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) Cipaglucosidase alfa (Pompe disease, combination with miglustat)

of 1 February 2024

At its session on 1 February 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 Cipaglucosidase alfa as follows:

Cipaglucosidase alfa

Resolution of: 1 February 2024
Entry into force on: 1 February 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 20 March 2023):

Pombiliti (cipaglucosidase alfa) is a long-term enzyme replacement therapy used in combination with the enzyme stabiliser miglustat for the treatment of adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency).

Therapeutic indication of the resolution (resolution of 1 February 2024):

See therapeutic indication according to marketing authorisation.

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

Adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency)

Appropriate comparator therapy:

Alglucosidase alfa

Extent and probability of additional benefit of cipaglucosidase alfa in combination with miglustat compared with alglucosidase alfa:

Hint for a minor additional benefit

Study results according to endpoints:[1]

Adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency)

1 Data from the dossier assessment of the IQWiG (A23-79) and from the addendum (A23-133), unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑	Advantage in the ability to move and in the energy level.
Health-related quality of life	∅	No data available.
Side effects	↔	No relevant difference for the benefit assessment.
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		

PROPEL study: RCT, direct comparison: Cipaglucosidase alfa + miglustat vs alglucosidase alfa + placebo, treatment over 52 weeks

Mortality

Endpoint	Cipaglucosidase alfa + miglustat		Alglucosidase alfa + placebo		Cipaglucosidase alfa + miglustat vs alglucosidase alfa + placebo
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator
Overall mortality					
	85	0 (0)	38	0 (0)	–

Morbidity

Endpoint	Cipaglucosidase alfa + miglustat		Alglucosidase alfa + placebo		Cipaglucosidase alfa + miglustat vs alglucosidase alfa + placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
R-PAct / PROMIS: deterioration in each case[b] (at week 52):					
Physical functioning (R-PAct)	85	1 (1)	38	0 (0)	–
Physical functioning (PROMIS Physical Function)	85	0 (0)		1 (3)	–
Fatigue (PROMIS Fatigue)	85	5 (6)	38	3 (8)	0.78 [0.18; 3.39] 0.739
Dyspnoea (PROMIS Dyspnoea Severity)	No suitable data				
Function of the upper extremities (PROMIS Upper Extremity)	85	4 (5)	38	0 (0)	1.41 [0.36; 5.54] 0.618
SGIC: Deterioration[c] (at week 52):					
General physical well-being	85	15 (18)	38	11 (29)	0.65 [0.33; 1.26]; 0.199
Breathing effort	85	7 (8)	38	4 (11)	0.79 [0.23; 2.75]; 0.715
Muscle power	85	15 (18)	38	11 (29)	0.65 [0.34; 1.25]; 0.195
Muscle function	85	12 (14)	38	11 (29)	0.50 [0.25; 1.02]; 0.057
Ability to move	85	9 (11)	38	13 (34)	0.32 [0.15; 0.67]; 0.002
Activities of daily living	85	8 (9)	38	5 (13)	0.82 [0.28; 2.41]; 0.714
Energy level	85	9 (11)	38	9 (24)	0.40 [0.18; 0.88]; 0.023
Muscle pain	85	16 (19)	38	9 (24)	0.78 [0.37; 1.66]; 0.515

[a] Cochran-Mantel-Haenszel (CMH) method; stratified by distance travelled in the 6MWT at start of study and enzyme replacement therapy status; endpoints collected using SGIC: missing values were replaced with the last value collected after start of study (post-baseline) (LOCF).

Endpoint	Cipaglucosidase alfa + miglustat		Alglucosidase alfa + placebo		Cipaglucosidase alfa + miglustat vs alglucosidase alfa + placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]

[b] Response threshold: 15% of the respective scale range (based on the transformed values).
[c] Defined as slightly deteriorated, severely deteriorated and very severely deteriorated compared to the start of study medication.

Abbreviations used:
6MWT: 6-minute walk test; CI: confidence interval; LOCF: last observation carried forward; N: number of patients evaluated; n: number of patients with (at least 1) event; PROMIS: Patient Reported Outcomes Measurement Information System; R-PAct: Rasch-built Pompe-specific Activity; RR: relative risk; SGIC: Subject's Global Impression of Change

Endpoint	Cipaglucosidase alfa + miglustat			Alglucosidase alfa + placebo			Cipaglucosidase alfa + miglustat vs alglucosidase alfa + placebo
	N[a]	Values at start of study MV (SD)	Change at week 52 MV (SE)	N[a]	Values at start of study MV (SD)	Change at week 52 MV (SE)	MD [95% CI]; p value[b]
Physical resilience							
6MWT [metres]	81	357.93 (111.84)	21.44 (5.75)[c]	37	350.14 (119.78)	16.11 (8.58)[c]	5.33 [-15.21; 25.88]; 0.608[c]
Motor function							
GSGC total value[d]	72	14.27 (5.04)	-0.56 (0.28)	31	13.97 (4.82)	0.74 (0.43)	−1.30 [−2.34; -0.26]; 0.015 SMD [95% CI] -0.51 [-0.94; -0.08]
Walking[e]	73	2.71 (1.09)	-0.09 (0.08)	35	2.67 (1.01)	0.12 (0.12)	-0.21 [-0.50; 0.08]
Climbing stairs[e]	67	3.63 (1.77)	-0.30 (0.14)	30	3.46 (1.84)	0.25 (0.21)	-0.55 [-1.06; -0.05]
Gowers manoeuvre[e]	63	4.41 (1.66)	0.12 (0.12)	27	4.52 (1.55)	0.10 (0.18)	0.01 [-0.42; 0.45]
Getting up from the chair[f]	73	3.84 (1.61)	-0.22 (0.12)	32	3.91 (1.54)	0.09 (0.19)	-0.31 [-0.76; 0.15]
Time [seconds] required to complete the individual GSGC tests[g] (presented additionally)							

Endpoint	Cipaglucosidase alfa + miglustat			Alglucosidase alfa + placebo			Cipaglucosidase alfa + miglustat vs alglucosidase alfa + placebo
	N[a]	Values at start of study MV (SD)	Change at week 52 MV (SE)	N[a]	Values at start of study MV (SD)	Change at week 52 MV (SE)	MD [95% CI]; p value[b]
- Walking [seconds]	80	9.68 (7.63)	-0.60 (0.63)	36	9.53 (5.44)	1.96 (0.95)	-2.56 [-4.85; -0.27]
- Climbing stairs [seconds]	78	13.95 (70.97)	-6.70 (0.85)	35	7.95 (9.67)	-3.64 (1.28)	-3.06 [-6.15; 0.04]
- Gowers manoeuvre [seconds]	61	10.84 (7.45)	-0.35 (0.79)	26	15.30 (11.68)	-1.92 (1.25)	1.57 [-1.44; 4.58]
- Getting up from the chair [seconds]	77	13.58 (86.05)	-7.50 (0.41)	33	4.42 (5.19)	-6.71 (0.63)	-0.80 [-2.305; 0.711]
TUG [seconds] (presented additionally)	75	12.88 (10.14)	-0.40 (0.76)	32	11.37 (4.99)	0.03 (1.19)	−0.43 [−3.29; 2.42]; 0.763
Health status							
EQ-5D VAS[h]	84	68.86 (18.25)	0.05 (1.54)	37	71.91 (15.20)	3.87 (2.36)	-3.82 [-9.51; 1.87]; 0.187

[a] Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at start of study can be based on other patient numbers.
[b] Unless otherwise stated, MV and SE (mean change at week 52 per treatment group) as well as MD, CI and p value (group comparison): ANCOVA without repeated measures modelling; adjusted for value at the start of study, enzyme replacement therapy status, sex, age, weight and height
[c] MV and SE (mean change at week 52 per treatment group) as well as MD, CI and p value (group comparison): MMRM; adjusted for value at the start of study, enzyme replacement therapy status, sex, age, weight and height
[d] Lower (decreasing) values mean better motor function (scale range 4 to 27); negative effects (intervention minus comparison) mean an advantage for the intervention.
[e] Lower (decreasing) values mean better motor function (scale range 1 to 7); negative effects (intervention minus comparison) mean an advantage for the intervention.
[f] Lower (decreasing) values mean better motor function (scale range 1 to 6); negative effects (intervention minus comparison) mean an advantage for the intervention.
[g] The time required is not included in the GSGC total value.
[h] Higher (increasing) values mean better health status (scale range 0 to 100); positive effects (intervention minus control) mean an advantage for the intervention.

Abbreviations used:

Endpoint	Cipaglucosidase alfa + miglustat			Alglucosidase alfa + placebo			Cipaglucosidase alfa + miglustat vs alglucosidase alfa + placebo
	N[a]	Values at start of study MV (SD)	Change at week 52 MV (SE)	N[a]	Values at start of study MV (SD)	Change at week 52 MV (SE)	MD [95% CI]; p value[b]
6MWT: 6-minute walk test; ANCOVA: analysis of covariance; GSGC: Gait, Stairs, Gowers Manoeuvre, Chair; CI: confidence interval; MD: mean difference; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; RR: relative risk; SD: standard deviation; SE: standard error; SMD: standardised mean difference; VAS: visual analogue scale							

Health-related quality of life

No data available.

Side effects

Endpoint	Cipaglucosidase alfa + miglustat		Alglucosidase alfa + placebo		Cipaglucosidase alfa + miglustat vs alglucosidase alfa + placebo
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value
AEs (presented additionally)	85	81 (95)	38	37 (97)	–
SAEs	85	8 (9)	38	1 (3)	3.58 [0.50; 25.61]; 0.205
Discontinuation due to AEs	85	2 (2)	38	1 (3)	0.86 [0.09; 8.63]; 0.898
Abbreviations used: n: number of patients with (at least 1) event; N: number of patients evaluated; SAE: serious adverse event; AE: adverse event;					

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

Adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency)

approx. 170 – 1,760 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 Pombiliti (active ingredient: cipaglucosidase alfa) at the following publicly accessible link (last access: 12 December 2023):

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

Treatment with cipaglucosidase alfa should only be initiated and monitored by doctors experienced in treating patients with Pompe disease or other congenital metabolic diseases or neruomuscular diseases.

4. Treatment costs

Annual treatment costs:

Adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency)

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Cipaglucosidase alfa	€ 624,935.79
Miglustat	€ 5,794.81
Total:	€ 630,730.60
Appropriate comparator therapy:	
Alglucosidase alfa	€ 616,383.28

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 January 2024)

Costs for additionally required SHI services: not applicable

5. 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 cipaglucosidase alfa

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients which, on the basis of the marketing authorisation under Medicinal Products Act, can be used in a combination therapy with cipaglucosidase alfa for the treatment of adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency):

Adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency)

- No active ingredient that can be used in a combination therapy that 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 medical treatment mandate, nor do they make statements about expediency or economic feasibility.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 1 February 2024.

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

Berlin, 1 February 2024

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

Prof. Hecken