Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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

At its session on 17 February 2022, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Migalastat in accordance with the resolution of 1 December 2016:

Migalastat

Resolution of: 17 February 2022
Entry into force on: 17 February 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 23 July 2021):

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.

1. Extent of the additional benefit and significance of the evidence

Migalastat 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 on orphan drugs. In accordance with 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.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

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

Extent of the additional benefit and significance of the evidence of Migalastat:

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

Study results according to endpoints:[1]

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no assessable data.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	n.a.	There are no assessable data.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

AT1001-020 study: Non-controlled phase III study

Relevant sub-population: mITT population (N = 15), age from 12 to < 16 years at the time of enrolment in the study

Mortality

Endpoint	Migalastat	
	N	*Patients with event n (%)*
No deaths have occurred		

Morbidity

Endpoint	Migalastat	
	N	*Patients with event n (%)*
Responder analyses for the PGI-C		
PGI-C - Diarrhoea		
Month 12 or premature discontinuation	15	12 (80.0)
Improvement[1)]	15	6 (50.0)
No change	15	6 (50.0)

[1] Data from the dossier assessment of the G-BA (published on 1. Dezember 2021), and from the amendment to the dossier assessment from 24. Januar 2022,, unless otherwise indicated.

Deterioration[2)]	15	0
PGI-C - Abdominal pain		
Month 12 or premature discontinuation	15	12 (80.0)
Endpoint	**Migalastat**	
	N	*Patients with event n (%)*
Improvement[1)]	15	5 (41.7)
No change	15	6 (50.0)
Deterioration[2)]	15	1 (8.3)
PGI-C - Total pain		
Month 12 or premature discontinuation	15	12 (80.0)
Improvement[1)]	15	6 (50.0)
No change	15	5 (41.7)
Deterioration[2)]	15	1 (8.3)
PGI-C - Activities of daily living		
Month 12 or premature discontinuation	15	12 (80.0)
Improvement[1)]	15	6 (50.0)
No change	15	5 (41.7)
Deterioration[2)]	15	1 (8.3)
Endpoint	**Migalastat**	
	N	n (%) MV (SD)
Changes in the FPHPQ (patient-reported age-appropriate versions of the FPHPQ)		
FPHPQ - Pain associated with heat or exertion[3)], version 8-12 years		
Baseline	3[4)]	3 (100) 33.0 (11.4)
Month 6 (change from baseline) [5)]	3[4)]	2 (66.7) -2.8 (0.7)

FPHPQ - Pain associated with heat or exertion[3], version 13–18 years		
Baseline	12[6]	10 (83.3) 28.0 (12.7)
Month 6 (change from baseline) [5]	12[6]	10 (83.3) 2.2 (7.4)
FPHPQ - Pain associated with cold [7], version 8-12 years		
Baseline	3[4]	3 (100) 19.7 (6.7)
Month 6 (change from baseline) [5]	3[4]	2 (66.7) -2.0 (2.8)
FPHPQ - Pain associated with cold [7], version 13-18 years		
Baseline	12[6]	10 (83.3) 16.8 (5.2)
Month 6 (change from baseline) [5]	12[6]	10 (83.3) 0.8 (2.7)
FPHPQ - Abdominal pain and fatigue [3], version 8-12 years		
Baseline	3[4]	3 (100) 31.0 (3.6)
Month 6 (change from baseline) [5]	3[4]	2 (66.7) 4.5 (2.1)
FPHPQ - Abdominal pain and fatigue [3], version 13-18 years		
Baseline	12[6]	10 (83.3) 25.8 (5.6)
Month 6 (change from baseline) [5]	12[6]	10 (83.3) 1.5 (6.6)

Health-related quality of life

Endpoint	**Migalastat**	
	N	n (%) MV (SD) *Change from baseline, MV (SD)*
Changes in the PedsQL, (patient-reported age-appropriate version of the PedsQL)		
PedsQL - Total score[8], version 8-12 years		
Baseline	3[4]	3 (100) 68.8 (23.2)
Month 6[5]	3[4]	2 (66.7) 94.6 (0.0) *13.1 (10.8)*

Endpoint	Migalastat	
	N	n (%) MV (SD) *Change from baseline, MV (SD)*
PedsQL - Total score[8], version 13-18 years		
Baseline	12[6]	10 (83.3) 71.0 (10.7)
Month 6[5]	12[6]	10 (83.3)[9] 77.4 (13.6) *6.5 (9.0)*
PedsQL - Physical health[8], version 8-12 years		
Baseline	3[4]	3 (100) 74.0 (21.3)
Month 6[5]	3[4]	2 (66.7) 96.9 (0.0) *10.9 (6.6)*
PedsQL - Physical health[8], version 13-18 years		
Baseline	12[6]	10 (83.3) 70.6 (15.6)
Month 6[5]	12[6]	10 (83.3)[9] 77.8 (19.2) *9.1 (13.9)*
PedsQL - Psychosocial health[8], version 8-12 years		
Baseline	3[4]	3 (100) 66.1 (24.4)
Month 6[5]	3[4]	2 (66.7) 93.3 (0.0) *14.2 (13.0)*
PedsQL - Psychosocial health[8], version 13-18 years		
Baseline	12[6]	10 (83.3) 71.2 (10.2)
Month 6[5]	12[6]	10 (83.3)[9] 77.3 (12.2) *5.1 (9.1)*

Side effects

Endpoint	Migalastat	
	N[10)]	*Patients with event n (%)*
Adverse events (AEs)	14	13 (92.9)
AE CTCAE grade ≥ 3	14	2 (14.3)
Serious adverse events (SAE)	14	1 (7.1)
Therapy discontinuation due to adverse events	14	0
AE with an incidence ≥ 10%, *MedDRA system organ class*, *preferred term*		
Gastrointestinal disorders	14	**2 (14.3)**
Infections and infestations	14	**9 (64.3)**
Influenza	14	2 (14.3)
Nasopharyngitis	14	2 (14.3)
Upper respiratory tract infection	14	5 (35.7)
Injury, poisoning and procedural complications	14	**2 (14.3)**
Investigations	14	**2 (14.3)**
Musculoskeletal and connective tissue disorders	14	**3 (21.4)**
Back pain	14	2 (14.3)
Nervous system disorders	14	**4 (28.6)**
Headaches	14	2 (14.3)
Psychiatric disorders	14	**2 (14.3)**
Respiratory, thoracic and mediastinal disorders	14	**3 (21.4)**
Skin and subcutaneous tissue disorders	14	**3 (21.4)**
Rash	14	2 (14.3)

[1)] Response categories "very much better", "better" and "a little better" summarised.
[2)] Response categories "very much worse", "worse" and "a little worse" summarised
[3)] Scale from 9 to 45; the higher the value the lower the number of conditions.
[4)] mITT population: For children aged ≤ 12 years, the version for 8- to 12-year-olds was used.
[5)] 3 study participants turned 13 during the course of the study and switched from the version for 8 to 12-year-olds to the one for 13 to 18-year-olds. Due to the version change, no results were reported by the pharmaceutical company for month 9 and month 12 or,

in the case of premature discontinuation, for all 3 study participants and for month 6 for 1 study participant. The return rate in relation to all study participants under 16 years of age was < 70% in month 9 and month 12 or in the case of premature discontinuation. Therefore, the FPHPQ and PedsQL data for both age versions are presented for the change from baseline to month 6.

[6] mITT population: For children aged > 12 years, the version for 13 to 18-year-olds was used.

[7] Scale from 5 to 25; the higher the value the lower the number of conditions.

[8] Scale from 0 to 100; the higher the value the better the quality of life.

[9] mITT population: Results for baseline values are available for 10 subjects, for changes from baseline to month 6 for 9 persons.

[10] mITT-safety population

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; FPHPQ: Fabry-specific Paediatric Health and Pain Questionnaire; MedDRA: Medical Dictionary for Regulatory Activities; mITT: modified Intention to Treat; MV: mean value; PGI-C: Patient Global Impression of Change; PedsQL: Pediatric Quality of Life Inventory; SD: standard deviation

2. Number of patients or demarcation of patient groups eligible for treatment

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

approx. 1 to 19 patients

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 (ERT).

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Migalastat hydrochloride	€ 244,642.29

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 January 2022)

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 17 February 2022.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 17 February 2022

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

Prof. Hecken