Justification

Gemeinsamer Bundesausschuss

of the Resolution of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Sebelipase alfa reassessment after expiry of the deadline (lysosomal acid lipase deficiency)

of 3 June 2021

Contents

1. Legal basis

According to Section 35a (1) SGB V, the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a paragraph 1, sentence 11, first half of the sentence of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, first half of the sentence of the German Social Code, Book V therefore assumes an additional benefit for an authorised orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, nos. 2 and 3 of the German Social Code, Book V in conjunction with Chapter 5, Sections 5 ff. of the Rules of Procedure of the G-BA (VerfO) has not been carried out. In accordance with Section 5, paragraph 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds €50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a paragraph 1 sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. However, the extent of the additional benefit is assessed exclusively on the basis of the authorisation studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of €50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). According to Section 35a paragraph 2 SGB V, the assessment by the G-BA 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 G-BA decides 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 pharmaceutical company submitted a dossier for the early benefit assessment for the active ingredient sebelipase alfa (Kanuma) to be assessed for the first time on 29 September 2015. For the resolution of 17 March 2016 made by the G-BA in this procedure, a time limit of 1 December 2018 was pronounced. At the request of the pharmaceutical company, this time limit was extended by a time limit until 1 December 2020 by resolution of the G-BA of 1 November 2018.

In accordance with Section 4, paragraph 3 paragraph 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5 Section 1, paragraph 2, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Kanuma starts when the deadline has expired.

For this purpose, the pharmaceutical company submitted the dossier for the benefit assessment to the G-BA in due time on 1 December 2020 (Section 4 (3) no. 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8 (1) no. 5 VerfO).

Sebelipase alfa for the treatment of lysosomal acid lipase is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional benefit is considered to be proven. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the authorisation studies carried out by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 15 March 2021 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. An oral hearing was also held.

The G-BA made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G12-01) and the statements made in the written statements and oral hearing process, as well of the addendum drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for the marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of Sebelipase alfa.

Based on this, the G-BA, taking into account the comments received and the oral hearing, arrived at the following assessment:

1 General Methods, version 6.0 from 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Sebelipase alfa (Kanuma) in accordance with the product information

KANUMA is used for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL deficiency).

Therapeutic indication of the resolution (resolution of 3/6/2021):

see approved therapeutic indication

2.1.2 Extend of the additional benefit and significance of the evidence:

a) Patients with rapidly progressive LAL deficiency already in infancy (< 6 months):

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

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

Justification:

For the evaluation of the additional benefit of sebelipase alfa in patients with LAL (lysosomal acid lipase) deficiency - the so-called Wolman disease - which already progresses rapidly in infancy (< 6 months), the pharmaceutical company presents data from the LAL-CL03 (VITAL), LAL-CL08 studies as well as the ALX-LALD-501 registry. Because of the single-arm design of the two studies, the company also presents non-adjusted indirect comparisons without a bridge comparator with two external control populations from the LAL-1-NH01 observational study.

LAL-CL03 (VITAL) and LAL-CL08

The LAL-CL03 study is an open-label, multicentre, single-arm, phase II/III dose-escalation study that enrolled 9 infants with failure to thrive due to LAL deficiency and treated them with sebelipase alfa for up to 5 years. Failure to thrive was operationalised by the pharmaceutical company as a significant weight loss or significantly worse weight-related development of the affected infant compared to the published age-specific norm values. At the start of treatment with sebelipase alfa, patients must not be older than 8 months. All included children had growth disturbance before 6 months of age.

In the first 2 weeks, the patients received an initial dosage of 0.35 mg/kg/week of sebelipase alfa, which was too low compared to the recommendations in the product information. The doses have been established compliant with the marketing authorisation.

The primary endpoint of the study was overall survival at 12 months. Additional endpoints included anthropometric and biochemical parameters, the Denver-II developmental test, and adverse events.

The LAL-CL08 study is an open-label, multicenter, single-arm phase II study with a treatment phase of up to 3 years with sebelipase alfa that included 10 children with rapidly progressive LAL deficiency (age ≤ 8 months at initiation of dosing with sebelipase). Inclusion in the study occurred when there was significant clinical concern by the principal investigator and sponsor of rapid disease progression requiring urgent medical intervention. Failure to thrive was not a mandatory inclusion criterion, and there is no information on growth failure before 6 months of age at baseline.

The starting dose was 1 mg/kg sebelipase alfa weekly. The dose could be escalated to 3 mg/kg weekly. Therefore, the patients in the LAL-CL08 study received a dose in accordance with the product information throughout the entire course of the study.

A primary endpoint was not defined because the primary objective of the study was to evaluate the safety of sebelipase alfa. Additional endpoints included anthropometric and biochemical parameters, the Denver Developmental Test, and adverse events.

Because the LAL-CL03 and LAL-CL08 studies are single-arm, uncontrolled studies, the risk of bias is assumed to be high. However, it must be taken into account that, apart from sebelipase alfa, there are no treatment alternatives and most patients die within the first year of life without treatment. Therefore, long-term data from untreated patients (for example, on morbidity endpoints such as child development and anthropometric parameters) can hardly be collected.

LAL-1-NH01

The LAL-1-NH01 natural history study is a retrospective, multinational, multicentre observational study of individuals whose LAL deficiency/Wolman phenotype manifested in infancy after 1 January 1985. All data were collected by consulting the patients' medical records. A total of 36 patients were included in the study.

Indirect comparison

The pharmaceutical company presents historical comparisons between the two single-arm LAL-CL03 (VITAL) and LAL-CL08 studies on sebelipase alfa and two external control populations from the LAL-1-NH01 study on the natural history of Wolman-type LAL deficiency for the endpoints overall survival, ALT(alanine aminotransferase) normalisation and age-related weight. The control populations were subpopulation 1, which included untreated individuals with early failure to thrive in the first 6 months (n = 21), and subpopulation 2, which included all untreated individuals with/without early failure to thrive (n = 25).

In general, single-arm studies and non-adjusted indirect comparisons without a bridge comparator have a high risk of bias. The validity of the comparison presented is further limited by the small number of cases in the intervention studies.

In addition, it is unclear whether sufficient comparability of patient populations can be assumed between the single-arm studies with sebelipase alfa and the control. Therefore, based on the limited clinical patient characteristics available for the LAL-CL03 and LAL-CL08 studies, it is not possible to reliably differentiate between LAL deficiency of the Wolman phenotype and the prognostically more favourable *cholesteryl ester storage disease (CESD)*. Data on absolute LAL deficiency and molecular genetic diagnostics, which do not always allow a clear differentiation between phenotypes in individual cases, but are nevertheless of interest for the overall consideration, were not provided by the pharmaceutical company in the dossier.

The rapid progression of the disease leading to death within the first year of life and the associated need for early therapeutic intervention also make it difficult to operationalise the inclusion criteria for the studies in such a clear way that in retrospect it is possible to differentiate between the Wolman phenotype and the prognostically more favourable CESD. The LAL-CL03 study included only infants who had failure to thrive as defined by clinical standards. In the opinion of the clinical commentators, this is most likely characteristic of the presence of a Wolman-type LAL deficiency. In the LAL-CL08 study, however, failure to thrive is not a mandatory inclusion criterion. Therefore, there are uncertainties regarding the

comparability of the included infants with the population of the historical comparison, especially in the LAL-CL08 study.

Evidence that the LAL-CL03 and LAL-CL08 studies included patients with better prognosis comes from baseline data for both populations. At the median time of the first administration of sebelipase alfa in the intervention group, half of the patients in the historical control had already died. Infants in the historical control had a median age at death of 3.0 months, whereas the median age of infants in the LAL-CL03 study was 3.0 months at the administration of the first dose and 2.8 months in the LAL-CL08 study.

Despite the uncertainties mentioned above, the indirect comparisons of the intervention studies (LAL-CL03, LAL-CL-08) with the historical control groups (LAL-1-NH01) are used for the benefit assessment because of the large effect on the mortality endpoint that cannot be explained by random effects based on these uncertainties. This also takes into account that rapidly progressive LAL deficiency in infancy is a very rare disease, which in the natural course of the disease has a very high probability of leading to the death of the patient within the first year of life, and for which there are no treatment alternatives except for sebelipase alfa. In addition, infants with rapidly progressive LAL deficiency are a particularly vulnerable patient population.

ALX-LALD-501

The multicentre, international, and non-interventional ALX-LALD-501 registry was commissioned as part of the approval process to obtain long-term longitudinal data from patients with LAL deficiency. The registry study population, as defined by the pharmaceutical company, includes 164 of 222 global patients who have, among other things, confirmed LAL deficiency and have a known sebelipase-alfa treatment status. Those treated with sebelipase alfa were required to have exposure to sebelipase alfa for ≥ 6 months. The pharmaceutical company submits data on anthropometric parameters, cholesterol levels, ALT values, quality of life (only for patient group b) and adverse events, among others, for the study population.

The registry data considered for the benefit assessment is an uncontrolled study design, which is why a high risk of bias is assumed.

The patient group with LAL deficiency in infancy included 16 patients treated with sebelipase alfa. Data on untreated patients are not available. For the intra-individual comparisons of the morbidity endpoints, only data with different observation periods or too low a return rate were available, so that only the data on adverse events are considered for the present benefit assessment. Contrary to the defined study populations, safety data are based on the safety population (n = 18). This includes all individuals who have ever been treated with sebelipase alfa regardless of a confirmed LAL diagnosis.

Mortality

Overall survival was assessed in the LAL-CL03 (VITAL) and LAL-CL08 studies. In addition, a non-adjusted indirect comparison of overall survival was performed for these studies with the external control population of the LAL-1-NH01 study.

The natural history study LAL-1-NH01 shows high overall mortality in untreated infants with rapidly progressive disease. Of the 25 infants included with Wolman-type LAL deficiency who were not required to have the early failure to thrive criterion (study cohort 2), only one survived to 12 months of age. By 24 months of age, all patients had died.

In the LAL-CL03 study, 6 of 9 patients and in the LAL-CL08 study, 9 of 10 patients survived to 12 months of life. Before 24 months of age, one additional patient died in each case. No further deaths occurred until the end of the study.

The comparisons of the intervention studies to the historical control showed a very significant statistically significant survival benefit for infants treated with sebelipase alfa compared to the historical control.

Overall, despite the methodological shortcomings described above, against the background of the high mortality of untreated infants with rapidly progressing LAL deficiency, as well as the magnitude of the effect, an advantage in overall survival and thus an additional benefit can be derived. Due to the high risk of bias, the results do not allow a quantitative assessment of the positive effects in terms of the extent of additional benefit.

Morbidity

Anthropometric parameters: Weight, weight in relation to length, body mass index

The anthropometric parameters of body weight, weight in relation to length and BMI are important in the present indication, as failure to thrive is a central feature of rapidly progressive LAL deficiency. These endpoints are considered to be patient-relevant morbidity parameters, especially in children with characteristic, disease-related growth disorders. Data adjusted for age and sex (z-scores) are preferred over absolute values.

In both single-arm studies, an increase in age-related weight, weight in relation to body height/length, and age-related BMI was observed in the intra-individual comparison to baseline.

While the values at baseline predominantly, especially in the study LAL-CL08, indicate a below-average physical development of the children compared to the normal population, at the end of the studies the anthropometric values are in the range of age-matched children of the normal population.

The relative weight gain in failure to thrive in infants and young children has a significant clinical significance in the therapeutic indication. However, the data presented are difficult to interpret in terms of their significance, as the disease is usually lethal if untreated, and thus no assessment is possible in comparison with the natural course in the present patient population.

Denver II Development Test

The Denver II developmental test is used in clinical practice as a screening tool to identify children with developmental disabilities. The test comprises 125 items divided into the 4 domains “fine motor skills and adaptation”, “gross motor skills”, “language skills” and “social contacts”, which together constitute a total score. Basically, the motor, social and linguistic development of the children is considered relevant to the patient. Regarding the development and validity of the questionnaire, only insufficient data were submitted by the pharmaceutical company and were also not subsequently submitted within the framework of the written statement procedure, so that the validity cannot be fully assessed.

The Denver II developmental test was collected for infants with rapidly progressive LAL deficiency in both intervention studies. Appropriate baseline data are not available due to the low return rate.

At the last available observation date, the children who survived in the LAL-CL03 study had no abnormalities in the various domains of the Denver II developmental test compared with the

normal population, whereas in the LAL-CL08 study, 3 of 5 children showed an abnormality based on the total score.

The normal development of children, which includes not only motor skills but also social contacts and the ability to speak, has a high clinical value in the therapeutic indication. However, with the validity of the measurement instrument unclear, the data presented are limited in their ability to be assessed, as the disease is usually lethal if untreated, and thus no assessment can be made in comparison to the natural history in the present patient population. In addition, interpretation is limited by the lack of appropriate baseline data and, furthermore, there is no clear equidirectional result between studies.

Quality of life

No data on quality of life are available. Therefore, conclusions on the extent of additional benefit cannot be derived for this endpoint.

Side effects

For infants with rapidly progressive LAL deficiency, summary data on severe adverse events (AEs), serious AEs, and AEs leading to discontinuation of study medication from the LAL-CL03 and LAL-CL08 studies, and the ALX-LALD-501 patient registry will be considered. However, due to the high mortality of untreated patients a control group is missing, the results are difficult to interpret in their significance. In the overall picture, no statement on the extent of the additional benefit can be derived.

Overall assessment

For patients with rapidly progressive LAL deficiency already in infancy (< 6 months), data are available from two single-arm intervention studies (LAL-CL03 (VITAL), LAL-CL08), a patient registry (ALX-LALD-501) and a historical control study (LAL-1-NH01). In addition, the pharmaceutical company presents in the dossier a non-adjusted indirect comparison of the intervention studies with two external control populations from the historical control study. Against the background of the severity and rarity of the disease, as well as the paediatric study population, these data are used for the benefit assessment despite the high risk of bias of a historical comparison and the resulting uncertainties regarding the comparability of the study populations due to the large effect in the endpoint mortality, which cannot be explained solely by random effects based on these uncertainties.

For the categories morbidity and side effects, an assessment of the additional benefit of sebelipase alfa is not possible, as suitable comparative data cannot be collected due to the mostly lethal course of the disease in untreated patients. However, data on anthropometric parameters and the Denver II developmental test compared to the age-adjusted normal population suggest that treatment with sebelipase alfa may allow at least some children to develop normally.

Data on quality of life are not available.

For overall survival, sebelipase alfa showed an advantage over the natural history of the disease. When evaluating these results, however, the high risk of bias due to the historical comparison must be taken into account. Furthermore, there is uncertainty as to whether the overall survival of infants from the LAL-CL03 and LAL-CL08 studies was affected by the inclusion of patients with better prognosis.

Given the high mortality of untreated infants with rapidly progressing LAL deficiency and the large effect, an advantage in overall survival for sebelipase alfa can be inferred. There is an additional benefit, but the actual size of the difference between patients treated with sebelipase alfa and untreated patients cannot be deduced from the data presented. The additional benefit of sebelipase alfa is therefore considered to be not quantifiable because the scientific evidence base does not allow for it.

Significance of the evidence

The assessment of the extent of additional benefit of sebelipase alfa is based on the evidence from two single-arm studies comparing it with a historical control group for the endpoint of mortality.

Single-arm studies and historical comparisons are generally associated with a high potential risk of bias because, as is also evident in this case, there may be uncertainties in the comparability of the study populations between the control study and the intervention groups due to the lack of randomisation or adjustment for patient characteristics. Therefore, even taking into account the limited number of cases, it is considered to be a hint.

b) Patients with LAL deficiency (not rapidly progressive in infancy (< 6 months))

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

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

Justification:

To answer the question on the extent of additional benefit of sebelipase alfa for patients with LAL deficiency that was not already rapidly progressive in infancy, the results of the studies LAL-CL02 (ARISE, controlled and uncontrolled phase) and LAL-CL06, as well as the registry ALX-LALD-501 are available.

Study LAL-CL02 (ARISE)

The LAL-CL02 (ARISE) study is a 20-week, multicentre, randomised, double-blind, placebo-controlled Phase III study to evaluate the efficacy and safety of sebelipase alfa in individuals with childhood and adult LAL deficiency. Included were 66 patients aged 4 years and older with reduced LAL enzyme activity and at least mildly elevated alanine transaminases levels (≥ 1.5x upper normal limit). The median age of the included patients was 11 years. Patients with severe liver dysfunction were excluded, among others.

Patients were randomised to receive a starting dose of 1 mg/kg every other week (n = 36) or placebo (n = 30). No dose changes were allowed during the double-blind treatment phase.

From week 22, a single-arm, open-label study phase up to 130 weeks followed by another open-label study phase (Expanded Treatment Period) for 104 weeks. Patients in the placebo arm were able to switch to the intervention group at the end of the double-blind study phase and thus also receive treatment with sebelipase alfa. Dosage adjustment was possible during the open extension phase. It was possible to increase the dose to 3 mg/kg every 2 weeks in accordance with the approval. In addition, in deviation from the recommendations of the

product information, a weekly administration of 3 mg/kg as well as a dose reduction to 0.35 mg/kg every 2 weeks was also possible.

The primary endpoint was normalisation of ALT levels. Additional endpoints included biochemical laboratory values, anthropometric examination data, fatigue, quality of life (Pediatric Quality of Live Inventory (PedsQL), Chronic Liver Disease Questionnaire (CLDQ)) and adverse events.

LAL-CL06 study:

The LAL-CL06 study is a multicentre, single-arm, open-label Phase II study primarily evaluating the safety of sebelipase alfa in individuals with childhood and adult LAL deficiency for up to 144 weeks of treatment. This study additionally included those subjects who were unable to participate in another study due to age, disease progression, prior treatment with hematopoietic stem cell or liver transplantation, less frequent disease manifestations, or disease characteristics. The median age at the time of the first dose of sebelipase alfa was 11.7 years.

The initial dose was 1 mg/kg sebelipase alfa every other week. Subsequently, dosage adjustment was possible as in the open-label phase of LAL-CL-03. The primary objective of the study was to evaluate the safety of sebelipase alfa, therefore no primary endpoint was defined. At the end of the 96-week treatment period, the primary analysis was performed. In addition to safety data, biochemical laboratory values, anthropometric examination data and information on quality of life (PedsQL, CLDQ) were collected.

ALX-LALD-501

For general information on the registry, please refer to the comments on patient group a).

The patient population with LAL deficiency that is not rapidly progressive in infancy includes 148 children and adults worldwide, 113 of whom have ever been treated with sebelipase alfa.

The data on morbidity and quality of life endpoints provided with the registry cannot be used for the present benefit assessment. A statistically evaluated comparison was presented by the pharmaceutical company for high- and low-density lipoprotein cholesterol (HDL-C, LDL-C) relative to baseline between subjects never and ever treated with sebelipase alfa. However, due to the lack of information on the actual observation times between the treatment groups, there is considerable uncertainty regarding the effect estimate, which is why the endpoint LDL-C for the patients in childhood and adulthood is not considered as a supplement. For the quality-of-life instruments (CLDQ, PedsQL and SF-36), no or limited (n = 2) results are available.

Therefore, only the data on adverse events are considered for the present benefit assessment. Contrary to the defined study populations, safety data are based on the safety population (n = 118), which includes all subjects who have ever been treated with sebelipase alfa regardless of a confirmed LAL diagnosis.

<u>Mortality</u>

In the LAL-CL02 and LAL-CL06 studies, deaths were recorded among the safety endpoints. No deaths occurred during the study period. Given the randomised comparison from the LAL-CL02 study, which is only available for 20 weeks, a conclusive assessment of long-term mortality is not possible.

Morbidity

Anthropometric parameters: Age-related weight, Body Mass Index (BMI)

The anthropometric parameters age-related weight and BMI (percentile) were collected in patients ≤ 18 years of age in the LAL-CL06 study. In the LAL-CL02 study, anthropometric parameters were recorded, but the data were not analysed by the pharmaceutical company.

The endpoints age-related weight and BMI are considered to be patient-relevant morbidity parameters, especially in children with characteristic, disease-related growth disorders. Data adjusted for age and sex (z-scores, percentiles) are preferred over absolute values.

In terms of anthropometric parameters, only small increases in age-related weight and age-related BMI were observed in the single-arm LAL-CL06 study in intra-individual comparisons. However, due to the uncontrolled study design, an assessment of the additional benefit based on the data presented is not possible.

Daytime sleepiness (fatigue)

Daytime fatigue was assessed in the LAL-CL02 and LAL-CL06 study using the FACIT fatigue questionnaire. Fatigue can generally be considered a patient-relevant endpoint. The FACIT-Fatigue Scale is a validated self-report instrument designed to measure fatigue in patients with chronic illness. Validation studies for patients with LAL deficiency or a comparable disease are not available. The instrument consists of 13 items that ask about the intensity of fatigue and the weakness and difficulty in performing daily activities due to fatigue within the last 7 days. Items are answered on a 5-point numerical scale (0 = not at all; 4 = very much).

The FACIT-Fatigue questionnaire was administered to all patients who were at least 17 years old. The results of the double-blind phase of the LAL-CL02 study for the total score or the individual domains did not differ significantly between the sebelipase alfa and the placebo group, neither at the beginning nor at the end of the study. No significant changes were observed during the open, uncontrolled study phase either.

For the study LAL-CL06 the return rates were too low, so that the data are not considered for the benefit assessment.

Denver II Development Test

The Denver II Developmental Test serves as a screening tool to identify children with developmental disabilities. The test comprises 125 items divided into the 4 domains “fine motor skills and adaptation”, “gross motor skills”, “language skills” and “social contacts”, which together constitute a total score. Basically, the motor, social and linguistic development of the children is considered relevant to the patient.

Regarding the development and validity of the questionnaire, only insufficient data were submitted by the pharmaceutical company and were also not subsequently submitted within the framework of the written statement procedure, so that the validity cannot be fully assessed.

The Denver II developmental test was collected in children ≤ 6 years of age in the LAL-CL06 study.

At week 96, the total score in all children (n = 6) was within the range of demographic normal values. At baseline, one child out of 7 showed developmental abnormality. An interpretation of these data is difficult, especially against the background of a missing control group.

ALT normalisation

In the LAL-CL02 study, ALT normalisation as the proportion of subjects who achieved normalisation of ALT levels at the end of the double-blind study phase (study week 20) was collected as the primary endpoint.

The endpoint is based on a laboratory parameter and is therefore not directly relevant to the patient. Elevation of ALT concentration is generally considered a sign of liver damage, although it has not been validated as a surrogate parameter. The endpoint ALT normalisation is therefore not considered for the assessment of additional benefit, but only presented as a supplement.

At the end of the double-blind phase at week 20, a statistically significant difference in favour of sebelipase alfa was demonstrated.

LDL-C concentration change

The endpoint “HbA1c” is a surrogate parameter and not per se relevant for patients. Since LDL-C is typically elevated in LDL deficiency and is important as a follow-up, the endpoint LDL-C concentration change is presented as a supplement.

In the double-blind phase of the LAL-CL02 study, there is an advantage of sebelipase over placebo. In the open-label study phase and in the LAL-CL06 study, a decrease in LDL concentration was observed in the intra-individual comparison to baseline.

Quality of life

Pediatric Quality of Life Inventory (PedsQL)

The PedsQL measures general health-related quality of life in children and adolescents with chronic conditions and was used in the LAL-CL02 and LAL-CL06 studies in study participants who were between 5 and ≤ 18 years of age. The questionnaire consists of four multi-dimensional scales (physical, emotional, social and school functioning) and 3 summative scores (total score, physical health summative score, psychosocial health summative score). The questionnaire consists of a Likert scale from 1 to 4 (1 = best function [never] to 4 = worst function [always]); the values are then transformed into a scale from 1 to 100. Higher scores indicate a higher quality of life.

For the double-blind study phase of the LAL-CL02 study, there were no statistically significant differences for the different domains including the total score between patients treated with sebelipase alfa and placebo. For the open-label study phase, the results of the last visit were comparable to those at baseline.

In the LAL-CL06 study, little change was observed from baseline to week 96 for the total score and individual domains.

Due to the uncontrolled design of the open study phase of study LAL-CL02 and study LAL-CL06, no conclusions can be drawn regarding the additional benefit of sebelipase alfa.

Chronic Liver Disease Questionnaire (CLDQ)

The CLDQ is a disease-specific instrument designed to assess health-related quality of life in adult patients with chronic liver disease. The CLDQ includes 29 items in 6 domains (abdominal symptoms, fatigue, systemic symptoms, activity, emotional function, anxiety/concerns). The questions are recorded on a scale from 1 = always present to 7 = never present and are not weighted. Individual domains and the total score have a range of 1 to 7. Higher scores indicate a higher quality of life. No data are available on the suitability of the instrument in patients with LAL deficiency.

For the present benefit assessment, data on the CLDQ questionnaire with sufficient return rates from the LAL-CL02 study of patients aged 17 years and older are available. In the double-blind phase, there is no significant difference between the treatment arms (sebelipase alfa vs placebo) for the total score and domains at week 20. For the open-label study phase, the results of the last visit were comparable to those at baseline.

Side effects

For individuals with non-rapidly progressive LAL deficiency in infancy, data on side effects are available from the LAL-CL02 and LAL-CL06 studies, as well as the ALX-LALD-501 patient registry.

Overall, few adverse events (AEs) were reported. In the LAL-CL02 study, there were no statistically significant differences between treatment arms for summary severe AEs, serious AEs, and AEs leading to treatment discontinuation during the 20-week double-blind study phase. The number of subjects with these events was also low in the open-label phase of the study. Effect estimates for AE at SOC *(System Organ Class*) and PT*(Preferred Term*) level were not provided by the pharmaceutical company. Infusion-associated reactions were reported as AEs of special interest.

No comparative data are available for the registry study and the LAL-CL06 study. The frequency of side effects in the LAL-CL06 study did not differ significantly with those of patients treated with sebelipase alfa in the LAL-CL02 study. In the registry study, the overall proportion of people with UE was lower than in the intervention studies.

Overall, with regard to the category “side effects”, neither an advantage nor a disadvantage of sebelipase alfa compared to placebo can be derived from the available data. Comparative studies on long-term safety are not available for this population.

Overall assessment

For patients with LAL deficiency (not rapidly progressive in infancy (< 6 months)), data are available from the LAL-CL02 and LAL-CL06 studies, and the ALX-LALD-501 patient registry.

Based on the data from the single-arm study LAL-CL06 as well as the open-label phase of LAL-CL-02, no conclusions on the additional benefit can be drawn due to the high risk of bias of single-arm studies and the lack of a comparison group. Therefore, the results on patient-relevant endpoints of the double-blind, controlled phase of the LAL-CL02 study at week 20 are particularly relevant for the decision.

For overall survival, neither an advantage nor a disadvantage of treatment with sebelipase alfa compared to placebo can be established. Against the background of the short duration of the study, however, the significance of these results is limited.

For the endpoint category morbidity, results are available for the endpoint fatigue. No statistically significant difference was found between sebelipase alfa and placebo.

Neither advantages nor disadvantages can be derived for health-related quality of life. Similarly, no statistically significant differences between sebelipase alfa and placebo can be detected in the endpoint category Side effects.

In the overall assessment of these results on the patient-relevant endpoints, the G-BA classifies the extent of the additional benefit of sebelipase alfa in the treatment of for patients with LAL deficiency (not already rapidly progressing in infancy (<6 months)), on the basis of the criteria in Section 5(8) sentences 1, 2 in conjunction with. Section 5 (7) sentence 1 number 4 AM-NutzenV as not quantifiable, because the scientific data basis does not allow quantification.

In the overall assessment, the G-BA classified the extent of the additional benefit of sebelipase alfa for patients with LAL deficiency (not already rapidly progressing in infancy (<6 months)) as not quantifiable on the basis of the criteria, because the scientific data situation does not allow a quantifiable statement on the extent of the additional benefit for patient-relevant endpoints.

Significance of the evidence

The study LAL-CL06, the open phase of the study LAL-CL02 as well as the data of the patient registry ALX-LALD-501 are associated with a high risk of bias due to the study design and do not allow conclusions on the additional benefit of sebelipase alfa due to the missing comparison group. The present evaluation is therefore based in particular on the results of the blinded, randomised, placebo-controlled study LAL-CL02. The results on patient-relevant endpoints from this study do not allow quantification of the extent of additional benefit in the overall assessment. The overall significance of the results for the observed additional benefit is low, which is why the significance of the evidence is classified as a “hint”.

2.1.3 Summary of the assessment

The present assessment is a new benefit assessment the active ingredient sebelipase alfa due to the expiry of the time limit of the resolution of 1 November 2018. Kanuma was approved as an orphan drug. Sebelipase alfa is used for long-term enzyme replacement therapy (EET) in patients of all ages with lysosomal acid lipase (LAL deficiency).

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

(a) patients with LAL deficiency already rapidly progressing in infancy (< 6 months); and (b) patients with LAL deficiency (not already rapidly progressing in infancy (< 6 months)).

a) Patients with rapidly progressive LAL deficiency already in infancy (< 6 months

For this patient group, the pharmaceutical company presents data from two single-arm intervention studies (LAL-CL03 (VITAL), LAL-CL08) and a patient registry (ALX-LALD-501). In addition, an indirect comparison of the intervention studies against a historical control study (LAL-1-NH01) is presented. These data are used for the benefit assessment due to the large effect in the endpoint mortality, against the background of the severity and rarity of the disease, as well as the paediatric study population for the benefit assessment despite the high risk of bias of a historical comparison and the uncertainties regarding the comparability of the study populations for the endpoint mortality.

For overall survival, sebelipase alfa showed an advantage over the natural history of the disease, but this cannot be quantified due to the uncertainties mentioned above. For the categories morbidity and side effects, an assessment of the additional benefit of sebelipase alfa is not possible because suitable comparative data cannot be collected due to the lethal course of the disease in untreated patients. However, data on anthropometric parameters and the Denver II developmental test compared to the age-adjusted normal population suggest that treatment with sebelipase alfa may allow at least some children to develop normally.

Data on quality of life are not available.

Single-arm studies and historical comparisons are generally subject to a high risk of bias. Furthermore, there are uncertainties regarding the comparability of the study populations between the control study and the intervention groups. Therefore, even taking into account the limited number of cases, the overall conclusion for sebelipase alfa is that there is a hint for a non-quantifiable additional benefit. The additional benefit of sebelipase alfa is therefore considered to be not quantifiable because the scientific evidence base does not allow for it.

b) Patients with LAL deficiency (not rapidly progressive in infancy (< 6 months))

For this patient group, data from the studies LAL-CL02 and LAL-CL06, as well as the patient registry ALX-LALD-501 were submitted by the pharmaceutical company. Based on the data from the single-arm study LAL-CL-06 as well as the open-label phase of LAL-CL-02, no conclusions on the additional benefit can be drawn due to the high risk of bias of single-arm studies and the lack of a comparison group. Therefore, the results on patient-relevant endpoints of the double-blind, controlled phase of the LAL-CL02 study at week 20 are particularly relevant for the decision.

Based on the data presented on overall survival, the morbidity endpoint fatigue, health-related quality of life and side effects, neither an advantage nor a disadvantage can be derived from treatment with sebelipase alfa compared to placebo.

In the overall assessment of the available results on the patient-relevant endpoints, the G-BA classifies the extent of the additional benefit of sebelipase alfa, on the basis of the criteria in Section 5(8) sentences 1, 2 in conjunction with. Section 5 (7) sentence 1 number 4 AM-NutzenV as not quantifiable, because the scientific data basis does not allow a quantification. The significance of the evidence is categorised as ‘hint’.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance. The G-BA bases its resolution on the patient numbers stated in the pharmaceutical company’s dossier.

a) In IQWIG’s assessment of patient numbers, these were considered plausible.

b) According to IQWIG’s assessment, the lower limit stated by the pharmaceutical company is within a plausible range. However, the range given is subject to uncertainties. Underestimation is likely, as patients with LAL deficiency may be misdiagnosed due to the rarity of the condition and similarity to other conditions.

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 Kanuma (active ingredient: sebelipase alfa) at the following publicly accessible link (last access: 10 February 2021):

https://www.ema.europa.eu/en/documents/product-information/kanuma-epar-product-information_de.pdf

Treatment with sebelipase alfa should only be initiated and monitored by specialists who are experienced in the treatment of patients with metabolic disorders or chronic liver disease.

2.4 Treatment costs

The treatment costs are based on the product information as well as the information in the Lauer-Taxe (last revised: 15 May 2021).

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 patient-individual 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 dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: The average body weight of adults is 77.0 kg and of children under 1 year 7.6 kg.[2]

Treatment duration:

Designation of the therapy	Treatment method	Number of treatments/patient/year	Treatment duration/treatment (days)	Days of treatment/patient/year
Medicinal product to be assessed				
a) Patients with rapidly progressive LAL deficiency already in infancy (< 6 months)				
Sebelipase alfa	once every 7 days	52.1	1	52.1
b) Patients with LAL deficiency (not rapidly progressive in infancy (< 6 months))				
Sebelipase alfa	once every 14 days	26.1	1	26.1

2 Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Consumption:

Designation of the therapy	Dosage/ application	Dosage/patient/days of treatment	Usage by strength/day of treatment	Treatment days/ Patient/ year	Average annual consumption by strength
Medicinal product to be assessed					
a) Patients with rapidly progressive LAL deficiency already in infancy (< 6 months)					
Sebelipase alfa	1 mg/kg = 7.6 mg -	7.6 mg	1 x 0.5 mg	52.1	52.1 x 0.5 mg
	5 mg/kg = 385 mg	385 mg	20 x 200 mg-		1,042 x 200 mg-
b) Patients with LAL deficiency (not rapidly progressive in infancy (< 6 months))					
Sebelipase alfa	1 mg/kg = 7.6 mg -	7.6 mg	1 x 0.5 mg	26.1	26.1 x 0.5 mg
	3 mg/kg = 231 mg	231 mg	12 x 200 mg-		313.2 x 200 mg-

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 Sections 130 and 130 a SGB V. For the calculation of the annual treatment costs, the required number of packs by strength was first determined on the basis of consumption. Having determined the number of packs of a particular strength, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Cost of medicinal product:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate § 130a SGB V	Cost after deduction of statutory rebates
Medicinal product to be assessed					
Sebelipase alfa 20 mg	1 IFK	€ 7,274.66	€ 1.77	€ 0.00	€ 7,272.89
Abbreviations: IFC = concentrate for the preparation of an infusion solution					

Last revised Lauer-Taxe: 15 May 2021

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 or patient information leaflet, the differences incurred for this must be taken into account as costs for additionally required SHI services.

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

No additional *SHI* services required are taken into account for the cost representation.

3. Bureaucratic costs

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

On 1 December 2020, the pharmaceutical company submitted a dossier for the benefit assessment of sebelipase alfa to the G-BA in due time in accordance with Chapter 5, Section 8, number 1, sentence 5 VerfO.

The benefit assessment of the G-BA was published on 15 March 2021 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting the written statements was 6 April 2021.

The oral hearing was held on 27 April 2021.

An amendment to the benefit assessment with a supplementary assessment was published on 11 March 2021.

In order to prepare a recommendation for a resolution, the Sub-Committee 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 were discussed at the session of the Sub-Committee on 26 May 2021, and the draft resolution was approved.

At its session on 3 June 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Sub-Committee Medicinal product	23 March 2021	Information of the benefit assessment of the G-BA
Working group Section 35a	21 April 2021	Information on written statement procedures received; preparation of the oral hearing
Sub-Committee Medicinal product	27 April 2021	Conduct of the oral hearing
Working group Section 35a	05 May 2021 19 May 2021	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Sub-Committee Medicinal product	26 May 2021	Concluding consultation of the draft resolution
Plenum	3 June 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 3 June 2021

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

Prof. Hecken