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
Olipudase Alfa (acid sphingomyelinase deficiency (ASMD) type A/B or B)

of 16 March 2023

At its session on 16 March 2023, 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 Olipudase alfa as follows:

Olipudase alfa

Resolution of: 16 March 2023
Entry into force on: 16 March 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 24 June 2022):

Xenpozyme is indicated as an enzyme replacement therapy for the treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in paediatric and adult patients with type A/B or type B.

Therapeutic indication of the resolution (resolution of 16 March 2023):

See therapeutic indication according to marketing authorisation.

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

Olipudase alfa 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 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).

a) <u>Adults with non-Central Nervous System (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) with type A/B or B</u>

Extent of the additional benefit and significance of the evidence of olipudase alfa:

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

b) <u>Children and adolescents with non-Central Nervous System (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) with type A/B or B</u>

Extent of the additional benefit and significance of the evidence of olipudase alfa:

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

Study results according to endpoints:[1]

a) Adults with non-Central Nervous System (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) with type A/B or B

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↑	Advantage in spleen volume
Health-related quality of life	↔	No relevant difference for the benefit assessment.
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 ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

ASCEND study: double-blind RCT, olipudase alfa vs placebo, 52 weeks, ≥ 18 years

[1] Data from the dossier assessment of the G-BA (published on 2. January 2023), unless otherwise indicated.

Mortality

ASCEND study Endpoint	Olipudase alfa		Placebo		Olipudase alfa vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value
Overall mortality					
No deaths occurred.					

Morbidity

ASCEND study Endpoint	Olipudase alfa			placebo			Olipudase alfa vs placebo
	N[a)]	Baseline MV (SD)	Week 52 LS mean (SE)	N[a)]	Baseline MV (SD)	Week 52 LS mean (SE)	LS mean difference [95% CI]; p value
Diffusion capacity of the lung for carbon monoxide (DL_{CO})[b)] (presented additionally)							
Percentage change in DL_{CO} from the setpoint	17	49.4 (11.0)	22.0 (3.3)	17	48.5 (10.8)	3.0 (3.4)	19.0 [9.3; 28.7]; < 0.001
Spleen volume[b)]							
Percentage change in spleen volume (MN)	18	11.7 (4.9)	-39.4 (2.4)	17	11.2 (3.8)	0.5 (2.5)	-39.9 [-47.1; -32.8]; < 0.001
Liver volume (presented additionally)[2]							
Percentage change in liver volume (MN)	17	1.4 (0.3)	-28.1 (2.5)	17	1.6 (0.5)	-1.5 (2.5)	-26.6 [-33.9; -19.3]; < 0.001
Brief Fatigue Inventory (BFI)[c)]							
BFI item 3 (strongest fatigue)	16	6.4 (2.6)	-1.9 (0.5)	15	7.0 (2.4)	-1.8 (0.5)	-0.06 [-1.57; 1.45]; 0.940
Brief Pain Inventory – Short Form (BPI-SF)[d)]							

[2] Data from the dossier

ASCEND study Endpoint	Olipudase alfa			placebo			Olipudase alfa vs placebo
	N[a)]	Baseline MV (SD)	Week 52 LS mean (SE)	N[a)]	Baseline MV (SD)	Week 52 LS mean (SE)	LS mean difference [95% CI]; p value
BPI-SF item 3 (worst pain)	16	4.7 (2.6)	-1.4 (0.6)	15	5.9 (2.7)	-2.3 (0.6)	0.9 [-0.8; 2.6]; 0.293
EQ-5D-5L-VAS[e)]							
	18	52.1 (17.0)	8.0 (4.2)	17	63.9 (20.7)	15.5 (4.3)	-7.5 [-20.1; 5.1]; 0.235
Patient Global Impression of Symptom Severity (PGIS)[f)]							
Abdominal disorders	12	1.9 (1.1)	-0.8 (0.2)	13	1.9 (1.2)	-0.5 (0.2)	-0.2 [-0.9; 0.4]; 0.466
Physical pain	12	1.5 (1.1)	-0.9 (0.3)	13	1.6 (1.2)	-0.4 (0.3)	-0.4 [-1.4; 0.5]; 0.319
Fatigue	12	2.3 (1.0)	-0.9 (0.2)	13	2.3 (1.2)	-0.9 (0.2)	0.04 [-0.7; 0.7]; 0.907
Dyspnea	12	1.8 (1.0)	-0.6 (0.2)	13	1.1 (1.0)	-0.6 (0.2)	-0.06 [-0.8; 0.7]; 0.860
Patient Global Impression of Change (PGIC)[g)]							
Abdominal disorders	18		1.3 (0.3)	16		0.5 (0.3)	0.7 [-0.2; 1.6]; 0.103
Physical pain	18		1.1 (0.3)	16		0.6 (0.3)	0.4 [-0.4; 1.3]; 0.320
Fatigue	18		1.1 (0.3)	16		0.4 (0.3)	0.7 [-0.2; 1.5]; 0.120
Dyspnea	17		1.1 (0.3)	16		0.3 (0.3)	0.8 [0.01; 1.6]; 0.048 *Hedges' g 0.70 [-0.01; 1.42]*[h]
Ability to perform daily activities	17		1.3 (0.3)	16		0.6 (0.3)	0.8 [-0.05; 1.6]; 0.064

ASCEND study Endpoint	Olipudase alfa		placebo		Olipudase alfa vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Reduction in spleen size ≥ 30% (responder analysis)[i] (presented additionally)					
Spleen size ≥ 30% at week 52	18	17 (94.4)	18	0 (0)	n.c. [n.c.; n.c.]; n.c.
Improvement in DL_{CO} by ≥ 15% (responder analysis)[i] (presented additionally)					
DL_{CO} ≥ 15% at week 52	18	5 (27.8)	18	0 (0)	-[j]

Quality of life

ASCEND study Endpoint	Olipudase alfa			placebo			Olipudase alfa vs placebo
	N[a]	Baseline MV (SD)	Week 52 MV (SD) LS mean [95% CI]	N[a]	Baseline MV (SD)	Week 52 MV (SD) LS mean [95% CI]	LS mean difference [95% CI]; p value
SF-36[k]							
Mental summated scale	18	43.8 (9.7)	0.3 (2.5)	17	45.3 (10.2)	0.2 (2.6)	0.09 [-7.4; 7.5]; 0.980
Physical summated scale	18	37.6 (7.0)	8.7 (1.8)	17	40.0 (10.7)	8.8 (1.9)	0.02 [-5.38; 5.42]; 0.995

ASCEND study Endpoint	Olipudase alfa		placebo		Olipudase alfa vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Total adverse events (presented additionally)					
	18	18 (100)	18	18 (100)	-
Serious adverse events (SAEs)					
	18	3 (16.7)	18	4 (22.2)	0.75 [0.19; 3.03]; 0.678
Severe adverse events[l)]					
	18	1 (5.6)	18	6 (33.3)	0.17 [0.02; 1.34]; 0.090
Therapy discontinuation due to adverse events					
	18	0 (0)	18	0 (0)	-
AE with an incidence of ≥ 20% in one of the study arms and a difference of ≥ 15% between the treatment groups ***MedDRA system organ class*** Preferred term					
Blood and lymphatic system disorders	**18**	**1 (5.6)**	**18**	**4 (22.2)**	**0.25 [0.03; 2.19]; 0.203**
Nervous system disorders	**18**	**13 (72.2)**	**18**	**9 (50.0)**	**1.44 [0.82; 2.54]; 0.194**
Headache	18	12 (66.7)	18	8 (44.4)	1.50 [0.80; 2.83]; 0.202
Respiratory, thoracic and mediastinal disorders	**18**	**9 (50.0)**	**18**	**5 (27.8)**	**1.80 [0.73; 4.47]; 0.198**
Cough	18	5 (27.8)	18	2 (11.1)	2.50 [0.53; 11.89]; 0.241
Gastrointestinal disorders Nausea	18	3 (16.7)	18	8 (44.4)	0.37 [0.11; 1.24]; 0.105
Vomiting	18	1 (5.6)	18	7 (38.9)	0.14 [0.02; 1.13]; 0.064
Reproductive system and breast disorders	**18**	**0 (0)**	**18**	**4 (22.2)**	-[j)]

a) The number corresponds to those subjects who were used to calculate the respective statistics for week 52.

b) Primary endpoint of the ASCEND study

c) Higher values correspond to greater fatigue.

ASCEND study Endpoint	Olipudase alfa		placebo		Olipudase alfa vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value

d) Higher values correspond to greater pain.
e) Higher values correspond to a better health status.
f) Higher values correspond to higher symptom severity.
g) Higher values correspond to an improvement.
h) Calculation of the G-BA
i) Only subjects with a baseline value were included in the responder analysis. Subjects with a missing value at week 52 were counted as non-responders.
j) No adequate estimate.
k) Higher values correspond to better quality of life.
l) Severe AEs: The study's own criteria were used for severity grading.

Abbreviations: BFI: Brief Fatigue Inventory; BPI-SF: Brief Pain Inventory – Short Form; EQ-5D-5L: European Quality of Life 5-Dimension 5-Level; CI: confidence interval; LS: least squares; MedDRA: Medical Dictionary for Regulatory Activities; MV: mean value; MN: multiple of the normal; n.c.: not calculable; PGIS: Patient Global Impression of Symptom Severity; RR: relative risk; SF-36: Short-Form 36; SD: standard deviation; SE: standard error; (S)AE: (serious) adverse event; VAS: visual analogue scale.

b) Children and adolescents with non-Central Nervous System (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) with type A/B or B

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	The data are not assessable.
Morbidity	↑	Advantage in body height (z score) and spleen volume, both at week 52 compared to baseline
Health-related quality of life	n.a.	The data are not assessable.
Side effects	n.a.	The data are not assessable.

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

ASCEND-Peds study: open-label, single-arm phase I/II study, 64 weeks, ≤ 18 years

Mortality

ASCEND-Peds study Endpoint	Olipudase alfa	
	N	Patients with event n (%)
Overall mortality		
No deaths occurred.		

Morbidity

ASCEND-Peds study Endpoint	N[a)]	Olipudase alfa ***Baseline*, MV (SD)** ***Change from baseline at week 52 LS mean [95% CI]; p value***
Percentage change in spleen volume	20	19.0 (8.8) *-49.2 [-53.4; -45.0];* *< 0.001*
Percentage change in DL_{CO} (presented additionally)	9[b)]	54.8 (14.2) *32.9 [13.4; 52.2];* *0.005*
Percentage change in liver volume (presented additionally)[2]	20	1.5 (0.3) *-40.6* *[-44.1; -37.1] < 0.001*
Body height (z score)	19	-2.1 (0.8) *0.6 [0.4; 0.7]; < 0.001*
PedsQL Multidimensional Fatigue Scale (patient-reported, version 5-18 years)		
Total score[c)]	13	73.5 (12.7) *13.3 [8.8; 17.8]; < 0.001*
PedsQL Multidimensional Fatigue Scale (parent-reported, version 2-4 years)		
Total score[c)]	4	81.3 (4.3) *9.4 [3.9; 14.8]; 0.018*
PedsQL Paediatric Pain Questionnaire (patient-reported, version 5–18 years)		
Current pain[d)]	11	4.4 (6.9) *-1.8 [-3.6; -0.1]; 0.044*
Worst pain[d)]	11	11.4 (16.1) *1.1 [-14.7; 16.9]; 0.879*

Quality of life

ASCEND-Peds study **Endpoint**	**N**[a)]	**Olipudase alfa** ***Baseline*, MV (SD)** ***Change from baseline at week 52*** ***LS mean difference [95% CI]; p value***
PedsQL core module (patient-reported, version 5-18 years)		
Total score[e)]	13	73.0 (11.9) *7.6 [4.2; 11.0]; < 0.001*
Physical health[e)]	13	76.9 (14.6) *9.4 [5.4; 13.3]; < 0.001*
Psychosocial health[e)]	13	70.8 (12.4) *6.8 [1.5; 12.0]; 0.016*
PedsQL core module (parent-reported, version 2-4 years)		
Total score[e)]	4	82.9 (8.8) *7.3 [-9.5; 24.0]; 0.202*
Physical health[e)]	4	87.5 (8.1) *11.7 [9.1; 14.3]; 0.003*
Psychosocial health[e)]	4	80.0 (11.5) *4.6 [-24.1; 33.4]; 0.561*

Side effects

ASCEND-Peds study **Endpoint**	**Olipudase alfa**	
	N	**Patients with event** **n (%)**
Total adverse events (presented additionally)	20	20 (100)
Serious adverse events (SAEs)	20	5 (25.0)
Severe adverse events[f)]	20	3 (15.0)
Therapy discontinuation due to adverse events	20	0 (0)

a) The number corresponds to those subjects who were used to calculate the respective statistics for week 52.
b) DL_{CO} was only measured from an age of ≥ 5 years at baseline by pulmonary function test
c) Higher values correspond to less fatigue.
d) Higher values correspond to more severe pain.
e) Higher values correspond to better quality of life.
f) The study's own criteria were used for severity grading.

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

Patients with non-Central Nervous System (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) with type A/B or B

approx. 70 - 80 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 Xenpozyme (active ingredient: olipudase alfa) at the following publicly accessible link (last access: 23 November 2022):

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

Treatment with olipudase alfa should only be initiated and monitored by doctors experienced in ASMD therapy.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient card). In particular, the training material contains information and warnings on the risk of severe hypersensitivity or anaphylaxis.

4. Treatment costs

Annual treatment costs:

Patients with non-Central Nervous System (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) with type A/B or B

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Olipudase alfa	€ 194,814.28 - € 1,168,885.70

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 March 2023)

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 Olipudase 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 olipudase alfa for the treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in children, adolescents and adults with type A/B or B:

a) Adults with non-Central Nervous System (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) with type A/B or B

- No active ingredient that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

b) Children and adolescents with non-Central Nervous System (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) with type A/B or B

- 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 16 March 2023.

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

Berlin, 16 March 2023

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

Prof. Hecken