Gemeinsamer Bundesausschuss

Asfotase alfa (Reassessment of an Orphan Drug after the € 50 Million Turnover Limit Was Exceeded: Hypophosphatasia)

Resolution of: 2 April 2020 valid until: unlimited
Entry into force on: 2 April 2020
Federal Gazette, BAnz AT 14 05 2020 B2

Therapeutic indication (according to the product information of 25 July 2019):

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

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

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.

Extent and probability of the additional benefit of asfotase alfa compared with best supportive care:

Hint for a non-quantifiable additional benefit

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.

Extent and probability of the additional benefit of asfotase alfa compared with best supportive care:

Additional benefit not proven

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.

Extent and probability of the additional benefit of asfotase alfa compared with best supportive care:

Additional benefit not proven

Study results according to endpoints:[1]

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

Pooled analysis of two single-arm studies under treatment with asfotase alfa (ENB 002 08/ENB 003 08 + ENB-010-10) compared with a historical control with BSC (ENB-011-10)

Endpoint category Endpoint	Asfotase alfa		BSC		Asfotase alfa vs BSC
	N	Patients with event n (%) Median time to event in days [95% CI]; [min; max][a]	N	Patients with event n (%) Median time to event in days [95% CI]; [min; max][a]	HR [95% CI]; p value[b]
Mortality					
Overall survival (primary analysis of the pharmaceutical company)[c]					
	78	9 (11.5) n.a.; [73; 3955]	48	35 (72.9) 271 [155; 428]; [1; 7211]	–[d]; < 0.001
Morbidity					
Respiratory function		–[e]		–[e]	–[e]
Quality of life					
		not collected		not collected	
Side effects					
AE, SAE, discontinuation because of AE		–[f]		not collected	–

[1] Data from the dossier evaluation of the IQWiG (A19-89) and the addendum (A20-19) unless otherwise indicated.

a. Measured from birth until the event or until censoring. Patients treated with asfotase alfa who had not died were censored at their last round. ENB-011-10: Patients who had not died (at the time of last data extraction: April 2013) or whose survival status was unknown (at the time of last contact) were censored.
b. p value: Log rank test.
c. For the comparative analyses (data of analysis: August 2018), the pharmaceutical company pools the results of the two asfotase alfa studies, Study ENB-002-08/ENB-003-08 (data cut-off: May 2017) and Study ENB-010-10 (data cut-off: April 2017) and considers only those patients who meet the enrolment criteria of Study ENB-011-10 (N = 78). In Study ENB-002-08/ENB-003-08 1 patient (9.1%) died; in Study ENB-010-10, 9 patients (13.0%) died. One deceased patient was therefore not included in the pooled analysis by the pharmaceutical company.
d. No presentation of effect estimate and CI because the corresponding HR from the Cox proportional hazards model cannot be interpreted meaningfully.
e. The comparative data presented by the pharmaceutical company cannot be used for the benefit assessment.
f. No analyses available to compare asfotase alfa with the comparator therapy.

HPP: hypophosphatasia; HR: hazard ratio; CI: confidence interval; n: patients with event; N: number of patients evaluated; n.a.: not achieved; RCT: randomised controlled trial

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑	Advantage in overall survival
Morbidity	n.a.	The data available are not assessable for the benefit assessment
Health-related quality of life	∅	No data available
Side effects	∅	There are no suitable data for the benefit assessment

Explanations:
↑: positive statistically significant and relevant effect with low/unclear reliability of data
↓: negative statistically significant and relevant effect with low/unclear reliability of data
↑↑: positive statistically significant and relevant effect with high reliability of data
↓↓: negative statistically significant and relevant effect with high reliability of data
↔: no statistically significant or relevant difference
∅ : There are no usable data for the benefit assessment
n.a.: not assessable

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

No data were submitted.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	∅	No data available
Morbidity	∅	No data available
Health-related quality of life	∅	No data available
Side effects	∅	No data available

Explanations:
↑: positive statistically significant and relevant effect with low/unclear reliability of data
↓: negative statistically significant and relevant effect with low/unclear reliability of data
↑↑: positive statistically significant and relevant effect with high reliability of data
↓↓: negative statistically significant and relevant effect with high reliability of data
↔: no statistically significant or relevant difference
∅ : There are no usable data for the benefit assessment
n.a.: not assessable

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

No suitable data were submitted for the benefit assessment.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	∅	There are no suitable data for the benefit assessment
Morbidity	∅	There are no suitable data for the benefit assessment
Health-related quality of life	∅	There are no suitable data for the benefit assessment
Side effects	∅	There are no suitable data for the benefit assessment

Explanations:
↑: positive statistically significant and relevant effect with low/unclear reliability of data
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↔: no statistically significant or relevant difference
∅ : There are no usable data for the benefit assessment
n.a.: not assessable

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

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

and

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

approx. 17 patients

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

approx. 1057 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for 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.

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Asfotase alfa	€ 176,779.96 – 569,490.19
Best supportive care	different for each individual patient
Appropriate comparator therapy:	
Best supportive care	different for each individual patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 March 2020

Costs for additionally required SHI services: not applicable

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

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Asfotase alfa	€ 176,779.96 – 569,490.19
Best supportive care	different for each individual patient
Appropriate comparator therapy:	
Best supportive care	different for each individual patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 March 2020

Costs for additionally required SHI services: not applicable

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

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Asfotase alfa	€ 550,035.96 – 1,571,123.57
Best supportive care	different for each individual patient
Appropriate comparator therapy:	
Best supportive care	different for each individual patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 March 2020

Costs for additionally required SHI services: not applicable