Resolution

Gemeinsamer Bundesausschuss

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

At its session on 17 March 2016, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on 18 February 2016 (Federal Gazette, BAnz AT 22/04/2016 B3), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient asfotase alfa as follows:

Asfotase alfa

Resolution of: 17 March 2016
Entry into force on: 17 March 2016
Federal Gazette, BAnz AT DD MM YYYY Bx

Approved therapeutic indication (according to the marketing authorisation of 28 August 2015):

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).[1]

1. Extent of the additional benefit of the medicinal product

Asfotase alfa is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 10 German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO). This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

a) Patients ≤ 5 years of age:

Extent of the additional benefit:

Non-quantifiable

b) Patients > 5 years of age:

Extent of the additional benefit:

Non-quantifiable

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

Study results according to endpoints[2]:

For a) age group 0 – ≤ 5 years with perinatal/infantile HPP

Mortality				
Overall survival[3;4]				
Group	**N***	**Patients with event n (%)**	**Median OS days [95% CI]**	**Intervention vs control Effect estimator [95% CI]; p value**
Historic control (ENB-011-10)	48	35 (72.9%)	270.5 days [155.00; 428.00]	*Unadjusted analysis:* [4] HR 10.9 [3.86; 30.81]; p<0.0001
AA (Pooled data from ENB-002-08/003-08 and ENB-10-10)	37	4 (10.8%)	n.c.	*Sensitivity analysis:* [5] HR 2.49 [0.48; 12.83]; p=0.2765
Morbidity				
Survival without invasive ventilation (IVFS)[6]				
Group	**N***	**n (%)**	**Time to onset of event[7] [95% CI]**	**Intervention vs control p value**
Historic control (ENB-011-10)	48	36 (75%)	236.0 days [78.00; 300.00]	<0.0001
AA (Pooled data from ENB-002-08/003-08 and ENB 010-10)	25	4 (16%)	n.c.	
Anthropometric data				
Endpoint category Endpoint	**AA ENB-002-08/ENB-003-08**		**AA ENB-010-10**	
	B/L **N MV (SD)**	***Change compared to B/L at w. 288*** **N MV (SD)**	***B/L*** **N MV (SD)**	***Change compared to B/L at w. 168*** **N MV (SD)**
Growth Height (z-score)	11 - 4.14	4 0.69 (1.55)	58 -3.11 (2.1)	10 0.24 (1.8)
Growth Weight (z-score)	11 -3.40 (1.54)	4 2.46 (3.03)	59 -3.17 (3.5)	10 0.26 (2.0)
Health-related quality of life				
Endpoint not recorded				
Side effects				
Endpoint category	**AA (pooled data from ENB-**		**Historic control**	

[2] Benefit assessment of the G-BA on the basis of the marketing authorisation and the results of the approval studies
[3] Data cut-off November 2013
[4] Subs. submitted data of pharm. company
[5] Cox regression model taking into account age at diagnosis, age at inclusion and year of diagnosis
[6] The analysis was based on patients in the intervention studies who were not ventilated at the start of the study and all patients in the historical control.
[7] Time to onset of event = defined as death or invasive ventilation

Endpoint	002/003 and ENB-010)		(ENB-011)	
	N*	Patients with event n (%)	N*	Patients with event n (%)
AE	70	70 (100%)	n.a.	n.a.
SAE	70	44 (62.9%)	n.a.	n.a.
Therapy discontinuation due to AE	70	6 (8.6%)	n.a.	n.a.
Reaction at the injection site	70	41 (58.6%)	n.a.	n.a.
Lipohypertrophy	70	1 (1.43%)	n.a.	n.a.
Craniosynostosis	70	16 (22.9%)	n.a.	n.a.
Ectopic calcification	70	2 (2.86%)	n.a.	n.a.
Abbreviations used: AA = Asfotase alfa; n.a. = not applicable/no data available; CI = confidence interval; n.c. = not calculable; n = number of patients with event; N* = total population; N = number of patients evaluated (varying per study or endpoint); AE = adverse event; SAE = serious adverse event				

For b) age group 5 – ≤ 12 years with perinatal/infantile and juvenile HPP

Mortality		
Endpoint not collected in this age group		
Morbidity		
Endpoint category **Endpoint**	**AA** **(ENB-006-09/ENB-008-10)** **N*=13**	
	B/L **N** **MV (SD)** **p[a]-value**	***Change compared to B/L at w. 240*** **N** **MV (SD)** **p[a]-value**
Growth Height (z-score)	13 -1.94 (1.82)	12 +0.68 (0.58) =0.0017
Growth Weight (z-score)	13 -1.64 (2.37)	12 +1.23 (0.81) =0.0003
	B/L **N** **MV (SD)** **p[a]-value**	***Change compared to B/L at w. 240*** **N** **MV (SD)** **p[a]-value**
Motor function BOT-2 (standardised score[b])	"running speed and agility" 13 3.69 (2.21)	"running speed and agility" 11 +8.82 (3.60) <0.0001
	"strength" 13 5.23 (3.68)	"strength" 11 +9.27 (4.56) <0.0001
	B/L **N** **Achieved % of expected figure**	***Change compared to B/L at w. 240*** **N** **Achieved % of expected figure**

	MV (SD) **Median**	**MV (SD)** **Median** **p value**
Motor function 6MWT	13 59.1% (15.0) 60.98%	11 +23.2% (13.7) 25.85% =0.0002
	B/L **N** **MV (SD)** **Median** **p value[d]**	***Change compared to B/L at w. 240*** **N** **MV (SD)** **Median** **p value[d]**
Pain/disability (POSNA PODCI) (standardised score[c])	13 25.5 (16.47) 27	12 22.5 (14.43) 22 0.0002

Health-related quality of life		
Endpoint not recorded		
Side effects		
Endpoint category **Endpoint**	**AA** **(ENB-006-09/ENB-008-10)** **N=13**	
		Patients with event n (%)
SAE	13	0
Discontinuation of the study medication due to AE	13	0
Reaction at the injection site	13	12 (92.3 %)
Lipohypertrophy	13	8 (61.5 %)
Craniosynostosis	13	7 (53.8 %)
Ectopic calcification	13	6 (46.2 %)

a: p value for comparison with baseline
b: Norm BOT-2 score (healthy children): MV (SD) = 15 (5)
c: POSNA PODCI scores are scaled from 0 to 100, with higher scores indicating an improvement in health.
d: p value based on t-test if mean value at round 0.

Abbreviations used: B/L = baseline; BOT-2 = Bruininks-Oseretsky Test of Motor Proficiency; n = number of patients with event; N*= total population; N = number of patients (varying per study or endpoint); POSNA PODCI = Pediatric Orthopedic Society of North America's Pediatric Outcomes Data Collection Instrument; 6MWT = Six-Minute Walk Test; AE = adverse events; SAE = serious adverse event.

For b) age group 13 – ≤ 66 years with primarily juvenile HPP (24 week control phase)

Mortality			
Endpoint not collected in this age group			
Morbidity			
Endpoint category **Endpoint**	**AA** **(ENB-009-10)** **N*=13**	**Untreated control** **(ENB-009-10)** **N*=6**	**p value**
	Change from B/L **N** **MV (SD)**	***Change from B/L*** **N** **MV (SD)**	
Motor function BOT-2[a]	"running speed and agility" 11 4.3 (4.1)	"running speed and agility" 2 0.5 (0.7)	0.1026
	"strength" 11 3.0 (2.8)	"strength" 2 4.0 (4.2)	0.8333
	Change from B/L **N** **Achieved % of expected figure** **MV (SD)**	***Change from B/L*** **N** **Achieved % of expected figure** **MV (SD)**	**p value**
Motor function 6MWT	12 8.78% (9.86)	3 1.4% (13.40)	0.1303
	Change from B/L **N** **MV (SD)**	***Change from B/L*** **N** **MV (SD)**	**p value**
Pain – BPI-SF	13 -3.5 (6.5)	4 -4.0 (6.0)	0.7315
Disability – LEFS	13 8.1 (15.5)	4 5.5 (13.7)	0.7248
Health-related quality of life			
Endpoint not recorded			
Side effects			

Endpoint category **Endpoint**	**AA** **(ENB-009-10)** **N*=13**		**Untreated control** **(ENB-009-10)** **N*=6**	
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**
SAE	13	2 (15.4%)	6	2 (33.3%)
Discontinuation of the study medication due to AE	13	0	6	0.
Reaction at the injection site	13	6 (46.2%)	6	1 (16.7%)
Adverse events cumulative[b)] over the entire period of the study N*= 19				

	N	Patients with event n (%)
SAE	19	7 (36.8%)
Discontinuation of the study medication due to AE	19	0
Reaction at the injection site	19	18 (94.7%)
Lipohypertrophy	19	4 (21.1%)
Craniosynostosis	19	0
Ectopic calcification	19	9 (47.4%)

a: Raw value, as standard values for standardised scores are only available up to the age of 21 years.
b: Includes the aforementioned studies on AA (ENB-009-10), N=13 and untreated controls (ENB-009-10), N=6: from week 24 all subjects treated with AA, duration of AA exposure was 96 weeks (N=19)

Abbreviations used: AA = asfotase alfa; B/L = baseline; BPI-SF = Brief Pain Inventory-Short Form; BOT-2 = Bruininks-Oseretsky Test of Motor Proficiency; LEFS = Lower Extremity Functional Scale; n = number of patients with event; N* = total population; N = number of patients evaluated (varying per study or endpoint); 6MWT = Six-Minute Walk Test; AE = adverse event; SAE = serious adverse event.

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

a) Patients ≤ 5 years of age and
b) Patients > 5 years of age

approx. 1,000 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: 13 January 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 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 limited, so studies should therefore be conducted by approval authorities to gather further data on adult dosing.

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

4. Treatment costs

Costs for additionally required SHI services: not applicable

Annual treatment costs[8]:

Designation of the therapy	Annual treatment costs per patient
Asfotase alfa[9]	€ 272,705.94–2,423,304.00

II. Entry into force

1. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 17 March 2016.

2. The period of validity of the resolution is limited to 1 December 2018.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de .

Berlin, 17 March 2016

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

Prof Hecken

[8] Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 February 2016, cost of medicinal product less statutory rebates
[9] The given range of treatment costs is for patients with a body weight of 9 kg (3 x weekly injections) to 76.3 kg.