GBA
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 (new assessment of orphan drug > 30 million: Acid Sphingomyelinase Deficiency (ASMD) type A/B or type B)

of 15 October 2026

At their session on 15 October 2026, the Federal Joint Committee (GBA) 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 information on the active ingredient Olipudase alfa in the version of the resolution of 16 March 2023 (Federal Gazette, BAnz AT 18.04.2023 B6) shall be replaced by the following information:**

Courtesy translation – only the German version is legally binding.

Olipudase alfa

Resolution of: 15 October 2026
Entry into force on: 15 October 2026
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 15 October 2026):

See therapeutic indication according to marketing authorisation.

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

a) Adults with non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or type B

Appropriate comparator therapy for olipudase alfa:

Best supportive care

Extent and probability of the additional benefit of olipudase alfa compared to best supportive care:

Hint of non-quantifiable additional benefit.

b) Children and adolescents with non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or type B

Appropriate comparator therapy for olipudase alfa:

Best supportive care

Extent and probability of the additional benefit of olipudase alfa compared to the appropriate comparator therapy:

Hint of non-quantifiable additional benefit.

Courtesy translation – only the German version is legally binding.

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 type 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 the endpoint "change in spleen volume".
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↔	No relevant differences 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		

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

Mortality

Endpoint	Olipudase alfa + BSC		Placebo + BSC		Olipudase alfa + BSC vs placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
Overall mortality[b]					
	18	0 (0)	18	0 (0)	-

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A26-48), unless otherwise indicated.

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Morbidity

Endpoint category; Endpoint	Olipudase alfa + BSC		Placebo + BSC		Olipudase alfa vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
Splenomegaly-related symptomatology					
Splenomegaly-related symptomatology	No suitable data				
Fatigue (BFI total score)	No data submitted				
Most severe fatigue (BFI item 3 – improvement at week 52[c])	18	6 (33.3)	17[d]	5 (29.4)	1.26 [0.45; 3.56]; 0.651
Pain (BPI-SF total score)	No suitable data				
Dyspnoea (FACIT-Dyspnoea-SF)	No suitable data				
Health status (improvement at week 52[e])					
EQ-5D VAS	18	10 (55.6)	18	7 (38.9)	0.85 [0.17; 4.39]; 0.844

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Endpoint category; Endpoint	Olipudase alfa			Placebo			Olipudase alfa vs placebo
	N[f]	Values at the start of the study MV (SD)	Mean percentage change MV (SE)[b]	N[f]	Values at the start of the study MV (SD)	Mean percentage change MV (SE)[g]	Mean difference [95% CI]; p value[g]
Spleen volume[h]							
Change at week 52	18	11.7 (4.9)	−39.5 (2.4)	17	11.2 (3.8)	0.5 (2.5)	−39.93 [−47.05; −32.80]; < 0.001
Change at week 236[i]	15	11.7 (4.9)	−59.7 (1.8)	–[j]			
Change at week 260[k] *(presented additionally)*	13	11.7 (4.9)	−62.1 (3.0)	–[l]			
Lung diffusion capacity for carbon monoxide (DL_{CO})[2] *(presented additionally)*							
Change at week 52	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
Liver volume[2] *(presented additionally)*							
Change at week 52	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

[2] Data from the dossier

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Endpoint category; Endpoint	Olipudase alfa + BSC		Placebo + BSC		Olipudase alfa vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Patient Global Impression of Severity (PGIS)[2] (improvement ≥ 0.6 points at week 52)					
Abdominal disorders	12	7 (58.3)	16	5 (31.3)	1.32 [0.54; 3.22] 0.522
Physical pain	12	6 (50.0)	16	6 (37.5)	0.92 [0.32; 2.62] 0.872
Fatigue	12	7 (58.3)	16	8 (50.0)	1.24 [0.43; 3.55] 0.674
Dyspnoea	12	7 (58.3)	16	4 (25.0)	1.29 [0.43; 3.90] 0.634
Patient Global Impression of Change (PGIC)[2] (improvement ≥ 1, 2 or 3 points at week 52)					
Abdominal disorders	18	11 (61.1)	18	6 (33.3)	1.83 [0.84; 3.99] 0.123
Physical pain	18	9 (50.0)	18	6 (33.3)	1.50 [0.65; 3.44] 0.328
Fatigue	18	10 (55.6)	18	7 (38.9)	1.43 [0.68; 2.99] 0.333
Dyspnoea	18	11 (61.1)	18	5 (27.8)	2.20 [0.93; 5.21] 0.072
Ability to perform daily activities	18	12 (66.7)	18	6 (33.3)	2.00 [0.94; 4.27] 0.072

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Health-related quality of life

Endpoint	Olipudase alfa		Placebo		Olipudase alfa vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
SF-36 (improvement at week 52[m])					
Physical Component Summary (PCS) score	18	8 (44.4)	18	8 (44.4)	0.97 [0.50; 1.90]; 0.935
Mental Component Summary (MCS) score	18	3 (16.7)	18	3 (16.7)	0.91 [0.25; 3.34]; 0.886

Side effects

Endpoint	Olipudase alfa		Placebo		Olipudase alfa vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
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 [n, 2]	18	1 (5.6)	18	6 (33.3)	0.17 [0.02; 1.34]; 0.090
Therapy discontinuation due to AEs	18	0 (0)	18	0 (0)	–
Infusion-related reactions	No suitable data				

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a. Logistic regression, adjusted for the value at the start of the study, except for the endpoint of SAEs
b. The results on overall mortality are based on the data on fatal AEs.
c. A reduction by ≥ 1.7 points (BFI-SF item 3) and ≥ 4 points (BPI-SF item 3), respectively compared with the start of the study is considered as clinically relevant improvement (scale range: 0 to 10).
d. Discrepancy between the information in Module 4 A and the study documents. The data presented are from Module 4.
e. An increase by ≥ 15 points compared to the start of the study is considered as clinically relevant improvement (scale range: 0 to 100).
f. Number of patients who were taken into account in the effect estimation; the values at the start of the study can be based on other patient numbers.
g. Analysis at week 52: MMRM with percentage change from baseline (presumably the difference from baseline, divided by the baseline value and expressed as a percentage) as the dependent variable, and adjusted for baseline value, age at baseline, treatment arm, visit, as well as the interaction between visit and treatment, using an unstructured covariance matrix; analysis at week 236/260: Covariance analysis with percentage change from baseline as the dependent variable, adjusted for the baseline value.
h. In the study, spleen volume was measured using MRI of the abdomen; it was initially expressed in cubic millimetres and then converted to the unit MN using the following formula: Spleen volume [MN] = spleen volume (cm^3) / (2 × weight [kg]).
i. The point in time at which at least 70% of patients are still included in the analysis.
j. Results for patients in the comparator arm who switched to olipudase alfa after the end of the randomised phase: values at the start of the study (MV [SD]): 11.2 (3.8); mean percentage change in N = 13 patients with values at week 236 (MV [SE]): −56.1 (1.9). MD [95% CI] between the treatment arms: 3.6 [−9.1; 1.8].
k. Change at the latest time point recorded in the study. It is unclear whether the low number of patients is due to administrative or other reasons.
l. Results for patients in the comparator arm who switched to olipudase alfa after the end of the randomised phase: values at the start of the study (MV [SD]): 11.2 (3.8); mean percentage change in N = 11 patients with values at week 260 (MV [SE]): −49.3 (3.3). MD [95% CI] between the treatment arms: −12.8 [−22.2; −3.5].
m. An increase in the PCS and MCS by ≥ 10 points is considered as clinically relevant improvement (scale range: 7.3 to 70.1 for the PCS and 5.8 to 69.9 for the MCS).
n. Severe AEs: The study criteria were used for severity grading. The operationalisation is unsuitable for reliably distinguishing between severe AEs and non-severe AEs.

BFI: Brief Fatigue Inventory; BPI-SF: Brief Pain Inventory – Short Form; BSC: Best Supportive Care; FACIT-Dyspnea-SF: Functional Assessment of Chronic Illness Therapy – Dyspnoea – Short Form; CI: confidence interval; MCS: mental component summary score; MMRM: mixed model for repeated measures; MN: multiple of the normal value; MRI: magnetic resonance imaging; MV: mean value; MD: mean difference; n: number of patients with (at least 1) event; N: number of patients evaluated; PCS: physical component summary score; RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SE: standard error; SF-36: Short Form 36 health survey; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale

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b) Children and adolescents with non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or type 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	↑	Improvement in spleen volume and body height (z score), each 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
∅: No data available.
n.a.: not assessable

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

Mortality

Endpoint	Olipudase alfa	
	N	Patients with event n (%)
Overall mortality[a]		
	20	0 (0)

Morbidity

Endpoint	Olipudase alfa		
	N[b]	Values at the start of the study MV (SD)	Change at time point MD[c] (SE)
Spleen volume[c]			
Percentage change at week 52 (12 months)	20	19.0 (8.8)	−49.2 (2.0)
Percentage change at week 157 (36 months)[d, e]	17	19.0 (8.8)	−67.4 (1.5)
Body height (z score)			
Change at week 52	19	−2.1 (0.8)[f]	0.6 (0.1)

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Change at week 183 (42 months)[d, e]	14	−2.1 (0.8)[e]	1.7 (0.1)
Percentage change in DL_{CO} [2] *(presented additionally)*			
Change at week 52	9	54.8 (14.2)	32.9 (8.3)
Percentage change in liver volume [2] *(presented additionally)*			
Change at week 52	20	2.7 (0.7)	-40.6 (1.67)
Fatigue *(presented additionally)*			
Total score PedsQL-MFS (change at week 52)[e, g, h]			
Patient-reported	*13*	*73.5 (12.7)*	*13.3 (2.0)*
Parent-reported	*18*	*79.0 (12.1)*	*7.9 (2.2)*
General fatigue (presented additionally)			
Patient-reported	*13*	*77.0 (15.6)*	*13.4 (2.4)*
Parent-reported	*18*	*72.9 (21.8)*	*15.7 (3.3)*
Sleep/rest fatigue (presented additionally)			
Patient-reported	*13*	*67.8 (12.9)*	*16.2 (3.0)*
Parent-reported	*18*	*75.7 (17.6)*	*8.6 (3.3)*
Cognitive fatigue (presented additionally)			
Patient-reported	*13*	*75.6 (18.1)*	*10.6 (2.1)*
Parent-reported	*18*	*88.4 (12.6)*	*−0.7 (3.4)*
Pain (PedsQL-PPQ – Change at week 52)[e, i, j] *(presented additionally)*			
Current pain intensity			
Patient-reported	*13*	*4.4 (6.9)*	*−1.8 (0.8)*
Parent-reported	*12*[f]	*4.4 (9.9)*	*0.6 (1.6)*
Worst pain			
Patient-reported	*11*[f]	*11.4 (16.1)*	*1.1 (7.0)*
Parent-reported	*12*[f]	*8.1 (17.3)*	*6.4 (6.0)*

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Health-related quality of life

Endpoint	Olipudase alfa		
	N[b]	Values at the start of the study MV (SD)	Change at time point MD[c] (SE)
PedsQL (change at week 52)[e, g, k] *(presented additionally)*			
GCS			
Patient-reported	*13*	*73.0 (11.9)*	*7.6 (1.5)*
Parent-reported	*18*	*70.7 (15.7)*	*10.8 (2.4)*
Psychosocial health score (presented additionally)			
Patient-reported	*13*	*70.8 (12.4)*	*6.8 (2.4)*
Parent-reported	18	71.0 (13.6)	8.2 (2.9)
Physical functioning score (presented additionally)			
Patient-reported	13	76.9 (14.6)	9.4 (1.8)
Parent-reported	18	70.0 (23.7)	15.5 (2.9)

Side effects

Endpoint	Olipudase alfa	
	N	Patients with event n (%)
Side effects		
AEs *(presented additionally)*	20	20 (100)
SAEs	20	5 (25)
Severe adverse events[m, 2]	20	3 (15.0)
Discontinuation due to AEs	20	0 (0)
Infusion-related reactions		No suitable data

a. The results on overall mortality are based on the data on fatal AEs.
b. Number of patients who were taken into account in the change; the values at the start of the study can be based on other patient numbers.
c. In the study, spleen volume was measured using MRI of the abdomen; it was initially expressed in cubic millimetres and then converted to the unit MN using the following formula: Spleen volume [MN] = spleen volume (cm^3) / (2 × weight [kg])
d. Results of the LTS13632 study. The start of the LTS13632 study is defined as the start of the preceding ASCEND-Peds study.
e. The point in time at which at least 70% of patients are still included in the analysis.
f. Discrepancy between the information in Module 4 A and the study documents. The data presented are from the study documents.

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g. The questionnaire is available for children 2 years of age and older. There are different age-specific versions for assessment by paediatric patients and/or their parents. Only a parent's version is available for children 2 – 4 years of age. According to the pharmaceutical company, a maximum of 15 patients may be included in the analysis of patient-reported data and a maximum of 19 patients in the analysis of parent-reported data.
h. Higher (increasing) values mean better symptomatology (scale range: 0 to 100).
i. The questionnaire is available for children 2 years of age and older. There are different age-specific versions for assessment by paediatric patients and/or their parents. Only a parent's version is available for children 2 – 4 years of age. However, this was not used in the ASCEND-Peds study. According to the pharmaceutical company, a maximum of 15 patients may be included in the analysis of patient- and parent-reported data.
j. Lower (decreasing) values mean better symptomatology (scale range: 0 to 100).
k. Higher (increasing) values mean better health-related quality of life (scale range: 0 to 100).
l. Higher (increasing) values mean better health-related quality of life (scale range: 0 to 100).
m. Severe AEs: The study criteria were used for severity grading. The operationalisation is unsuitable for reliably distinguishing between severe AEs and non-severe AEs.

GCS: Generic Core Scales; CI: confidence interval; MFS: Multidimensional Fatigue Scale; MV: mean value; MD: mean difference; n: number of patients with (at least 1) event; N: number of patients evaluated; n.c.: not calculable; PedsQL: Paediatric Quality of Life Inventory; PPQ: Paediatric Pain Questionnaire; RCT: randomised controlled trial; SD: standard deviation; SE: standard error; SAE: serious adverse event; AE: adverse event

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

Children, adolescents and adults with non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or type B

Approximately 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: 8 September 2026):

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 specialists 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.

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4. Treatment costs

Children, adolescents and adults with non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or type B

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Olipudase alfa	€ 125,267.12 – € 1,052,681.65
Best supportive care	Different from patient to patient
Appropriate comparator therapy:	
Best supportive care	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 15 August 2026)

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the GBA website on 15 October 2026.

The justification for this resolution will be published on the GBA website at www.g-ba.de.

Berlin, 15 October 2026

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Dr Optendrenk

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