Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) 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 Asfotase Alfa (Reassessment of an Orphan Drug after the € 50 Million Turnover Limit Was Exceeded: Hypophosphatasia)

of 2 April 2020

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of 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 G-BA electronically, including all clinical trials the pharmaceutical company has 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 statutory health insurance funds,
6. Requirements for a quality-assured application.

The G-BA 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 G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

Asfotase alfa (Strensiq®) was listed for the first time on 1 October 2015 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices. Strensiq® for the treatment of hypophosphotasia 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.

At its session on 17 March 2016, the G-BA passed a resolution on the benefit assessment asfotase alfa in the therapeutic indication “long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease” in accordance with Section 35a SGB V. The period of validity of the resolution is limited to 1 December 2018. On 1 November 2018, the G-BA decided to extend the limitation until 1 December 2019. The limitation of the period of validity of the resolution on the benefit assessment of asfotase alfa has its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. As also stated in the justification of the resolution of 17 March 2016 and 1 November 2018, on the one hand, it resulted from the conditions attached to the marketing authorisation of asfotase alfa (e.g. the establishment of a clinical register). On the other hand, the G-BA considered that, because of the limited data basis, additional measures are required for the medicinal product to be evaluated as per the regulations in Section 35a SGB V. These measures go beyond the requirements for marketing authorisation and are intended to permit the extent of the additional benefit to assessed appropriately.

If the turnover of the orphan drugs with statutory health insurance at pharmacy sales prices as well as outside statutory medical care, including value added tax, exceeds € 50 million in the last twelve calendar months, the pharmaceutical company must, within three months of being requested to do so by the Federal Joint Committee, submit evidence in accordance with Section 5, paragraph 1 through 6 demonstrating the additional benefit compared with the appropriate comparator therapy.

The pharmaceutical company was informed about the exceeding of the € 50 million turnover limit by letter dated 28 June 2019 and was requested to submit a dossier for the benefit assessment in accordance with 35a SGB V. The pharmaceutical company submitted the final dossier to the G-BA in due time in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 6 VerfO on 15 October 2019.

As a result, the requirement to resubmit data by 1 December 2019 in accordance with the resolutions of 17 March 2016 and 1 November 2018 was no longer appropriate, and the limitation was repealed by the resolution of 22 November 2019.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 January 2020, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of asfotase 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, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has 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 asfotase alfa.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at 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 asfotase alfa (Strensiq ®) in accordance with the product information

Strensiq is indicated for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Small children (≤ 5 years) with perinatal or infantile hypophosphatasia (onset of disease until the age of 6 months):

Appropriate comparator therapy:

- Best supportive care

Best supportive care (BSC) is the therapy that ensures the best possible, patient-individual, supportive treatment to alleviate symptoms and improve the quality of life.

b) Small children (≤ 5 years) with juvenile hypophosphatasia (onset of disease from the age of 6 months)

Appropriate comparator therapy:

- Best supportive care

Best supportive care (BSC) is the therapy that ensures the best possible, patient-individual, supportive treatment to alleviate symptoms and improve the quality of life.

c) Children (> 5 years), adolescents, and adults with perinatal, infantile, or juvenile hypophosphatasia (disease onset up to 18 years)

Appropriate comparator therapy:

- Best supportive care

Best supportive care (BSC) is the therapy that ensures the best possible, patient-individual, supportive treatment to alleviate symptoms and improve the quality of life.

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

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 Federal Joint Committee 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.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. In the present therapeutic indication, asfotase alfa is the only medicinal product that has been approved.

On 2. In the present indication, among other things, remedies (primarily physiotherapy and occupational therapy) according to the catalogue of remedies2, aids (orthopaedic aids, walking aids, and respiratory aids) and, if necessary, surgical measures may be indicated. In the present therapeutic indication, the latter are necessary, especially for the treatment of bone fractures and other surgical or neurosurgical interventions.

On 3. In the therapeutic indication hypophosphatasia, the G-BA passed the following resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

Asfotase alfa: Resolution according to Section 35a SGB V of 17 March 2016 (Orphan Drug Status; is repealed with the present resolution).

On 4. The general state of medical knowledge was represented by a systematic literature search for systematic reviews, meta-analyses, HTA reports, and evidence-based systematic guidelines in the present indication. For the treatment of patients with hypophosphatasia, there is no evidence from literature with these inclusion criteria except for the resolution of the G-BA on asfotase alfa of 17 March 2016 according to Section 35a SGB V. Supplementary documents were therefore included to determine the appropriate comparator therapy. These contain recommendations mainly concerning asfotase alfa but also other supportive treatment options.

In summary, there are so far only very limited therapeutic options for patients with hypophosphatasia because only the active ingredient of the pharmaceutical company (asfotase alfa) has been approved for the present therapeutic indication. Other treatment options include supportive treatment to alleviate symptoms and improve quality of life. Among other things, remedies (primarily physiotherapy and occupational therapy) according to the catalogue of remedies, aids (orthopaedic aids, walking aids, and respiratory aids) and, if necessary, surgical measures may be indicated. In the present therapeutic indication, the latter are necessary, especially for the treatment of bone fractures and other surgical or neurosurgical interventions.

Accordingly, the G-BA has determined best supportive care as an appropriate comparator therapy. Best supportive care (BSC) is the therapy that ensures the best possible, patient-individual, supportive treatment to alleviate symptoms and improve the quality of life.

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

2.1.3 Extent and probability of the additional benefit

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

a) Small children (≤ 5 years) with perinatal or infantile hypophosphatasia (onset of disease until the age of 6 months)

For small children with perinatal or infantile hypophosphatasia, there is a non-quantifiable additional benefit for asfotase alfa compared with best supportive care.

[2] Catalogue of prescribable remedies according to Section 92, paragraph 6 SGB V as the second part of the directive on the prescription of remedies for use in non-contractual medical care

Justification:

For the age group of patients up to and including 5 years with perinatal or infantile hypophosphatasia (HPP), Study ENB-002-08, the follow-up study ENB-003-08 and Study ENB-010-10 as well as the historical control study ENB-011-10 were presented by the pharmaceutical company for the benefit assessment.

Study ENB-002-08 is a single-arm, multi-centre, international, open-label Phase II study on the safety, tolerability and pharmacology of asfotase alfa with a treatment duration of 24 weeks. Included were 11 patients with severe HPP who were no older than 36 months at the start of study and in whom the disease had already manifested itself before the age of 6 months. The dosage did not correspond to the recommended dosage (according to the product information) of 6 mg/kg asfotase alfa per week over the entire period. At the start of study, patients received a single i.v. dose of 2 mg/kg asfotase alfa and were treated with 3 mg/kg/week s.c. one week later. After one month, it was possible to increase the dosage to 6 mg/kg/week in the absence of efficacy. After 3 months, the dosage could be adjusted to 6 mg/kg/week or 9 mg/kg/week according to the course of the disease. Eight of the patients included in the study were treated with the dosage recommended in the marketing authorisation.

Patients who had successfully completed this study (n = 10) were included in extension study ENB-003-08 (one patient discontinued Study ENB-002-08). The treatment duration ranged from one day to 7.5 years (median 6.6 years). Patients were further treated with the asfotase alfa dosage they received at the end of Study ENB-002-08.

Study ENB-010-10 is a single-arm, multi-centre, international, open-label Phase II study on the safety, efficacy, and pharmacokinetics of asfotase alfa in infants and children aged five years or younger with HPP. The symptoms of HPP must have occurred before the age of 6 months (perinatal or infantile HPP). In the study, patients received 6 mg/kg/week asfotase alfa. After completion of a 24-week initial period of treatment, all patients were eligible for further treatment in the open extension phase. The treatment duration ranged from 6 days to 6.1 years (median: 2.3 years).

To present the results, the data from studies ENB-002-08/003-08 and ENB-010-10 on asfotase alfa were pooled. In both studies, the primary endpoint was the change in the Radiographic Global Impression of Change (RGC-I) at week 24. Endpoints on mortality, respiratory function, and adverse events (AE) were also collected. There were no restrictions on pre- or accompanying treatment. The results were compared with data from Study ENB-011-10, which investigated the natural course of disease with supporting treatment measures.

Study ENB-011-10 is a global retrospective epidemiological study based on data from medical records. A total of 48 patients with severe perinatal or infantile hypophosphatasia were included. Treatment with asfotase alfa at any time led to disqualification. The data extraction included information on supportive medication and non-medicinal methods for the treatment of HPP. All information on survival status and respiratory support measures was collected. The data collection primarily concerned the first 5 years of life of the patients. In addition to the primary endpoint overall survival and various operationalisations to assess respiratory function, no other endpoints were investigated. AE were also not surveyed in the study.

Historical comparison

The pooled data of the single-arm studies on asfotase alfa were compared with the data of a historical follow-up under supportive care based on medical records. In general, the historical comparison results in a very high risk of bias. In addition, there are considerable limitations in the comparability of data because of different data collection for the endpoint mortality. Whereas in the single arm studies on asfotase alfa, overall survival was recorded from the start of study; in the historical control, this was recorded from the time of birth.

As a result, there is a systematic bias in the patients considered because especially severely affected and possibly difficult to treat patients who die early were not included in the asfotase alfa studies. The median age at study enrolment in the pooled asfotase alfa studies was thus

15 months. At this age, however, on the basis of medical records, approx. 65% of the patients in the study had already died.

The studies were also conducted at different time periods between which the symptomatic treatment and diagnosis had changed. The studies on asfotase alfa (ENB-002-08/ENB-003-08 and ENB-010-10) were carried out between 2008 and 2016, while the data for the comparator group were obtained from medical records from between 1970 and 2011. The G-BA is therefore also critical of the fact that the pharmaceutical company did not carry out research on the appropriate comparator therapy in order to identify more recent data for a historical comparison.

In order to estimate the influence of the confounders “year of diagnosis” and “age at study enrolment” on overall survival, various sensitivity analyses were performed. Although these confirmed the influence on overall survival, they showed robust effects in favour of asfotase alfa compared with the comparator therapy.

Other important potential confounders are the time of disease manifestation (perinatal or infantile) and the severity of the disease. However, these were not addressed by the pharmaceutical company in the dossier.

Based on the historical comparison, the pharmaceutical company presents an evaluation of respiratory function “survival without invasive ventilation” in the dossier for the endpoint category morbidity. In the single-arm studies ENB-002-08/003-08 and ENB-010-10 on asfotase alfa, patients who had already received invasive ventilation at the start of study were excluded from the analyses. In contrast, the results of all patients who received invasive ventilation within the first 5 years of life were included in the analyses of the historical control (ENB-011-10). This results in different objectives. For the asfotase alfa studies, it is investigated whether patients who were not yet ventilated at the time of study enrolment also do not require ventilation under asfotase alfa. However, the analysis of the historical control documents whether patients were invasively ventilated within the first 5 years of life. The basic risk of receiving invasive ventilation is therefore different in the different groups in the comparison. The comparative analysis presented by the pharmaceutical company can therefore not be used for the benefit assessment because of the different objects of investigation.

Despite the methodological deficiencies and uncertainties mentioned above, the pooled data from Studies ENB-002-08/003-08 and ENB-010-10 on asfotase alfa compared with a historical control group with supportive measures (ENB-011-10) for the endpoint mortality will be used for the benefit assessment under the following special circumstances: Perinatal and infantile hypophosphatasia is a very rare disease associated with a high mortality rate in the natural course of the disease. With the exception of asfotase alfa, there are no treatment alternatives beyond best supportive care. Moreover, small children with hypophosphatasia are a particularly vulnerable patient population.

Extent and probability of the additional benefit

Mortality

In Studies ENB-002-08/003-08 and ENB-010-10 on asfotase alfa and Study ENB-011-10, overall survival was assessed based on medical records.

The pooled analysis of ENB-002-08/003-08 and ENB-010-10 compared with the historical control with supportive measures shows a statistically significant, distinct survival advantage for infants treated with asfotase (mortality of 11.5%) compared with the historical control (mortality of 72.9%).

Overall, despite the methodological shortcomings described above, the extent of the effect means that an advantage in overall survival and thus an additional benefit can be derived. However, because of the high risk of bias, the extent of the additional benefit cannot be estimated.

Morbidity

For the endpoint category morbidity, the pharmaceutical company presents only data from the historical comparison of respiratory function. For the combined endpoint "survival without invasive ventilation", the individual components of mechanical ventilation (tracheostomy or intubation) or death were assessed. These are patient-relevant outcomes.

Because of the aforementioned methodological limitations, the evaluations on respiratory function are not usable and cannot be considered for the assessment of the additional benefit.

Quality of life

The health-related quality of life was not investigated in the studies submitted.

Side effects

No side effects were recorded in the historical control group (ENB-011-10). Thus, for this endpoint category, no comparative analyses are available for the benefit assessment.

Overall assessment/conclusion

For the assessment of the additional benefit of asfotase alfa compared with the appropriate comparator therapy of best supportive care for the treatment of small children with perinatal or infantile hypophosphatasia, data from two pooled single-arm studies (ENB-002-08/003-08 and ENB-010-10) and one historical control (ENB-011-10) are available for the endpoint overall survival. Against the background of the severity and rarity of the disease as well as the paediatric study population, the data for the benefit assessment were used for the benefit assessment despite the high risk of bias of a historical comparison and shortcomings because of the different data collection methods.

For morbidity, evaluations of respiratory function were presented by the pharmaceutical company; however, these cannot be used for the benefit assessment because of different data collection methods and operationalisations in the historical control and in the asfotase studies. No comparative data are available on health-related quality of life and side effects.

For the overall survival, there was a clear advantage of asfotase alfa compared with BSC. However, when assessing these results, the high risk of bias resulting from historical comparison as well as differences in data collection must be taken into account. The difference observed for the endpoint is so large that it cannot be explained by the effect of confounders alone. There is an additional benefit; however, the extent of the difference between treatment groups cannot be derived from the data provided. The additional benefit of asfotase alfa compared with BSC is therefore classified as non-quantifiable because the scientific data basis does not allow quantification.

Reliability of data (probability of additional benefit)

For the benefit assessment, a historical comparison of two single-arm, open studies on asfotase alfa with a non-interventional study based on medical records was presented. Historical comparisons generally show a high degree of uncertainty of results. Moreover, the significant differences in data collection contribute to the systematic bias. Furthermore, for the comparison of asfotase alfa with supportive measures, there are differences and uncertainties, especially with regard to age at onset of disease and the time of manifestation of hypophosphatasia (perinatal vs infantile).

The overall rating of the reliability of data is therefore classified as a hint.

b) Small children (≤ 5 years) with juvenile hypophosphatasia (onset of disease from the age of 6 months)

For small children with juvenile hypophosphatasia, the additional benefit of asfotase alfa compared with the appropriate comparator therapy is not proven.

Justification:

No data were submitted for infants (≤ 5 years) with juvenile hypophosphatasia.

c) Children (> 5 years), adolescents, and adults with perinatal, infantile, or juvenile hypophosphatasia (disease onset up to 18 years)

For small children, adolescents, and adults with perinatal, infantile, or juvenile hypophosphatasia, the additional benefit of asfotase alfa compared with the appropriate comparator therapy is not proven.

Justification:

For children older than 5 years, adolescents, and adults perinatal, infantile, or juvenile hypophosphatasia, no data suitable for the benefit assessment were submitted. For various reasons set out below, Studies ENB-009-10 and ENB-006-09 (and their expansion Study ENB-008-10), Study ALX-HPP-502s (or sub-study ALX-HPP-502s), the EmPATHY study, and the data on register ALX-HPP-501 presented in the dossier were not used for the benefit assessment.

Study ENB-009-10 is a randomised, controlled, open-label study involving 19 patients aged 13 to 65 years with hypophosphatasia with infantile (n = 4), juvenile (n = 14) or adult (n = 1) onset. Patients were randomised to receive either two different doses of asfotase alfa – 0.3 or 0.5 mg/kg body weight per day – or no treatment. Dose adjustments were possible during the study. This open-label, randomised study phase continued for 24 weeks. This was followed by an open non-controlled extension phase of up to 72 months.

The dosage of asfotase alfa during the randomised treatment phase (2.1 and 3.5 mg/kg body weight per week in both study arms) did not comply with the marketing authorisation. The study can therefore not be used for the benefit assessment. The marketing authorisation describes a dosage of 6 mg/kg body weight per week, which is possible in 2 different dosage schemes. Only in the course of the single-arm extension phase was the dosage increased to the amount recommended in the marketing authorisation. However, because of the lack of a comparator arm, it is also not suitable for estimating an additional benefit compared with BSC.

Studies ENB-006-09 and ENB-008-10 are an open-label, randomised dose-finding study over 24 weeks and its extension study over at least 72 months. The randomised phase included 13 patients aged 5 to12 years and with an infantile (< 6 months; n = 5) or juvenile (≥ 6 months to < 18 years n = 8) onset of disease who were treated with either 6 or 9 mg/kg body weight per week. Because of the lack of a comparator arm, the pharmaceutical company presents data on treatment with supportive measures based on medical records (ALX-HPP-502s) and carries out a historical comparison. However, in ALX-HPP-502s, only data from patients with juvenile HPP were collected. The age of the patients was between 5 and 15 years. The data presented refer exclusively to radiologically determined endpoints Rickets Severity Scale (RSS), Radiographic Global Impression of Change (RGI-C).

No comparative data are available for patient-relevant endpoints such as the 6 minute walk test and BOT-2. The same applies for anthropometric parameters, which are considered to be patient-relevant morbidity parameters, especially in children with characteristic disease-related growth disorders. The present evaluations in relation to reference values of the healthy population, which were re-evaluated by IQWIG as an addendum to the benefit assessment, were not used for the present benefit assessment because of the high uncertainty of results of the before-and-after comparisons. In some patients with HPP, a spontaneous improvement

(honeymoon phase) occurs at the onset of adolescence in relation to symptomatology and the course of the disease. The potential therapeutic effects can therefore not be conclusively distinguished from a natural course.

The EmPATHY longitudinal study, which is currently ongoing in Germany, included adults who had developed the disease in childhood. The data cut-off presented provides evaluations of retrospectively collected changes under treatment with asfotase alfa. Because of a lack of data on the appropriate comparator therapy, the data are not suitable for deriving the additional benefit of asfotase alfa compared with the appropriate comparator therapy.

ALX-HPP-501 is an indication-based, international patient registry (currently n = 622) in which data from patients with hypophosphatasia are collected. Inclusion in the register is independent of the age of the patient or the age at onset of the disease. The patients were treated either with asfotase alfa or with exclusively supportive measures. In the course of the marketing authorisation, the establishment of the register was requested by the EMA under “exceptional circumstances” in order to obtain further data on long-term efficacy and safety, among other things. In the context of the limitation of the resolution of the previous benefit assessment on asfotase alfa, the G-BA endorses this requirement and also requested usable data on patient-relevant outcomes for the benefit assessment in the German healthcare context.

Although the establishment of a register has been formally implemented, it is not possible to take register data into account for various reasons. Apart from methodological shortcomings in data collection and evaluation, it is mainly the incomplete data collection and the significant differences between the patients treated with asfotase alfa and those who received only supportive measures that were decisive for the exclusion. Patients treated with asfotase alfa showed a greater burden of symptoms in their disease history than patients treated according to BSC. A comparison of these groups to derive the additional benefit is therefore not appropriate. Moreover, the comparative data on patient-relevant outcomes presented are associated with further uncertainties because data were collected from only a small proportion of patients.

Overall assessment/conclusion

The pharmaceutical company presents data from a randomised controlled trial (ENB-009-10), an observational longitudinal study (EmPATHY) and a patient registry (ALX-HPP-501) for children older than 5 years, adolescents, and adults with perinatal, infantile, or juvenile hypophosphatasia. Furthermore, data from a randomised dose-finding study (ENB-006-09) and its extension study (ENB-008-10) were compared with a historical control based on medical records (ALX-HPP-502s).

The studies presented were not used for the benefit assessment because either the dosage was not in compliance with the marketing authorisation (ENB-009-10) or no comparison with the appropriate comparator therapy BSC was possible (EmPATHY). For the historical comparison presented, only radiological and no patient-relevant endpoints were available. The evaluations of patient-relevant outcomes of study ENB-006-09/ENB-008-10 (BOT-2, 6-minute walking test and anthropometric parameters) in relation to reference values of the healthy population were not suitable for the present benefit assessment because of the high uncertainty of results of before-and-after comparisons.

The register data are also not suitable for the assessment of the additional benefit. In addition to deficiencies in data collection and evaluation, the differences in burden of symptoms between patients who were treated with asfotase alfa or who were treated purely symptomatically as well as incomplete data collection are considered critical.

All in all, no suitable data are available to assess the additional benefit compared with the appropriate comparator therapy. An additional benefit is thus not proven.

2.1.4 Summary of the assessment

The present assessment concerns the renewed benefit assessment of the active ingredient asfotase alfa because the € 50 million turnover limit was exceeded. Asfotase alfa was approved as an orphan drug under "exceptional circumstances". Asfotase alfa is indicated for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease.

In the therapeutic indication to be considered, 3 patient groups were distinguished:

a) Small children (≤ 5 years) with perinatal or infantile hypophosphatasia (onset of disease until the age of 6 months)

Best supportive care (BSC) was determined as an appropriate comparator therapy by the G-BA. For this patient group, the pharmaceutical company presents a historical comparison in which two pooled single-arm studies on treatment with asfotase (ENB-002-08/ENB-003-08 and ENB-010-10) were compared with the historical control study on supportive measures based on medical records (ALX-HPP-502s). Against the background of the severity and rarity of the disease as well as the paediatric study population, the data for the benefit assessment were used for the benefit assessment despite the high risk of bias of a historical comparison and shortcomings because of the different data collection methods.

For the overall survival, there was a clear advantage of asfotase alfa compared with BSC. Because of the high risk of bias resulting from the historical comparison and differences in data collection, there are uncertainties in the interpretation of the result. For quality of life and side effects, either no data were submitted or the data were not assessable (respiratory function).

In the overall view, for patient population a) there is a hint for a non-quantifiable additional benefit for asfotase alfa compared with best supportive care.

b) Small children (≤ 5 years) with juvenile hypophosphatasia (onset of disease from the age of 6 months)

Best supportive care (BSC) was determined as an appropriate comparator therapy by the G-BA. The pharmaceutical company does not present any studies for this patient group. Therefore, in the overall picture, for patient population b), an additional benefit is not proven.

c) Children (> 5 years), adolescents, and adults with perinatal, infantile, or juvenile hypophosphatasia (disease onset up to 18 years)

Best supportive care (BSC) was determined as an appropriate comparator therapy by the G-BA. For this group of patients, the pharmaceutical company presents the randomised controlled Study ENB-009-10 and the EmPATHY Study as well as the data on the ALX-HPP-501 register. In addition, a historical comparison based on medical records (ALX-HPP-502) with a single-arm study on asfotase alfa (ENB-006-09/ENB-008-10) is presented.

However, the studies are not suitable for the benefit assessment because either no comparator group was available (EmPATHY), asfotase alfa was not used in compliance with the marketing authorisation (ENB-009-10), or only radiological endpoints were recorded (historical comparison). The evaluations of patient-relevant outcomes of study ENB-006-09/ENB-008-10 (BOT-2, 6-minute walking test and anthropometric parameters) in relation to reference values of the healthy population were not suitable for the present benefit assessment because of the high uncertainty of results of before-and-after comparisons.

The registry data was not considered for the benefit assessment, particularly because of significant differences in patient characteristics as well as incomplete data collection.

Therefore, in the overall picture, for patient population c), an additional benefit is not proven.

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 (SHI). The G-BA bases its resolution on the number of patients stated in the dossier of the pharmaceutical company.

The pharmaceutical company assumes that a total of 1,074 patients living in Germany have hypophosphatasia that appeared in childhood and adolescence. Of these, the sub-populations of small children with perinatal/infantile (patient population a) or juvenile (patient population b) manifestation of the disease together comprise 17 patients.

For the calculation, the pharmaceutical company refers to the publication by Beck et al (2009), which contains Germany-specific data on the incidence of hypophosphatasia in childhood and adolescence. The pharmaceutical company uses a model to calculate the number of patients in the target population using demographic data from the Federal Statistical Office (birth cohorts from 1946 to 2015) and the periodic mortality tables for Germany (2013/2015). The pharmaceutical company thus calculated 1,225 patients in Germany in whom hypophosphatasia occurred in childhood and adolescence. Taking into account a SHI proportion of 87.7%, the pharmaceutical company determines 1,074 (462 to 2,252) patients in the SHI target population.

The figure seems to be an overestimate because the general mortality rates were used, and the disease-specific mortality rates are higher than the general ones.

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 Strensiq® (active ingredient: asfotase alfa) at the following publicly accessible link (last access: 9 January 2020):

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

Treatment with asfotase alfa should only be initiated and monitored by specialists who are experienced in the treatment of patients with metabolic or bone disorders.

This medicinal product was approved under “exceptional circumstances”. This means that because of the rarity of the disease, it was not possible to obtain complete information about the medicinal product. The EMA examines any new information made available and will update the summary of product characteristics as appropriate.

As an additional measure for risk minimisation, mandatory training material must be made available to patients and caregivers to provide guidance on how to correctly administer asfotase alfa and to highlight the risks of medication errors and reactions at the site of injection. The training material should contain the following information: Package leaflet, instructions for self-injection for patients, instructions for injection for parents or caregivers with children who are patients.

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 March 2020).

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”, the time intervals between individual treatments, and for the maximum treatment duration if specified in the product information.

For the calculation of the dosages as a function of body weight, the average body measurements from the official representative statistics “Microcensus 2017 – body measurements of the population” were used as a basis (average body weight): Children less than one year: 7.6 kg; 5 years: 20.8 kg; 6 years: 23.6 kg; adults 77.0 kg).[3]

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.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Patient population a) + b) + c)				
Asfotase alfa	3 – 6 × within 7 days	156.4 – 312.9	1	156.4 – 312.9
Best supportive care	different for each individual patient			
Appropriate comparator therapy				
Patient population a) + b) + c)				
Best supportive care	different for each individual patient			

[3] Federal health reporting. Average body measurements of the population (2013, both sexes), www.gbe-bund.de

Usage and 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					
Patient population a) + b)					
Asfotase alfa	< 1 year: 2 mg/kg = 15.2 mg –	15.2 mg	1 × 18 mg	156.4 –	156.4 × 18 mg
	1 mg/kg = 7.6 mg	7.6 mg	1 × 18 mg	312.9	312.9 × 18 mg
	5 years: 2 mg/kg = 41.6 mg –	41.6 mg	1 × 40 mg + 1 × 18 mg –	156.4 –	156.4 × 40 mg + 156.4 × 18 mg
	1 mg/kg = 20.8 mg	20.8 mg	1 × 28 mg	312.9	312.9 × 28 mg
Best supportive care	different for each individual patient				
Patient population c)					
Asfotase alfa	6 years: 2 mg/kg = 47.2 mg –	47.2 mg –	1×x 40 mg + 1 × 18 mg –	156.4 –	156.4 × 40 mg + 156.4 × 18 mg
	1 mg/kg = 23.6 mg	23.6 mg	1 × 28 mg	312.9	312.9 × 28 mg
	Adults: 1 mg/kg = 77 mg	77 mg	1 × 80 mg	312.9	312.9 × 80 mg
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Patient population a) + b) + c)					

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Best supportive care	different for each individual 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 Sections 130 and 130 a 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 the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package 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					
Asfotase alfa 18 mg	12 SFI	€ 13,565.45	€ 1.77	€ 0.00	€ 13,563.68
Asfotase alfa 28 mg	12 SFI	€ 21,096.15	€ 1.77	€ 0.00	€ 21,094.38
Asfotase alfa 40 mg	12 SFI	€ 30,132.99	€ 1.77	€ 0.00	€ 30,131.22
Asfotase alfa 80 mg	12 SFI	€ 60,255.79	€ 1.77	€ 0.00	€ 60,254.02
Best supportive care	different for each individual patient				
Appropriate comparator therapy					
Best supportive care	different for each individual patient				
Abbreviations: SFI = solution for injection					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 March 2020

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 standard expenditure in the course of the treatment are not shown.

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

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 15 October 2019, the pharmaceutical company submitted a dossier for the benefit assessment of asfotase alfa to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, Number 6 VerfO.

By letter dated 15 October 2019 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient asfotase alfa.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 January 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 15 January 2020. The deadline for submitting written statements was 5 February 2020.

The oral hearing was held on 24 February 2020.

By letter dated 24 February 2020, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 20 March 2020.

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 were discussed at the session of the subcommittee on 24 March 2020, and the proposed resolution was approved.

On 2 April 2020, the G-BA resolved by written statement to amend the Pharmaceuticals Directive.

The patient representatives support the resolution.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	23 January 2018	Determination of the appropriate comparator therapy
Working group Section 35a	18 February 2020	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	24 February 2020	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	3 March 2020 17 March 2020	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	24 March 2020	Concluding discussion of the draft resolution
Plenum	2 April 2020	Written resolution on the amendment of Annex XII of the AM-RL

Berlin, 2 April 2020

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

Prof. Hecken