Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V – Asfotase Alfa

of 17 March 2016

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.

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 of the Council of 16 December 1999, according to Section 35a, paragraph 1, sentence 10, 1st half sentence 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 need not be submitted (Section 35a, paragraph 1, sentence 10, 2nd half sentence SGB V). Section 35a, paragraph 1, sentence 10 1st half sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an evaluation of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, numbers 2 and 3 SGB V in conjunction with the Chapter 5, Sections 5 et seq. of the Rules of Procedure of the G-BA (VerfO) has not been carried out. Only the extent of the additional benefit has to be demonstrated.

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 retail prices including VAT exceeds € 50 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 11 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, paragraphs 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). On the basis of the statutory requirement in Section 35a, paragraph 1, sentence 10 SGB V that the additional benefit of an orphan drug is deemed to have been proven through the grant of 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, in the case of 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. Rather, the extent of the additional benefit provided by the G-BA is evaluated exclusively on the basis of the approval studies.

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 11 SGB V). According to Section 35a, paragraph 2 SGB V, the assessment of 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 shall pass a resolution 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

The relevant date for the first placing on the market of the active ingredient asfotase alfa in accordance with Chapter 5, Section 8, number 1, sentence 2 VerfO is 1 October 2015. The pharmaceutical company submitted the final dossier to the G-BA 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, number 1 VerfO on 30 September 2015.

Asfotase alfa 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.

In accordance with Section 35a, paragraph 1, sentence 10, 1st half sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit is assessed on the basis of the approval studies 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 4 January 2016 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G12-01) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for 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 through 4 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 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

Approved therapeutic indication of asfotase alfa

Strensiq is indicated for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease (see section 5.1 of the product information).[2]

Extent of the additional benefit

With the exception of one RCT (ENB-009-10 study), the studies on which the benefit assessment was based were uncontrolled intervention studies, some of the results of which were compared with data from two historical control groups. These intervention studies included hypophosphatasia (HPP) patients aged 0–5 years (incl.) with perinatal/infantile HPP onset (ENB-002-08/ENB-003-08, ENB-010-10 studies), aged 5–12 years with both perina-

[1] General Methods, version 4.2 dated 22 April 2015. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

[2] Product information for asfotase alfa (Strensiq®), last revised: December 2015

tal/infantile and juvenile HPP (ENB-006-09/ENB-008-10 study) and aged 13–66 years with mainly juvenile HPP onset (ENB-009-10 study).
The distribution into age subgroups is linked with the clinical characterization of HPP. The spectrum of clinical symptoms depending on age at the onset of HPP is broad and very heterogeneous. The approved populations include HPP patients with life-threatening symptoms (respiratory insufficiency), patients with skeletal deformities resulting in impaired motor function and varying degrees of pain, and patients who may have fewer symptoms. As the HPP patients in the studies differ in age, manifestation, degree of severity and age of onset, and as the results and the (age-specific) endpoints collected in the studies are not comparable, in order to determine additional benefit, patients were placed into separate subgroups according to age.

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

a) Patients ≤ 5 years of age:

For patients with paediatric-onset of hypophosphatasia, there is a non-quantifiable additional benefit.

b) Patients > 5 years of age:

For patients with paediatric-onset of hypophosphatasia in childhood, there is a non-quantifiable additional benefit.

Justification:

Issues relevant to the benefit assessment common to all patient subgroups

All the studies on which the benefit assessment is based have methodological shortcomings, and thus there are uncertainties regarding the validity and interpretability of the study results. As noted in both the benefit assessment and the EMA's assessment report[3] on asfotase alfa, the primary endpoint and interpretation of the endpoint were altered during the course of the studies due to various protocol changes and amendments, and dosing or inclusion and exclusion criteria were modified based on the data collected. For instance, in three of the four intervention studies, the dosage recommendations of 6 mg/kg/week in the product information were not followed or only partially followed. The reliability of the data from the studies is further limited by the lack of prospective parallel control groups and, therefore, the fact that some of the results of the studies were analysed as a change from baseline. Before and after comparisons, together with an open uncontrolled study design, are generally associated with a high risk of bias for an active ingredient under investigation. Due to the lack of blinding and the small number of patients enrolled, ENB-009-10, the only randomised controlled trial comparing asfotase alfa treatment with non-treatment (and not with placebo) over a 24-week period, was also liable to high risk of bias for the assessed endpoints. In addition, the EMA is critical of the large number of test strategies employed. The EMA considered that a blinded, controlled study design with a focus on a few relevant endpoints would be beneficial for the reliability of the study findings. To improve the significance of the study results for some of the endpoints, the pharmaceutical company conducted historical controls (two retrospective

[3] EPAR asfotase alfa, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003794/WC500194340.pdf, page 49

observational studies on the natural history of HPP). However, in addition to the potential bias inherent to prospective non-randomised studies (e.g. lack of structural equality between intervention and control, and selection bias), the use of historical controls results in further confounding factors, such as changes during the course of the study to the indication, diagnostics or generally improved medical care (e.g. ventilation technology).

a) Patients ≤ 5 years of age:

For the subgroup of patients up to 5 years of age, the benefit assessment was based on the study ENB-002-08 (11 patients) and its follow-up study ENB-003-08 (10 patients), and on study ENB-010-10 (59 patients). The historical control study ENB-011-10 was also drawn on to support the findings.

Study ENB-002-08 was an open non-randomised and non-controlled phase 2 study on the safety, tolerability and pharmacokinetics of asfotase alfa. Onset of hypophosphatasia occurred in all patients before the age of 6 months. The age at inclusion into the study was between 0.5 and 35 months. Patients who successfully completed this study were included into the ENB-003-08 extension study and received the same dose of asfotase alfa as at the time of completion of ENB-002-08. One patient withdrew from ENB-002-08 and was therefore not included into the extension study. Due to numerous protocol changes, dosage was not evenly distributed over the entire treatment period. According to the product information, the recommended dosage of asfotase alfa is 6 mg/kg per week. In the study, however, after a single i.v. dose of 2 mg/kg asfotase alfa the dose was increased to 3 mg/kg/week s.c. one week later. After one month it was permissible, depending on the outcome, to increase the dosage to 4.5 mg/kg/week or 6 mg/kg/week or 9 mg/kg/week. Study ENB-002-08 lasted 24 weeks and study ENB-003-08 is planned to last 60 months (ongoing). Interim analyses were planned *a priori* at various points in time.

Study ENB-010-10 is an open phase 2 study on the safety, efficacy and pharmacokinetics of asfotase alfa in infants and children with HPP aged five years or younger. Patients must suffer from perinatal or infantile (defined as experiencing the first signs/symptoms of HPP before the age of 6 months) HPP. Patients in the study received a total of 6 mg/kg/week of asfotase alfa (either 2 mg/kg/3x weekly or 1 mg/kg/6x weekly). After completion of a 24-week initial period of treatment, all patients were eligible for further treatment in the open-label extension treatment period (ETP).

To present the results, the data from studies ENB-002-08/003-08 and ENB-010-10 on asfotase alfa were pooled.

Furthermore, the retrospective study ENB-011-10 on the natural history of patients with HPP (including clinical progression) was used to support the findings of the study for this age group as a comparison to the pooled data from the intervention studies ENB-002-08/EBN-003-08 and ENB-010-10 for patients with perinatal/infantile HPP. This study included 48 patients with perinatal/infantile HPP (based on their medical records), of whom 13 patients were alive at the time of data extraction. The mean age of living patients (N=13) was 506.9 (SD:319.24) weeks. The mean age of HPP onset for these patients was 34.2 days (0–179 days). ENB-011-10 provides data on overall survival and survival without invasive ventilation.

Details of the endpoint findings can be found below:

Mortality:

The pharmaceutical company operationalises survival time as the time span between entry into the study and death from any cause. In contrast, for the historical control (ENB-011-10), overall survival was defined as the time between birth and death. To perform a comparative survival analysis with the historical control group, the operationalisation of the historical control (time from birth to event) was applied.

Data on mortality from the pooled survival analysis for patients from the intervention studies (ENB-002-08/ENB-003-08 and ENB-010-10) are based on a data cut-off from 20 November 2013. A total of 37 patients from the asfotase alfa studies and 48 patients from the historical control group (ENB-011-10) were included in the comparison.

For patients treated with asfotase alfa, overall survival was significantly better than in the historical control group. While 4 out of 37 (10.8%) patients in the asfotase group died, 35 out of 48 patients (72.9%) in the historical control group died ($p<0.0001$). Patients in the historical control group had a median survival time of 270.5 days, however calculating median survival time in patients treated with asfotase alfa is not yet possible.

Despite the uncertainties associated with historical comparison, it is assumed that the natural course of hypophosphatasia is associated with a high mortality rate due to the lack of adequate treatment options. Thus, it seems plausible for the perinatal/infantile form to compare the objective overall survival endpoint in the intervention studies with the historical control (taking into account the limitations mentioned above). When historical controls are drawn on, there is a significant risk of bias, due, for example, to the lack of structural equivalence between intervention and control or due to the confounding factor of time. The pharmaceutical company addressed these uncertainties by performing sensitivity analyses to estimate the impact of the year of diagnosis on survival or age at inclusion into the study. This clearly showed that, in particular, the time of diagnosis (year of diagnosis) in the historical control group had an influence on overall survival: survival for patients born in 2000 or later was longer than that of patients diagnosed before 2000. Comparison of 37 asfotase alfa patients vs 48 patients in the historical control reveals that the survival chance of treated patients was higher than in the historical control group, regardless of the year of diagnosis.

A further factor was the age at inclusion. The mean inclusion age in patients treated with asfotase alfa was 38 weeks. At this time, more than 30% had already died in the historical control group. For this reason, a sensitivity analysis was performed involving only those patients from the historical control group who survived at least 38 weeks (N=25). From the asfotase alfa studies, only patients younger than 72 weeks (N=21) were included in the analysis. In the evaluated period, 12 out of 25 patients (48%) in the historical control group and 19.0% of the patients treated with asfotase alfa died. In this analysis, the overall survival benefit for treated patients compared to control patients was no longer statistically significant ($p=0.1049$). Taking into account the age at diagnosis, the age at inclusion into the study and the year of diagnosis, the difference in survival between the historical control and the asfotase alfa group was no longer significant (HR 2.49 [95% CI 0.48; 12.83]; $p=0.2765$).

These sensitivity analyses illustrate the limitations associated with historical controls. Nevertheless, it is possible to base the evaluation of the extent of the additional benefit of asfotase alfa on a comparison with the results for the mortality endpoint of the historical control, as it can be assumed that the observed therapeutic effects can be confirmed in clinical application, even if the improved survival findings with asfotase alfa are associated with a high degree of uncertainty.

It remains unclear why the pharmaceutical company has not submitted the most recent data cut-off (from November 2014) for the overall survival results, instead of the analyses presented from the 20 November 2013 data cut-off.

Overall, the different mortality rates in the studies ENB-002-08/ENB-003-08 and ENB-010-10 and the historical control (10.8% vs 72.9%) allow an additional benefit to be derived for asfotase alfa. In view of the previously mentioned uncertainties associated with the historical control, the additional benefit cannot be quantitatively assessed on the basis of the results.

Morbidity

Survival without invasive ventilation (IVFS) and ventilation-free survival

The pharmaceutical company operationalises "survival without invasive ventilation (IVFS)" as the time span between the time of inclusion into the study and the initiation of invasive ventilation (with endotracheal intubation or tracheostomy) or death from any cause. In contrast, for the historical control (ENB-011-10), this endpoint was defined as the time between birth and commencement of this event. To perform a comparative survival analysis with the historical control group, the operationalisation of the historical control (time from birth to event) was applied.

The analysis was based on patients from the intervention studies (pooled analysis of studies ENB-002/ENB-003 and ENB-010-10) who at baseline did not depend on respiratory support and patients from the historical control group (ENB-011-10). A total of 25 patients in the asfotase alfa group and 48 patients in the historical control group were included in the comparison. Data on IVFS from the pooled survival analysis for patients from the intervention studies (ENB-002-08/ENB-003-08 and ENB-010-10) were from the data cut-off of 20 November 2013.

An event was observed in 4 of 25 patients (16.0%) in the treated patient group compared to 36 of 48 patients (75.0%) in the historical control group ($p<0.0001$). This endpoint is a combined endpoint from differing endpoint categories (mortality and morbidity). In the historical control (n=48), 17 deaths occurred prior to mechanical ventilation and 19 events occurred concomitantly with mechanical ventilation. In the intervention studies (pooled analysis of studies ENB-002/ENB-003 and ENB-010-10) (n=25), 1 death occurred prior to mechanical ventilation and 3 events genuinely involved mechanical ventilation.

The endpoint “survival without invasive ventilation (IVFS) and ventilation-free survival” is patient-relevant. Invasive ventilation is considered a serious symptom in this indication.

The differences in the proportion of patients with events in the treatment groups (16% vs. 75%) suggest an additional benefit for asfotase alfa. As the IVFS endpoint is a combined endpoint (mortality and morbidity), the limitations associated with the historical comparison of overall survival should also be borne in mind. For this reason, and also owing to the aforementioned additional uncertainties associated with the historical control, it is, nevertheless, not possible to quantitatively derive the extent of the additional benefit with the results obtained.

Motoric function, locomotion, mobility

Motoric function, locomotion and mobility were assessed using the instruments BSID-III[4], PDMS-2[5] and BOT-2[6]. These instruments are limited to certain age groups, and, therefore, could not be used in their entirety throughout the study.

BSID-III is a generic instrument to determine the developmental level of children aged 1 to 42 months. Individual scales from BSID-III were used to determine changes in gross motor skills, fine motor skills and cognitive development. In the ENB-10-10 study, baseline values were obtained for 38 patients, but by week 144 this was reduced to 3 patients. A graphical representation of the age-equivalent patient scores was presented for the ENB-002-08/ENB-003-08 study.

PDMS-2 was employed to determine motor skills (both gross motor skills – such as reflexes, balance, and movement – and fine motor skills). Generally, PDMS-2 was used between 43 and 71 months of age, replacing BSID-III. This tool was employed in both ENB-10-10 and ENB-002-08/ENB-003-08, but in very few patients, and consequently was of little value due to the small number of cases.

BOT-2 assesses gross and fine motor skills (fine motor control, hand coordination, body co-ordination) of children and adolescents aged 4 to 21 years. For study ENB-10-10 a graphical representation of the age-equivalent patient values was presented. Baseline values were obtained for 38 patients, but by week 144 this was reduced to 3 patients. For the ENB-002-08/ENB-003-08 study, data are only available for 5 patients, which were not aggregated and cover different observational periods.

Improvements in motor function are considered to be patient-relevant, however, this study was designed as an open uncontrolled study, involving a before-and-after comparison. Although all the data presented depict improvements in scores, no valid conclusions on additional benefit can be derived from the results. The relevance of the changes is unclear for all the instruments employed, as no information is presented on the clinically relevant difference in HPP patients.

Anthropometric parameters

Anthropometric parameters can be considered to be patient-relevant morbidity parameters, especially in children with characteristic disease-related growth disorders. Data adjusted for age and gender are preferentially drawn on over absolute values. The z-scores obtained are based on a sample of healthy children from the USA. No consideration was made for country-specific z-scores. Specific growth charts for children with hypophosphatasia are not available.

Both in study ENB-010-10 and in study ENB-002-08/ENB-003-08 mean height and weight z-scores rose over the course of the study. In ENB-010-10, the height and weight z-scores scores increased from baseline to week 168 by a mean of 0.24 and 0.26 (baseline -3.11 and -3.17, respectively), while in ENB-002-08/ENB-003-08, the height and weight z-scores increased by week 288 by a mean of 0.69 (baseline -4.14) and 2.46 (baseline -3.40), respectively.

Due to the limited reliability of before and after comparisons, especially in combination with an open uncontrolled study design, the extent of the additional benefit for this endpoint is non-quantifiable.

Bone mineralisation

In the ENB-002-08/ENB-003-08 and ENB-10-10 studies, RGI-C and RSS scores[7] were employed as primary endpoints for measuring bone mineralisation.

[4] Bayley Scales of Infant and Toddler Development, Third Edition
[5] Peabody Developmental Motor Scales-2
[6] Bruininks-Oseretsky Test of Motor Proficiency – Second Edition

The RGI-C rating scale evaluates changes in HPP-associated rickets over time by means of X-ray imaging on a scale from -3 to +3. A score of -3 indicates severe worsening of HPP-associated rickets, while +3 indicates almost complete or complete recovery of HPP-associated rickets compared to baseline.
RSS was used to evaluate the severity of rickets on an absolute scale of 0–10 using X-ray images of the wrists and knees. A total RSS score of 10 indicates severe rickets, while a score of 0 indicates no rickets.

The evidence provided by the pharmaceutical company is not adequate to demonstrate a clear correlation or validation of the surrogate endpoints (bone mineralisation) with/for the patient-relevant endpoints (such as pain, respiratory function, mobility, walking ability, mortality). Given this, RGI-C and RSS scores are considered to be purely radiologic endpoints and not patient-relevant. However, this has no influence on the overall assessment of the extent of the additional benefit, since, in addition to the recording of bone mineralisation endpoint data, patient-relevant endpoints were also directly collected.

Quality of life

Health-related quality of life was not investigated in the studies. Additional benefit for asfotase alfa cannot therefore be derived for this endpoint.

Side effects

Adverse events / serious adverse events / therapy discontinuation due to adverse events / adverse events of special interest

All patients enrolled in ENB-002-08/ENB-003-08 and ENB-010-10 (N=70) were included in the assessment of the aforementioned endpoints. All patients in the studies had at least one adverse event during treatment with asfotase alfa. Approximately 63% of the patients experienced a serious adverse event. 8.6% of patients were forced to discontinue treatment due to an adverse event. One of the most frequent events was a reaction at the injection site (58.6%). AEs considered to be of particular interest by the EMA include lipohypertrophy, craniosynostosis and ectopic calcifications (calcifications of the eyes (conjunctiva and cornea) and nephrocalcinosis).

Due to the lack of control data and the small patient population, the available side-effect findings are of limited significance. Overall, the side effects are classified as patient-significant. However, no valid conclusions can be drawn on the extent of the additional benefit relating to the discussed AEs of special interest, given the available data basis, given (in particular) the limited safety data and given the described limitations of the study. In its evaluation report, the EMA also addresses the lack of data on long-term safety and has called for further reviews of corresponding data on the safety of treatment with asfotase alfa.

No conclusions can be drawn from the side-effect data on the extent of the additional benefit.

Summary:

In the present scenario and indication, the findings on all-cause mortality and survival without invasive ventilation/ventilation-free survival, demonstrating an additional benefit for asfotase alfa, are particularly relevant for decision-making. Assuming that the natural course of hypo-

[7] RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Scale

phosphatasia is associated with a high mortality rate and severe symptoms, and also due to the lack of adequate treatment options, it is considered appropriate, despite the uncertainties associated with a historical comparison and single-arm studies, to draw on the study findings on all-cause mortality and survival without invasive ventilation/ventilation-free survival to determine the additional benefit. In assessing these results, it is important to consider the high risk of bias inherent with the use of the historical comparison and the open study design and, with it, the lack of blinding of patients and treated persons. Due to the methodological limitations of the study and the historical comparison and the overall limited evidence base, the G-BA, taking into account the severity of the disease and the therpeutic aim of treatment, classifies, on the basis of the criteria in Article 5 paragraph 7 AM-NutzenV, the extent of the additional benefit of asfotase alfa as non-quantifiable. Thus, on the basis of the data submitted, it is not possible to quantitatively assess the extent of the effect or the additional benefit into one of the three categories “low”, “considerable”, or “substantial”. An additional benefit exists but is non-quantifiable because the scientific data basis does not permit this.

b) Patients > 5 years of age

Patients 5 – 12 years of age

The evaluation of the extent of the additional benefit of asfotase alfa for the population of children and adolescents with HPP at age ≥5 and ≤12 years is based on the study ENB-006-09/ENB-008-10.

Study ENB-006-09 was an open, randomised dose-regimen study (6 mg/kg/week vs. 9 mg/kg/week) involving 13 patients. ENB-008-10, an open single-arm study, is the follow-up study to ENB-006-09 and included 12 patients who had completed ENB-006-09. In 5 patients hypophosphatasia onset occurred before 6 months, in 8 patients after 6 months. The median age of patients at inclusion into the study was 8.8 years; of these, 2 patients, however, were 12 years old and 11 patients were under 12 years old.

ENB-006-09 lasted 24 weeks, while ENB-008-10 was planned to last up to 42 months (according to the study report) or up to 72 months (according to the dossier). The recommended dosage of asfotase alfa stipulated in the product information is 6 mg/kg per week. This dosage was administered in only one of the two interventions in the first 24 weeks. During the extension phase (ENB-008-10), all patients (N=12) initially received 3 mg/kg per week. The fourth protocol amendment increased the dose to 6 mg/kg per week. In the presentation of the results in the resolution, no distinction is made on the basis of dosage, and the results of both study arms are presented collectively.

The retrospective observational study ALX-HPP-502 (N=32) investigated the natural course of juvenile HPP. This study served as a historical control for the ENB-006 studies for the endpoints growth and improvement of HPP-associated rickets (as measured by RGI-C). All 32 patients enrolled in this study had juvenile HPP, defined as the first onset of HPP symptoms at an age of ≥ 6 months to < 18 years. The mean age at first onset of HPP was 17.5 months. The median age at the time of data extraction was 18.85 years (7.7–31.6 years).

Details of the endpoint findings can be found below:

Mortality:

The mortality endpoint was not explicitly reported in the ENB-006-09/ENB-008-10 study, so it is impossible to deduce the extent of additional benefit with regards to mortality.

Morbidity:

Bone mineralisation

ENB-006-09/ENB-008-10 recorded bone-mineralization based on RGI-C score as a primary endpoint. Please note the aforementioned comments regarding the relevance of the endpoint in the < 5 years old age group. In addition, studies carried out on the validity of RGI-C only relate to patients under 13 years of age. In the presented patient group, some patients were already over 13 years of age at the conclusion of the study, so it is possible that the investigations performed on some of these patients may be invalid.

A relationship between RGI-C and patient-relevant endpoints has not been satisfactorily demonstrated (e.g. no validation with external study data, no correlation at effect level). In the group of patients > 13 years old, no investigations on validity whatsoever have been presented. Thus, no conclusions can be drawn on the validity of RGI-C as a surrogate for morbidity.

Motoric function (6-minute walking tests)

Improvement in walking ability was assessed by means of a 6 minute walking test. The 6-minute walking test determined how far patients could walk down a corridor in six minutes assisted by any type of walking aid and variable (including wheelchairs, walkers, etc.). However, no data is available on how many patients actually required a walking aid, the nature of the walking distances covered or whether the same conditions existed for the patients. The distance covered within the 6 minutes was recorded in metres and, as an additional parameter, the percentage of the expected value compared to healthy children (taking into account sex, age and height of patients). Compared to baseline, the combined AA group (N=13) showed a median significant improvement in walking distance of 124.00 metres ($p<0.0001$) at week 24 and 221.00 metres ($p<0.0001$) at week 240. Starting at 60.98% of the expected distance for healthy children, the median increased by 17.66% at week 24 and by 25.85% at week 240.

No information is available on the validity within the HPP population, nor with regards to the minimum clinically relevant difference (taking into account the different age groups). It is, therefore, unclear whether the changes seen in 6MWT are relevant, and, thus, 6MWT as an endpoint cannot be used to quantify patient-relevant additional benefit.

Motoric function (BOT-2[6])

At the commencement of the ENB-006 study, the standardised median running speed and agility score was 3.00 points (N=13), which had significantly improved by 8.00 points over baseline by week 240 ($p<0.0001$). The standardised median strength score was 4.00 points, which had significantly improved by 9.00 points over baseline by week 240 ($p<0.0001$). No information is available on the minimum clinically relevant difference in the HPP population.

Pain/disability (POSNA PODCI[8])

POSNA PODCI is an instrument for assessing general health, pain and the ability to perform everyday and energetic activities and was developed for children and adolescents aged 2 to 18 with bone and muscle disorders. The standardised scores range from 0 to 100, with lower scores indicating greater impairment.

PODCI was recorded throughout the study to evaluate the functional status of patients. At the time of first data collection, the standardised median score for asfotase alfa patients (N=13) was 27.0 which had significantly improved by 22.5 points over baseline by week 240.

In children of ≤ 10 years, parents completed the parental version of the POSNA-PODCI questionnaire. Children who were 11 years old at the start of the study independently completed the questionnaire version for adolescents.

According to the study report, the analysis of the findings is based on the data from the parent questionnaire.

Impairment in daily life and pain are assessed as patient-relevant endpoints. However, no information is available on the validity of POSNA PODCI in children with HPP. The clinical relevance threshold in this population is also unknown. In addition, interpretation of the parent and child questionnaires would have required consideration of different validity data.

In particular, due to the small number of subjects, the lack of a control group and the lack of figures to assess clinical relevance, no conclusion can be drawn on the extent of the additional benefit for this endpoint.

Anthropometric parameters

At the beginning of the study, the median z-score in the combined asfotase alfa group was -1.26 for height and -1.21 for weight. A significant improvement in median z-score for height of 0.65 (p=0.0017) was observed in week 240 compared to baseline. By week 240, median z-score for weight was significantly improved (p=0.0003) at +1.23 compared to baseline.

The findings compared to baseline cannot be considered as meaningful. In patients who survive the first few years of the disease, there is often at the onset of adolescence a spontaneous improvement in symptoms and the course of the disease. Data collected in this age group cannot distinguish between potential therapeutic effect and natural progression. Therefore, it is not meaningful to compare the data with those at the beginning of treatment five years previously.

The baseline comparisons carried out do not permit quantification of the additional benefit. In addition to biasing factors, such as low population study size, incomplete validation of the instruments employed, the open study design, an occasionally non-compliant dosage, and the use of concomitant medication, it can be assumed that the baseline comparisons are potentially highly biased due to the possibility of a natural regression of HPP symptoms in the age group studied.

There are no statistically significant differences between the data and the historical control. In comparing the historical control data with the ENB-006-09/ENB-008-10 data, it should be borne in mind that these data are subject to a very high risk of bias. Compared to the perina-

[8] Pediatric Orthopedic Society of North America's Pediatric Outcomes Data Collection Instrument

tal/infantile form, the juvenile HPP patient population is more heterogeneous in terms of clinical symptoms. This is the result of the definition of HPP onset employed – between ≥ 6 months and < 18 years – and, with it, the varying severity of the disease in the patients. In addition, the EBN-006/EBN-008 intervention study included approximately 60% of patients with juvenile HPP and 30% with infantile HPP, while the ALX-HPP-502 historical control study included only patients with juvenile HPP. It must therefore be assumed that there are imbalances in the baseline characteristics, including unmeasured variables, which pose a high confounding risk.

As a result, analyses comparing these findings with the historical control are not drawn on to derive an additional benefit.

Health-related quality of life

No data on health-related quality of life are available for the ENB-006-09/ENB-008-10 study, so no conclusion can be drawn on the extent of the additional benefit for health-related quality of life.

Side effects

In the EPAR, the positive effects of asfotase alfa are contrasted with the discussed AEs of special interest (reactions at the injection site, lipohypertrophy, craniosynostosis, ectopic calcification). Of the 13 study participants, 12 (92.3%) had reactions at the injection site, 8 (61.5%) had lipohypertrophy, 7 (53.8%) had craniosynostosis and 6 (46.2%) had ectopic calcification.

No serious adverse events and no discontinuations of the study medication due to adverse events were recorded.

Due to the lack of control data and the small patient population, the available side-effect findings are of limited significance. Overall, the side effects are classified as patient-significant. However, no valid conclusions can be drawn on the extent of the additional benefit relating to the discussed AEs of special interest, given the available data basis, given (in particular) the limited safety data and given the described limitations of the study. In its evaluation report, the EMA also addresses the lack of data on long-term safety and has called for further reviews of corresponding data on the safety of treatment with asfotase alfa.

<u>Patients > 12 years of age</u>

Patients over 12 years of age were assessed in the study ENB-009-10. ENB-009-10 was a randomized controlled open-label study in the first 24 weeks with a follow-up single-arm study design. In the study, patients (N=19) were randomised into three different study arms: 1 x daily s.c. Dose of 0.3 mg/kg (2.1 mg/kg/week) asfotase alfa (N=7), 1x daily s.c. Dose of 0.5 mg/kg (3.5 mg/kg/week) asfotase alfa (N=6) or no treatment (untreated control group) (N=6). The study's patients suffered from infantile, juvenile or adult HPP and were aged between 13 and 66 years when enrolled.

With regard to the approval population, it should be noted that in 2 out of 19 patients HPP did not occur until adulthood, while in one patient no data were available on age of onset. In the remaining patients onset was either juvenile (N=12) or infantile (N=4). At the end of the 24-week control phase, patients in the control group were also treated with AA, thus the study was uncontrolled after week 24. In the open-label extension phase, all patients were treated daily with 0.5 mg/kg (3.5 mg/kg/week) for approximately 24 additional weeks. Subsequently (week 48) the dose was increased to 6 mg/kg/week. The study has not yet been completed, and all patients are currently in the 96th week of treatment.

Details of the endpoint findings can be found below:

Mortality:

Mortality as an endpoint was not explicitly recorded in the ENB-009-10 study.

Morbidity

Motoric function (6-minute walking tests)

After 24 weeks of treatment with asfotase alfa, in 12 out of 13 subjects there was an improvement in the 6-minute walking distance of 8.8 percent of the of the distance expected in healthy children, whereas in the untreated control group 3 out of 6 patients were unable to walk for 6 minutes due to physical impairment. The 3 patients in the untreated control group who were able to complete the 6-minute walking distance improved by 1.6 percent of the distance expected in healthy children. The baseline mean values and medians in the control group were significantly lower than in the combined AA group and the individual intervention groups. In a comparison between the AA group and the individual intervention groups, no statistically significant difference was observed at week 24.

Motoric function (BOT-2[6])

At the commencement of data collection, the total median running speed and agility score for the combined AA group (N=13) was 6.0 points, which by week 24 had improved by 4.0 points compared to baseline ($p<0.0001$) and by week 192 by 3.5 points. The total median strength score for the combined AA group was 12.0 points, which by week 24 had improved by 3.0 points compared to baseline ($p<0.0001$) and by week 240 by 1.0 points ($p<0.0001$). In both sub-tests, the individual dosage groups of 2.1 mg/kg/week and 3.5 mg/kg/week showed an improvement compared to weeks 24 and 192 in comparison to baseline. In a comparison between the combined AA group and the untreated control group, no statistically significant difference was observed at week 24.

Motoric function (LEFS[9])

LEFS is an instrument for self-assessment of functional restrictions in the lower extremities based on 20 questions on everyday activities (e.g. getting out of the bathtub, picking up an object, climbing 10 steps, running on uneven ground).

After 24 and 192 weeks of treatment with AA, the combined AA group (N=13) showed in each case a median improvement of 5.0 points compared to baseline. The untreated control group (N=6) had improved by 2 points compared to baseline at week 24 (no AA treatment) and by 8.0 points at week 48 (AA treatment). In a comparison between the combined AA group and the untreated control group, no statistically significant difference was observed at week 24.

[9] Lower Extremity Functional Scale

Pain

BPI-SF [10]

BPI-SF is a questionnaire for self-assessment of pain experienced within the preceding 24 hours. The questionnaire includes items on pain intensity (4 items, sensory dimension), impairment of daily activities due to pain (7 items, reactive dimension) and pain relief, pain quality and assessment of the cause of pain.

On a scale of 0 (no pain) to 10 (strongest pain) it prompts patients to record the intensity (sensory dimension) of the "strongest", "marginal", "average" and "momentary pain" they experience. Scores are recorded for each of the items. In the reactive dimension, an average score is reported. A lower value is associated with less pain.

After 24 weeks, both the combined AA group (N=13) and the individual dosage groups (2.1 mg/kg/week [N=7] and 3.5 mg/kg/week [N=6)) reported a reduction in the pain score compared to baseline. Thus the median pain score in the combined AA group decreased by 2 points at week 24 and by 4 points at week 192. The untreated control group (N=6) had improved by 4 points compared to baseline at week 24 (no AA treatment) and by 0.4 points at week 48 (AA treatment). In a comparison between the combined AA group and the untreated control group, no statistically significant difference was observed at week 24.

Growth

The growth endpoint was only collected for adolescent patients. This included 3 patients in the AA group and 3 patients in the untreated control group. The growth parameters (height and weight) improved over time, but this should be interpreted critically due to the small number of cases. In a comparison between the combined AA group and the untreated control group, no statistically significant difference was observed at week 24.

In the morbidity endpoints, there were no significant differences in pain experienced (BPI-SF) and functional limitations in the lower extremities (LEFS) after 24 weeks of asfotase alfa treatment compared to the untreated control group. Patients described an improvement in these endpoints compared to baseline during long-term therapy.

No conclusions, however, can be drawn on the extent of the additional benefit.

Health-related quality of life

No data on health-related quality of life are available for the ENB-009-10 study, so no conclusion can be drawn on the extent of the additional benefit for health-related quality of life.

Side effects

In the EPAR, the positive effects of asfotase alfa are contrasted with the discussed AEs of special interest (reactions at the injection site, lipohypertrophy, craniosynostosis, ectopic calcification). Of the 19 study participants, 18 (94.7%) had reactions at the injection site, 4 (21.1%) had lipohypertrophy and 9 (47.4%) had ectopic calcification. No craniosynostosis was observed.

No discontinuations of the study medication due to adverse events were recorded.

[10] Brief Pain Inventory Short Form

Serious adverse events occurred in 7 (36.8%) of the 19 study participants, with two of these SAEs already occurring in the untreated control group of the study prior to 24 weeks.

Due to the lack of control data and the small patient population, the available side-effect findings are of limited significance. Overall, the side effects are classified as patient-significant. However, no valid conclusions can be drawn on the extent of the additional benefit relating to the discussed AEs of special interest, given the available data basis, given (in particular) the limited safety data and given the described limitations of the study. In its evaluation report, the EMA also addresses the lack of data on long-term safety and has called for further reviews of corresponding data on the safety of treatment with asfotase alfa.

Summary:

In the age group > 5 years, the findings of the studies for patients of 12–66 years (study ENB-009-10) and patients 5–12 years (study ENB-006-09/ENB-008-10) can be considered relevant for decision-making. There is a very high degree of uncertainty regarding the efficacy in juvenile HPP. Although the data in the age group 5–12 years does indicate a benefit for asfotase alfa in the growth and improvement of motor function endpoints, the findings are of only limited value due to a lack of control and uncertainties regarding the clinical relevance of the changes to baseline.

In the 13–66 years patient age group, none of the patient-relevant endpoints (motor function, pain, and disability) were statistically changed compared to the untreated control after 24 weeks of treatment with asfotase alfa. The other study data also do not permit any quantitative conclusions to be drawn on the extent of the additional benefit, partly due to the lack of control data.

A (controlled) observation period of 24 weeks is considered too short to demonstrate the effects of AA, for instance an improvement in function through improved bone structure.

Due to the methodological limitations of the studies and the overall limited evidence base, the G-BA, taking into account the severity of the disease and the therapeutic aim of the treatment of the disease, classifies, on the basis of the criteria in Article 5 paragraph 7 AM-NutzenV, the extent of the additional benefit of asfotase alfa as non-quantifiable, on the grounds that the scientific data do not support such a benefit. Thus, on the basis of the data submitted, it is not possible to quantitatively assess the extent of the effect or the additional benefit into one of the three categories “low”, “considerable”, or “substantial”.

Limitation:

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. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In this case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V. On the one hand, these are the consequence of the requirements placed on the marketing authorisation of asfotase alfa (see 1.).
On the other hand, the G-BA considers that, due to 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 (see 2).

1. Compliance with the requirements of the marketing authorisation

The medicinal product Strensiq®, containing the active ingredient asfotase alfa, was authorised by the competent authorisation authority, the European Medicines Agency (EMA), under "exceptional circumstances" in accordance with Section 14 paragraph 8 of Regulation (EC) No. 726/2004 in conjunction with Section 22 of Directive 2001/83/EC.

These circumstances allow, in exceptional cases and after consultation with the applicant, for marketing authorisation to be granted under certain conditions, in particular those relating to the safety of the medicinal product, to the information held by the competent authorities of any incident relating to usage, and to the measures that need to be taken. The marketing authorisation may be granted only if the applicant can demonstrate that, for objective and verifiable reasons, they can provide no comprehensive data on the efficacy and safety of the medicinal product, used as intended, while, in addition, such authorisation must be based on one of the grounds listed in Annex I to Directive 2001/83/EC. The continued validity of the marketing authorisation shall be subject to annual reassessment of these conditions.

For this reason, the EMA has linked the marketing authorisation of asfotase alfa to the condition that the pharmaceutical company is to submit further comprehensive clinical data on the efficacy and safety of the medicinal product asfotase alfa (Strensiq®) to the approval authority for evaluation. This includes the establishment of a prospective register (see the EPAR on Strensiq®, page 91) to, among other things, collect data on long-term efficacy, safety and quality of life.

These measures, however, merely serve to ensure that data be generated to enable an assessment of whether the medicinal product, after its marketing authorisation, continues to meet the minimum requirements for prescribability under statutory health insurance regarding quality, efficacy and safety, as stipulated in Section 2 paragraph 1 sentence 3 and Section 12 paragraph 1 SGB V. However, the assessment of the benefit of asfotase alfa as defined in Section 35a paragraph 1 SGB V, which aims to determine the basis for an appropriate and cost-effective supply of those insured with this medicinal product, requires further action.

2. The need for further action to obtain scientific evidence

Resolutions on the assessment of the extent of the additional benefit of a medicinal product for the treatment of a rare disease are based on Chapter 5, Section 12, No. 1 of the Rules of Procedure (VerfO) and are a statement on whether the use of the medicinal product is appropriate within the meaning of Section 12 SGB V. The criterion for assessing the appropriateness of a medical intervention is the generally recognised state of medical knowledge as defined in Section 2 paragraph 1 sentence 3 SGB V. Taking into account the case-law of the German Federal Social Court on the care standard defined in Section 2 paragraph 1 sentence 3 SGB V, this generally presupposes that reliable, scientifically verifiable statements

can be made on the extent of the additional benefit on the basis of clinical studies conducted in a scientifically sound manner (see the judgement of 1 March 2012 B 1 KR 7/10 R, Rn65 on the generally recognised state of medical knowledge pursuant to Section 2 paragraph 1 sentence 3 SGB V BSG).

The distinctive features of rare diseases do not, in principle, justify lowering the evidence standards stipulated in Section 2 paragraph 3 SGB V for the evaluation of orphan drugs.

However, the therapeutic scenario underlying the use, as authorised, of the medicinal product is characterised by special circumstances, which, as an exception, can be interpreted as justifying a decision not to require the conduct and submission of a further, randomised, controlled clinical trial to assess the extent of the additional benefit of the medicinal product. These circumstances are due, in particular, to the fact that no treatment alternatives to long-term enzyme replacement therapy are currently available for the patient population covered by the therapeutic indication, including patients that are particularly vulnerable (infants and children).

Against this background, the G-BA considers it justified to resolve that further scientific evidence is required for a sufficiently reliable assessment of the extent of the additional benefit of asfotase alfa with regard to patient-relevant endpoints (mortality, morbidity, quality of life and side effects), but also that the pharmaceutical company should arrange for a clinical registry to be established in which additional data for patients treated with asfotase alfa in Germany are recorded, over and above the requirements of the EMA. The aim of this registry would be to record representative data on patient-relevant endpoints specific to the German health care system that would not otherwise be fully and sufficiently represented in the EMA's register. Collection of such data also serves the purpose of benefit assessments as per Section 35a paragraph 1 SGB V, namely to create a basis for the assessment of requirements for quality-assured application of the medicinal product and, thus, to ensure the medicinal product is prescribed in a cost-effective manner.

At the end of the limitation period, data must be submitted to the G-BA from this registry as well as from the extension studies ENB-008-10 and ENB-009-10 and from the phase 2a study, which allow a more reliable assessment of the extent of the additional benefit with regard to patient-relevant endpoints (mortality, morbidity, quality of life and side effects) of a long-term therapy with asfotase alfa. These data must also redress the uncertainties described in 2.1 above regarding the assessment of the extent of the additional benefit. Ideally, all patients receiving asfotase alfa treatment in Germany should be included in the register.

An extension of the deadline until 1 December 2018 is considered appropriate for this purpose.

The pharmaceutical company may request clarification on the G-BA's specific demands on the data to be submitted by the deadline and on the establishment of the register as per Chapter 5, Section 7 of the G-BA Rules of Procedure (VerfO).

In accordance with Section 3, number 5 AM-NutzenV and in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of asfotase alfa shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier on the medicinal product asfotase alfa (Strensiq®) to the G-BA, at the latest on the day of expiry of the deadline (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5, Section 8, number 5 VerfO).

The possibility that a benefit assessment of asfotase alfa can be carried out at an earlier point in time for other reasons remains unaffected by this.

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

The target population of approximately 1,000 patients includes all patients with hypophosphatasia onset in childhood and adolescence, regardless of age.

The information on the number of patients is based on the target population in statutory health insurance (SHI). The G-BA bases the resolution on the patient numbers stated in the pharmaceutical company's dossier, which were rounded off due to the inaccuracy of the estimate. Because of the uncertainty in the data basis, a more precise indication is not possible.

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: 4 February 2016):

https://www.ema.europa.eu/en/documents/product-information/strensiq-epar-product-information_en.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 has been authorised under "exceptional circumstances". This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The EMA will review any new information that may become available and update the summary of product characteristics.

As an additional measure to minimise risk, mandatory training material must be made available to patients and caregivers[11] 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 insert, instructions for self-injection for patients, instructions for injection for parents or caregivers with children who are patients.

The studies on asfotase alfa only included patients up to 65 years of age. Overall, the data available on adult patients is very limited. Further data on dosing in adults therefore needs to be collected by the regulatory authorities.

Furthermore, no patients younger than 5 years with juvenile onset hypophosphatasia were examined (onset of disease ≥ 6 months).

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: 1 February 2016).

[11] See EMA: Summary of product characteristics: conditions or restrictions for the safe and effective use of the medicinal product,

Costs of the medicinal product:

Figures on consumption have been calculated as the mean annual usage of vials.

The weekly injections recommended in the product information were used as a basis for the calculation.

On the representation of the costs

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates according to Section 130a SGB V and Section 130, paragraph 1 SGB V. To calculate the costs of the medicinal products, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs by quantity, the pharmaceutical costs were then calculated on the basis of the costs per pack after deduction of the statutory rebates. The calculation involved specifying an upper and a lower expense range for treatment.

Treatment duration:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year, even if the actual treatment duration is patient-individual and/or is shorter on average.

The costs are calculated according to the dosing scheme recommended by the product information: 2 mg/kg body weight for 3 x weekly subcutaneous injections or 1 mg/kg body weight for 6 x weekly subcutaneous injections.

Designation of the therapy	Treatment mode	Treatment days per patient per year[12]
Asfotase alfa	3 x per week 6 x per week	156 312

Usage and consumption:

For dosages depending on body weight or body surface, the mean body measurements from the official representative statistics “Microcensus 2013 – mean body measurements of the population” were used as a basis. (mean body weight: 76.3 kg for patients over 18 years).

In patients under 18 years of age, body weights vary greatly, so that no average value can be derived for the individual age groups from the official German representative statistics. To calculate consumption based on the cheapest therapeutic alternative, a body weight of ≤ 9 kg in a dosing scheme of 3 x weekly 2 mg/kg body weight is assumed.

[12] Calculated and standardised for one year.

Designation of the therapy	Potency	Dosage[13]	Quantity per package (vials)	Mean annual consumption (vials)
Asfotase alfa BW = 76.3 kg	80 mg	3/week 152.6 mg 6/week 76.3 mg	12 × 0.8 ml	312 x 0.8 ml (100 mg/ml; 80 mg)
Asfotase alfa BW ≤ 9 kg	18 mg	3/week 18 mg	12 × 0.45 ml	156 x 0.45 ml (40 mg/ml; 18 mg)

Costs:

Costs of the medicinal product:

Designation of the therapy	Costs (pharmacy sales price)	Costs after deduction of statutory rebates
Asfotase alfa 80 mg	€ 98,850.57	€ 93,204.00 [€ 1.77[14]; € 5,644.80[15]]
Asfotase alfa 40 mg	€ 49,430.35	€ 46,606.18 [€ 1.77[14]; € 2,822.40[15]]
Asfotase alfa 28 mg	€ 34,604.28	€ 32,626.83 [€ 1.77[14]; € 1,975.68[15]]
Asfotase alfa 18 mg	€ 22,249.23	€ 20,977.38 [€ 1.77[14]; €1,270.08[15]]

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 February 2016

Costs for additionally required SHI services:

No costs for additionally required SHI services must be considered.

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 any further medicinal products authorised for the therapeutic indication in accordance with the product or package information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Only costs directly related to the use of the medicinal product are taken into account. Medical treatment costs, hospital costs incurred for application of the medicinal product (e.g. infusion vials, infusion equipment), for monitoring the success of the treatment or the course of the disease, costs incurred for routine investigations (e.g. standard laboratory services, such as blood counts, that do not exceed standard expenditure over the course of treatment), and medical fee-based services are not shown.

[13] 2 mg/kg body weight 3 x weekly or 1 mg/kg body weight 6 x weekly s.c. injection
[14] Rebate according to Section 130 SGB V
[15] Rebate according to Section 130 a SGB V

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

In a letter dated 16 June 2015, received on 17 June 2015, the pharmaceutical company requested consultation in accordance with Section 8 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV). The consultation meeting took place on 12 August 2015.

The pharmaceutical company submitted a dossier on 7 September 2015. The administrative office of the G-BA performed a formal preliminary assessment of the completeness of the dossier in accordance with Chapter 5, Section 11, paragraph 2 VerfO. The final dossier was submitted on 30 September 2015. The relevant date for the first placing on the market of the active ingredient asfotase alfa in accordance with Chapter 5, Section 8, number 1, sentence 2 VerfO is 1 October 2015.

The benefit assessment of the G-BA was published on 4 January 2016 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 written statements was 25 January 2016.

The oral hearing was held on 9 February 2016.

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 8 March 2016, and the proposed resolution was approved.

At its session on 17 March 2016, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Working group Section 35a	4 August 2015	Consultation on questions arising from the advisory requirement according to Section 8 AM-NutzenV
Subcommittee Medicinal Products	11 August 2015	Consultation and consensus of the answers to the advisory requirement
Subcommittee Medicinal Prod-	8 December 2015	Information on the results of the completeness check of the dossier

ucts		
Subcommittee Medicinal Products	22 December 2015	Knowledge of the benefit assessment of the G-BA
Working group Section 35a	2 February 2016	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	9 February 2016	Conduct of the oral hearing
Working group Section 35a	16 February 2016 1 March 2016	Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal Products	8 March 2016	Advice and consensus on the draft resolution
Plenum	17 March 2016	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 17 March 2016

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

Prof Hecken