Justification

for the Resolution of the Federal Joint Committee (GBA) 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

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1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (GBA) assess the benefit of all reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the GBA electronically, including all clinical studies the pharmaceutical company have conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The GBA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the GBA decide on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient olipudase alfa (Xenpozyme) was listed for the first time on 1 October 2022 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices. Xenpozyme for the treatment of Acid Sphingomyelinase Deficiency (ASMD) type A/B or type B 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.

At their session on 16 March 2023, the GBA decided on the benefit assessment of olipudase alfa for the therapeutic indication "Acid Sphingomyelinase Deficiency (ASMD) type A/B or type B" in accordance with Section 35a SGB V.

If the sales of the orphan drug through the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including value-added tax, exceed an amount of € 30 million in the last twelve calendar months, the pharmaceutical company must

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submit evidence in accordance with Chapter 5, Section 5, paragraphs 1 to 6 Rules of Procedure (VerfO) within three months of being requested to do so by the Federal Joint Committee, and in this evidence, must demonstrate the additional benefit compared to the appropriate comparator therapy.

By letter dated 19 January 2026, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 4 May 2026, due to exceeding the € 30 million turnover limit within the period from November 2024 to October 2025. Pursuant to Section 4, paragraph 3, number 4 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 6 of the Rules of Procedure, the pharmaceutical company submitted the final dossier to the GBA in due time on 4 May 2026.

The GBA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 3 August 2026 on the GBA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The GBA came to a resolution on whether an additional benefit of olipudase alfa compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the GBA have evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of olipudase alfa.

In the light of the above, and taking into account the statements received and the oral hearing, the GBA have made the following assessment:

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

2.1.1 Approved therapeutic indication of Olipudase alfa (Xenpozyme) in accordance with the product information

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 15.10.2026):

See the approved therapeutic indication

[1]General Methods, version 8.0 from 19.12.2025. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children, adolescents and 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

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the GBA and Section 6, paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the GBA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the GBA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if they determine by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved for the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved for the therapeutic indication.

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An appropriate comparator therapy may also be non-medicinal therapy, the best possible supportive therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

On 1. Apart from olipudase alfa (Xenpozyme), no other medicinal products are approved for the therapeutic indication in question.

On 2. Non-medicinal treatments as part of the appropriate comparator therapy are not considered in the present therapeutic indication.

On 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Olipudase alfa: resolution of 16 March 2023

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

For the treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or B, there is a guideline on the clinical management of ASMD type A, B and A/B (Geberhiwot, T et al., 2023). Both the guideline and the clinical experts recommend the active ingredient olipudase alfa as the only available disease-specific therapy option for this therapeutic indication. However, as an active ingredient under assessment, olipudase alfa cannot be considered an appropriate comparator therapy. In addition to specific treatment with olipudase alfa, the guideline recommends supportive therapy to alleviate symptoms and improve quality of life.

On the basis of the generally recognised state of medical knowledge, "Best Supportive Care" (BSC) is therefore determined as the appropriate comparator therapy for the active ingredient olipudase alfa in the treatment of children, adolescents and adults with non-CNS manifestations of ASMD with type A/B or type B. BSC is defined as the therapy that provides the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

Any change to the appropriate comparator therapy requires a decision by the GBA based on a prior review of the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO.

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2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of olipudase alfa is assessed as follows:

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

Hint of non-quantifiable additional benefit.

Justification:

The pharmaceutical company presented results from the ASCEND study, as well as the associated long-term treatment phase for the comparison of olipudase alfa with BSC in adults with non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or type B.

The ASCEND study is a completed, double-blind phase III study which investigated the safety and efficacy of olipudase alfa compared with placebo. A total of 36 adult subjects with documented ASMD were enrolled in the study and randomised in a 1:1 ratio to receive treatment with olipudase alfa (N = 18) or placebo (N = 18). Whilst the majority of study participants were characterised by ASMD type B, 6 subjects in the intervention group and 3 subjects in the comparator group had ASMD type A/B. At the start of the study, the spleen volume of subjects in both treatment groups was more than 11 times the normal value.

In addition to the largely on-label administration of olipudase alfa or placebo, all study participants received concomitant medication for the treatment of the broadest range of ASMD symptoms. Among others, ASMD symptoms affecting the nervous system, the digestive tract and the cardiovascular system were treated. The therapy recommendations set out in an international consensus guideline[2] do not mention any specific active ingredients or treatment options. There are currently no national guidelines on the treatment of ASMD. Given the lack of explicit therapy recommendations for subjects with ASMD and the fact that the study imposed only few restrictions on permitted concomitant therapies, the appropriate comparator therapy BSC can be regarded as having been adequately implemented in the ASCEND study.

In both study arms, treatment with the study medication was administered in 2 phases. For the benefit assessment, the comparative, initial 52-week treatment phase is used (2nd data cut-off from 15 March 2021). Some of the results from the subsequent long-term treatment phase, lasting up to four years, were also additionally considered.

The primary endpoints of the study were the percentage change in spleen volume and the diffusion capacity of the lungs for carbon monoxide (DLCO).

Extent and probability of the additional benefit

Mortality

There were no deaths in the ASCEND study.

[2] Geberhiwot et al. Consensus clinical management guidelines for acid sphingomyelinase deficiency (Niemann-Pick disease types A, B and A/B). Orphanet J Rare Dis 2023; 18(1): 85. https://doi.org/10.1186/s13023-023-02686-6.

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Morbidity

Splenomegaly-related symptomatology

No suitable data are available for the endpoint of splenomegaly-related symptomatology.

Fatigue: Brief Fatigue Inventory (BFI)

In the ASCEND study, the BFI questionnaire was used for fatigue assessment. Data were collected using the instrument at the start of the study and subsequently every 6 months until the end of the study. The BFI is a validated questionnaire for assessing fatigue as a patient-relevant endpoint.

Only results for item 3 of the BFI, corresponding to the most severe fatigue, were presented in the benefit assessment dossier. The assessment includes the pre-specified responder analysis with an improvement by ≥ 1.7 points, which represents a change by ≥ 15% of the scale range.

For the endpoint of worst fatigue *(BFI item 3)*, there was no statistically significant difference between the treatment groups.

No data are available on the total BFI score, which would be suitable for representing the endpoint of fatigue as a whole.

Pain: Brief Pain Inventory – Short Form (BPI-SF)

In the ASCEND study, the BPI-SF questionnaire was used for pain assessment. The BPI-SF is regarded as a valid pain assessment tool.

As the return rates for the BPI-SF differed by more than 15% between the treatment groups even at the start of the study, the analyses presented are not suitable for inclusion in the benefit assessment.

Dyspnoea (Functional Assessment of Chronic Illness Therapy – Dyspnoea – Short Form)

In the ASCEND study, the endpoint of dyspnoea was assessed using the FACIT-Dyspnoea-SF. The FACIT-Dyspnoea-SF is a valid dyspnoea assessment tool.

As the return rates differed by more than 15% between the treatment groups even at the start of the study, the analyses presented are not suitable for inclusion in the benefit assessment.

Health status: EQ-5D-5L-VAS (visual analogue scale of the European Quality of Life Questionnaire – 5 Dimensions)

The endpoint of health status was assessed in the ASCEND study using the visual analogue scale (VAS) of the EQ-5D questionnaire.

For the EQ-5D VAS, there was no statistically significant difference between the treatment groups of the ASCEND study.

Percentage change in spleen volume

Spleen volume was measured in the ASCEND study using magnetic resonance imaging (MRI) of the abdomen. The endpoint of percentage change in spleen volume was assessed as the primary endpoint at week 52 in the ASCEND study.

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A prolonged reduction in the pathologically elevated spleen volume is considered patient-relevant in the present therapeutic indication due to the risk of splenic rupture and the risk of splenectomy with the associated risks of the occurrence of post-splenectomy complications (especially immune incompetence or the occurrence of severe bacterial infections).

For the endpoint of percentage change in spleen volume, the ASCEND study showed a statistically significant advantage of olipudase alfa over placebo. Furthermore, the results from the long-term treatment phase of the ASCEND study show that spleen volume continues to decrease over the course of the study, resulting in mild splenomegaly on average.

Lung diffusion capacity for carbon monoxide (DLCO)

Lung diffusion capacity was assessed as the primary endpoint in the ASCEND study. This reflects the lungs' ability to take in oxygen from the air and release carbon dioxide.

For the endpoint of percentage change in DLCO, the ASCEND study showed a statistically significant advantage of olipudase alfa over placebo at week 52.

DLCO is regarded as a surrogate endpoint. The results for this endpoint are only presented additionally due to the insufficient surrogate validation.

Liver volume

Liver volume was assessed in the ASCEND study using magnetic resonance imaging (MRI) of the abdomen.

For the endpoint of percentage change in liver volume, the ASCEND study showed a statistically significant advantage of olipudase alfa over placebo at week 52.

A prolonged reduction in the pathologically elevated liver volume combined with a noticeable decrease in impairing disease symptoms and improvement in the quality of life for the patient is considered patient-relevant. However, no improvement in symptomatology or quality of life was shown for olipudase alfa. Even though a reduction in liver volume could be shown in the study, the extent to which the reduction in liver volume achieved during therapy with olipudase alfa is relevant for the patients still remains unclear. The results for this endpoint are therefore only presented additionally.

Patient Global Impression of Symptom Severity (PGIS)/ Patient Global Impression of Change (PGIC)

The ASCEND study used the patient-reported questionnaires Patient Global Impression of Symptom Severity of ASMD (PGIS ASMD) and Patient Global Impression of Change (PGIC) to assess the severity of disease symptoms and the change in health status, respectively. Both questionnaires contain 4 questions each on abdominal disorders, pain, fatigue and dyspnoea, and the PGIC also includes an additional question on activities of daily living.

The PGIS assesses the severity of symptoms using a five-point scale from 0 (no symptoms) to 4 (very severe symptoms). For this endpoint, those subjects who achieved a reduction by ≥ 0.6 points at week 52 were counted as responders.

The PGIC assesses the change in health status using a seven-point scale (1 major improvement = 3; 2 significant improvement = 2; 3 minor improvement = 1; 4 no change = 0; 5 minor deterioration = -1; 6 significant deterioration = -2; 7 major deterioration = -3). Subjects who achieved an improvement of 1, 2 or 3 points at week 52 were classified as responders.

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The pharmaceutical company presented pre-specified responder analyses for both endpoints. However, there are conflicting figures regarding the respective return rates.

For both the PGIS and the PGIC, there were no statistically significant differences between the treatment arms.

Quality of life

Short Form-36 Health Survey (SF-36)

In the ASCEND study, health-related quality of life was assessed using the Short Form-36 Health Survey (SF-36).

The ASCEND study showed no statistically significant difference between the treatment groups in either the physical component summary score (PCS) or the mental component summary score (MCS) of the SF-36.

Side effects

For the endpoints of SAEs, severe AEs and discontinuation due to AEs, the ASCEND study showed no statistically significant difference between the treatment groups in each case.

With regard to the available data on severe AEs, it should be noted that these were defined in the ASCEND study as AEs which, in the opinion of the principal investigator, prevent the patient from carrying out daily activities and require treatment. This operationalisation is not suitable for reliably distinguishing between severe AEs and non-severe AEs. Furthermore, the operationalisation does not guarantee that severe AEs for which there is no treatment option have been assessed.

Overall assessment

The results of the ASCEND study are used for the benefit assessment of olipudase alfa in adults with non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or type B.

There were no deaths in the ASCEND study.

For the endpoint of worst fatigue (assessed using BFI item 3), the endpoint of health status (assessed using the EQ-5D VAS), and the endpoints of PGIS and PGIC in the endpoint category of morbidity, there was no statistically significant difference between the treatment groups in each case.

For the endpoint "percentage change in spleen volume", there was a statistically significant advantage of olipudase alfa over placebo. In this specific data basis, the percentage change in spleen volume is considered patient-relevant and is used in the benefit assessment. In principle, the noticeable advantages associated with a reduction in spleen volume should also be reflected in other endpoints (symptomatology and health-related quality of life); however, this is not evident from the available data. Consequently, the extent of the demonstrated advantage of olipudase alfa in terms of reduction in spleen volume is non-quantifiable overall.

For either the physical component summary score (PCS) or the mental component summary score (MCS) of the SF-36 in the health-related quality of life endpoint category, there was no statistically significant difference between the treatment groups.

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For the endpoints of SAEs, severe AEs and discontinuation due to AEs in the endpoint category of side effects, there was no statistically significant difference between the treatment groups in each case.

In the overall assessment, a non-quantifiable additional benefit of olipudase alfa based on the demonstrated advantage in the reduction of spleen volume is therefore identified in adults with non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or type B.

Reliability of data (probability of additional benefit)

For the ASCEND RCT presented, the risk of bias at study level is assessed as low. However, the significance of the results is limited by the small number of patients enrolled in the study.

The risk of bias in the results for the endpoints of percentage change in spleen volume and worst fatigue (BFI item 3) is classified as high. In the case of spleen volume, this is due to a significant difference (6 percentage points) in the percentage of patients not included in the analysis. For the endpoint of worst fatigue (BFI item 3), the high risk of bias is due to the fact that there are differing figures regarding return rates.

In terms of the significance of the evidence, the overall assessment results in a hint.

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

Hint of non-quantifiable additional benefit.

Justification:

The pharmaceutical company presented the ASCEND-Peds study and the associated long-term LTS13632 study for the benefit assessment of olipudase alfa in children and adolescents with non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or type B.

The ASCEND-Peds study was a completed, open-label, single-arm phase I/II study, which primarily investigated the safety and tolerability of olipudase alfa. A total of 20 children and adolescents with documented ASMD were enrolled in the study. Given the exclusion of subjects with acute or rapidly progressing neurological impairments, it is reasonable to assume that only study participants with ASMD type A/B or type B were recruited. At the start of the study, the spleen volume of the participating children and adolescents was 19 times the normal value.

In addition to the largely on-label administration of olipudase alfa, concomitant medication in the form of best supportive care was permitted for the treatment of ASMD symptoms.

The 64-week treatment phase of the ASCEND-Peds study was followed by the open-label, single-arm LTS13632 study. In this study, all participants in the ASCEND-Peds study were able to continue receiving treatment with olipudase alfa for a further 3 to 9 years.

Long-term safety and tolerability were assessed as the primary endpoints of the study.

Based on the single-arm study data, it is generally not possible to draw any comparative conclusions regarding the natural course of the disease under best supportive care for the paediatric patient population.

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Extent and probability of the additional benefit

Mortality

There were no deaths in the ASCEND-Peds study and the associated LTS13632 study.

However, the non-comparator data presented do not allow an assessment in comparison with the natural course of the disease under best supportive care.

Morbidity

Percentage change in spleen volume

Spleen volume was measured using magnetic resonance imaging (MRI) of the abdomen.

In children and adolescents, the results of the ASCEND-Peds study and the associated long-term LTS13632 study also show an improvement in splenomegaly from severe splenomegaly in 60% (n = 12) of patients to moderate splenomegaly, on average, at week 157.

A prolonged reduction in the pathologically elevated spleen volume is patient-relevant in the present therapeutic indication due to the risk of splenic rupture and the risk of splenectomy with the associated risks of the occurrence of post-splenectomy complications (especially immune incompetence or the occurrence of severe bacterial infections).

Although the single-arm study data do not allow for comparative conclusions regarding the natural course of the disease under best supportive care, spontaneous remission of the elevated spleen volume during the natural course of the disease without causal treatment cannot be assumed. The data are therefore used here for the derivation of an additional benefit.

Taken together, the administration of olipudase alfa led to a significant reduction in the spleen volume at week 52 compared to baseline; however, the extent of this reduction is non-quantifiable.

Body height (z score)

The z score for the anthropometric parameter of body height is a tool for assessing possible deviations from the reference population of children and adolescents of the same age.

The ASCEND-Peds study and the associated long-term LTS13632 study show an increase in age-related body height and a convergence towards the values of the reference population.

Patients in the present therapeutic indication usually have a reduced body height in the natural course of the disease compared to the normal population. While the values at baseline predominantly indicate a below-average physical development of the children compared to the normal population, the anthropometric values converged towards the values of children of the same age in the normal population at the end of the ASCEND-Peds study.

Overall, the data presented can nevertheless only be interpreted with difficulty in terms of their significance, as no assessment is possible on the basis of the data presented in direct comparison to the natural course of the disease.

Taken together, the administration of olipudase alfa showed a relevant increase in body height at week 52 compared to baseline; however, the extent of this increase is non-quantifiable.

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Lung diffusion capacity for carbon monoxide (DLCO)

The endpoint of percentage change in DLCO was assessed at week 52 in the ASCEND-Peds study. For the endpoint of percentage change in DLCO, the single-arm ASCEND-Peds study showed an improvement from baseline at week 52.

DLCO is regarded as a surrogate endpoint. The results for this endpoint are only presented additionally due to the insufficient surrogate validation.

Liver volume

A prolonged reduction in the pathologically elevated liver volume combined with a noticeable decrease in impairing disease symptoms and improvement in the quality of life for the patient is considered patient-relevant.

The endpoint of percentage change in liver volume was assessed at week 52 in the ASCEND-Peds study. Even though a reduction in liver volume could be shown in the study, the extent to which the reduction in liver volume achieved during therapy with olipudase alfa is relevant for the patients still remains unclear. The results for this endpoint are therefore only presented additionally.

Fatigue: PedsQL Multidimensional Fatigue Scale

The single-arm study data presented do not allow any conclusions to be drawn regarding the assessment of the fatigue endpoint in comparison with the natural course of the disease under best supportive care. Therefore, the results are only presented additionally.

Pain: PedsQL Paediatric Pain Questionnaire

The single-arm study data presented do not allow any conclusions to be drawn regarding the assessment of the pain endpoint in comparison with the natural course of the disease under best supportive care. Therefore, the results are only presented additionally.

Quality of life

Paediatric Quality of Life Inventory (PedsQL)

The single-arm study data presented do not allow any conclusions to be drawn regarding the assessment of the health-related quality of life endpoint in comparison with the natural course of the disease under best supportive care. Therefore, the results are only presented additionally.

Side effects

SAEs occurred in 5 subjects (25%) and severe AEs occurred in 3 subjects (15%) out of 20 patients. No subject discontinued treatment due to AEs.

Overall, however, no conclusions can be drawn from the single-arm study data regarding the assessment of olipudase alfa in comparison with the natural course of the disease under best supportive care.

Overall assessment

The pharmaceutical company presented the multicentre, single-arm ASCEND-Peds study and the associated long-term LTS13632 study for the benefit assessment of the patient population

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of children and adolescents. Data in the endpoint categories of mortality, morbidity, quality of life and side effects were collected in the ASCEND-Peds study.

Based on the single-arm study data, it is generally not possible to draw any comparative conclusions regarding the natural course of the disease under best supportive care for the paediatric patient population.

There were no deaths in the ASCEND-Peds study.

In the endpoint category of morbidity, treatment with olipudase alfa led to a significant reduction in spleen volume. A prolonged reduction in the pathologically elevated spleen volume is patient-relevant in the present therapeutic indication due to the risk of splenectomy and the risk of splenic rupture. On the basis of the data presented, it is not possible to make a direct comparator assessment of the effect of olipudase alfa in comparison with the natural course of the disease. However, in the case of this disease and given such a severe enlargement of the spleen as was initially observed in the ASCEND-Peds study, an improvement or spontaneous remission of the elevated spleen volume cannot be expected with treatment comprising best supportive care. For this reason, the results of the single-arm study in children and adolescents can be used for the derivation of an additional benefit for the endpoint "percentage change in spleen volume" in this specific setting.

Nor is it possible to make a direct comparator assessment of the effect of olipudase alfa on the development of age-related body height (z score) in comparison with the natural course of the disease. While the values at baseline predominantly indicate a below-average physical development of the children compared to the normal population, the anthropometric values converged towards the values of children of the same age in the normal population at the end of the ASCEND-Peds study.

For both the endpoint category of health-related quality of life and the endpoint category of side effects, the single-arm study data do not allow any conclusions to be drawn regarding the assessment of olipudase alfa in comparison with the natural course of the disease under best supportive care.

Overall, the extent of the demonstrated advantages for the endpoints "reduction in spleen volume" and body height (z score) cannot be quantified, as the data presented do not allow for a direct comparison with the natural course of the disease.

In the overall assessment, a non-quantifiable additional benefit of olipudase alfa was identified for the treatment of children and adolescents with non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or type B.

Reliability of data (probability of additional benefit)

Due to the single-arm, non-comparator design of the ASCEND-Peds study and the associated long-term LTS13632 study, the reliability of the results is subject to major uncertainties.

Therefore, a hint must be established regarding the significance of the evidence.

2.1.4 Summary of the assessment

The present assessment is the new benefit assessment of the active ingredient olipudase alfa due to the exceeding of the € 30 million turnover limit. The medicinal product 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.

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In the therapeutic indication to be considered, two patient groups were distinguished:

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

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

The GBA determined best supportive care as the appropriate comparator therapy for both patient groups.

Patient group a

The results of the ASCEND study are used for the benefit assessment of olipudase alfa in adults with non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or type B.

There were no deaths in the ASCEND study.

For the endpoints of worst fatigue, health status, PGIS and PGIC in the endpoint category of morbidity, there was no statistically significant difference between the treatment groups in each case.

For the endpoint "percentage change in spleen volume", there was a statistically significant advantage of olipudase alfa over placebo. The percentage change in spleen volume is considered patient-relevant in this context. In principle, the noticeable advantages associated with a reduction in spleen volume should also be reflected in other endpoints (symptomatology and health-related quality of life); however, this is not evident from the available data. Consequently, the extent of the demonstrated advantage of olipudase alfa in terms of the reduction in spleen volume is non-quantifiable overall.

Neither in the endpoint category of health-related quality of life (as measured by the SF-36) nor in the endpoint category of side effects was there any statistically significant differences between the treatment groups.

Overall, the significance of the results is limited due to the small number of patients enrolled in the study.

In the overall assessment, a hint of a non-quantifiable additional benefit of olipudase alfa based on the demonstrated advantage in the reduction of spleen volume was identified in adults with non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or type B.

Patient group b

The pharmaceutical company presented the multicentre, single-arm ASCEND-Peds study and the associated long-term LTS13632 study for the benefit assessment of the patient population of children and adolescents.

There were no deaths in the ASCEND-Peds study.

In the endpoint category of morbidity, treatment with olipudase alfa led to a significant reduction in spleen volume. A prolonged reduction in the pathologically elevated spleen volume is patient-relevant in the present therapeutic indication. On the basis of the data presented, it is not possible to make a direct comparator assessment of the effect of olipudase alfa in comparison with the natural course of the disease. However, in the case of this disease

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and given such a severe enlargement of the spleen as was initially observed in the ASCEND-Peds study, an improvement or spontaneous remission of the elevated spleen volume cannot be expected with treatment comprising best supportive care.

Nor is it possible to make a direct comparator assessment of the effect of olipudase alfa on the development of age-related body height (z score) in comparison with the natural course of the disease. While the values at baseline predominantly indicate a below-average physical development of the children compared to the normal population, the anthropometric values converged towards the values of children of the same age in the normal population at the end of the ASCEND-Peds study.

For both the endpoint category of health-related quality of life and the endpoint category of side effects, the single-arm study data do not allow any conclusions to be drawn regarding the assessment of olipudase alfa in comparison with the natural course of the disease under best supportive care.

Overall, the extent of the demonstrated advantages for the endpoints "reduction in spleen volume" and body height (z score) cannot be quantified, as the data presented do not allow for a direct comparison with the natural course of the disease.

Overall, the significance of the results is limited due to the single-arm, non-comparator design of the studies.

In the overall assessment, a hint of a non-quantifiable additional benefit of olipudase alfa was identified in children and adolescents with non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) with type A/B or type B.

2.2 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

The number of patients is the target population in statutory health insurance (SHI). The information is based on patient numbers based on the information provided by the pharmaceutical company in the dossier.

However, the number of patients in the statutory health insurance target population stated by the pharmaceutical company is subject to uncertainties overall due to the methodological procedure, and is an underestimate. This underestimation is particularly due to uncertainties in determining the birth prevalence and median survival time. A survey based, for example, on current prescription figures would allow for a more accurate estimate of the target population.

2.3 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

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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.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 August 2026). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is different from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For the calculation of the dosages depending on body weight, the average body measurements from the official representative statistics "2025 Microcensus – body measurements of the population"[3] were applied. The average body weight of adults is 78.3 kg and of children under 1 year 8.4 kg.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

The treatment costs for best supportive care are different for each individual patient. Because best supportive care has been determined as an appropriate comparator therapy, this is also reflected in the medicinal product to be assessed. The type and scope of best supportive care can vary depending on the medicinal product to be assessed and the comparator therapy.

[3]Federal Health Reporting. Average body measurements of the population (2025, both sexes), www.gbe-bund.de

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

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Olipudase alfa	Continuously, 1 x every 14 days	26.1	1	26.1
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
Best supportive care	Different from patient to patient			

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Olipudase alfa	Children aged < 1 year				
	3 mg/kg	25.2 mg	1 x 20 mg + 2 x 4 mg	26.1	26.1 x 20 mg + 52.2 x 4 mg
	Adults				
	3 mg/kg	234.9 mg	11 x 20 mg + 4 x 4 mg	26.1	287.1 x 20 mg + 104.4 x 4 mg
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of

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the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Olipudase alfa 20 mg	25 PCI	€ 90,543.24	€ 1.77	€ 5,170.31	€ 85,371.16
Olipudase alfa 4 mg	1 PCI	€ 735.46	€ 1.77	€ 41.36	€ 692.33
Abbreviations: PCI = powder for a concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 15 August 2026

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At their session on 27 May 2025, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 4 May 2026, the pharmaceutical company submitted a dossier for the benefit assessment of olipudase alfa to the GBA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 6 VerfO.

By letter dated 4 May 2026 in conjunction with the resolution of the GBA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with

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new active ingredients in accordance with Section 35a SGB V, the GBA commissioned the IQWiG to assess the dossier concerning the active ingredient olipudase alfa.

The dossier assessment by the IQWiG was submitted to the GBA on 30 July 2026, and the written statement procedure was initiated with publication on the GBA website on 3 August 2026. The deadline for submitting written statements was 24 August 2026.

The oral hearing was held on 7 September 2026.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the Subcommittee's session on 6 October 2026, and deliberation of the draft resolution was concluded.

At their session on 15 October 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	27 May 2025	Determination of the appropriate comparator therapy
Working group Section 35a	2 September 2026	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	7 September 2026	Conduct of the oral hearing
Working group Section 35a	16 September 2026 30 September 2026	Consultation on the dossier assessment by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	6 October 2026	Concluding discussion of the draft resolution
Plenum	15 October 2026	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 15 October 2026

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

Dr Optendrenk

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