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) Pegunigalsidase alfa (Fabry disease)

of 21 March 2024

At its session on 21 March 2024, 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. Annex XII shall be amended in alphabetical order to include the active ingredient Pegunigalsidase alfa as follows:

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Pegunigalsidase alfa

Resolution of: 21 March 2024
Entry into force on: 21 March 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 4 May 2023):

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 March 2024):

See therapeutic indication according to marketing authorisation.

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

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

Appropriate comparator therapy:

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

Extent and probability of the additional benefit of pegunigalsidase alfa over agalsidase beta:

An additional benefit is not proven.

Study results according to endpoints:[1]

1 Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A23-95) unless otherwise indicated.

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Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↔	No relevant differences for the benefit assessment.
Health-related quality of life	∅	No data available.
Side effects	↔	No relevant differences overall for the benefit assessment. In detail, advantages for chest pain and respiratory, thoracic and mediastinal disorders.
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 ∅: No data available. n.a.: not assessable		

BALANCE study: Pegunigalsidase alfa **vs** agalsidase beta

Mortality

Endpoint	Pegunigalsidase alfa		Agalsidase beta		Pegunigalsidase alfa vs agalsidase beta
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Overall mortality	52	0	25	0	-

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Morbidity

Endpoint	Pegunigalsidase alfa		Agalsidase beta		Pegunigalsidase alfa vs agalsidase beta
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[b]
Worst pain (BPI-SF item 3)[a]	45	12 (26.7)	22	3 (13.6)	1.96 [0.61; 6.22] 0.300[b]
Pain severity (BPI-SF items 3–6 improvement at week 104)[a] (presented additionally)	45	5 (11.1)	22	1 (4.5)	2.44 [0.30; 19.68]; 0.433[b]
Impairment due to pain (BPI-SF item 9a–g improvement at week 104)[a]	45	5 (11.1)	22	2 (9.1)	1.22 [0.26; 5.81]; 0.800[b]
Endpoint for clinical morbidity / symptomatology of Fabry disease	No suitable data				
Health status (EQ-5D VAS, improvement at week 104)[c]	34	5 (15)	18	3 (17)	0.87 [0.21; 3.69]; 0.855

Health-related quality of life

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

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Side effects

Endpoint	Pegunigalsidase alfa		Agalsidase beta		Pegunigalsidase alfa vs agalsidase beta
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[b]
AEs (presented additionally)	52	47 (90.4)	25	24 (96.0)	–
Severe AEs[d]	52	8 (15.4)	25	6 (24.0)	0.64 [0.25; 1.65]; 0.413[b]
SAEs	52	15 (28.9)	25	7 (28.0)	1.03 [0.48; 2.20]; 0.987[b]
Discontinuation due to AEs	52	2 (3.8)	25	0 (0.0)	2.45 [0.12; 49.26][e]; 0.403[b]
Infusion-related reactions	No suitable data				
Chest pain (PT, SAEs)	52	0 (0.0)	25	2 (8.0)	0.10 [0.00; 1.97][e]; 0.042[b, f]
Respiratory, thoracic and mediastinal disorders (SOC, severe AEs)[g]	52	0 (0.0)	25	3 (12.0)	0.07 [0.00; 1.31][e]; 0.011[b, f]

a. A decrease by ≥ 15% compared to the start of study is considered a clinically relevant improvement (scale range 0 to 10). According to the information provided by the pharmaceutical company, 15% corresponds to a point value of 1.5 points, but only integer changes in the point value (≥ 2 points) could be selected and taken into account for the analysis.
b. IQWiG calculation, unconditional exact test (CSZ method according to Martín Andrés & Silva Mato, 1994)
c. An increase by ≥ 15 points compared to the start of study is considered clinically relevant (scale range 0 to 100).
d. Operationalised as CTCAE grade ≥ 3
e. In the case of 0 events in a study arm, the correction factor 0.5 was used in both study arms when calculating effect and CI.
f. Discrepancy between p value (exact) and CI (asymptotic) due to different calculation methods.
g. Includes 1 event each of the PTs acute respiratory failure, chronic obstructive pulmonary disease and pulmonary embolism

Abbreviations: BPI-SF: Brief Pain Inventory – Short Form; EQ-5D: European Quality of Life - 5 Dimensions; CI: confidence interval; n: number of patients with (at least 1) event; N: number of patients evaluated; PT: preferred term; RCT: randomised controlled trial; RR: relative risk; SOC: system organ class; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale

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

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

Approx. 60 to 1,260 patients

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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.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pegunigalsidase alfa	€ 357,190.82
Appropriate comparator therapy:	
Agalsidase alfa	€ 351,764.45
Agalsidase beta	€ 320,304.68
Migalastat	€ 244,639.69

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 March 2024)

Costs for additionally required SHI services: not applicable

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

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

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.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the

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medical treatment mandate, nor do they make statements about expediency or economic feasibility.

III. The resolution will enter into force on the day of its publication on the website of the G-BA on 21 March 2024.

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

Berlin, 21 March 2024

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

Prof. Hecken

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