.

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 is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Designation of the therapy	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 hydrochloride	123 mg	123 mg	1 x 123 mg	182.5	182.5 x 123 mg

Costs:

Costs of the medicinal products:

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 usage. 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.

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 hydrochloride 123 mg	14 HC	€ 18,768.85	€ 1.77	€ 0.00	€ 18,767.08

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
Abbreviations: HC = hard capsules					

LAUER-TAXE® last revised: 15 January 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account.

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 had to be taken into account.

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

On 19 August 2021, 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 2, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 1 December 2021 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 22 December 2021.

The oral hearing was held on 10 January 2022.

An amendment to the benefit assessment with a supplementary assessment was submitted on 24 January 2022.

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 were discussed at the session of the subcommittee on 8 February 2022, and the draft resolution was approved.

At its session on 17 February 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	23 November 2021	Information of the benefit assessment of the G-BA
Working group Section 35a	4 January 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	10 January 2022	Conduct of the oral hearing
Working group Section 35a	18 January 2022 1 February 2022	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal product	8 February 2022	Concluding discussion of the draft resolution
Plenum	17 February 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 17 February 2022

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

Prof. Hecken