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 – Cerliponase Alfa

of 21 December 2017

At its session on 21 December 2017 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 17 November 2017 (Federal Gazette, BAnz AT 2 January 2018 B2), as follows:

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

Cerliponase alfa

Resolution of: 21 December 2017
Entry into force on: 21 December 2017
Federal Gazette, BAnz AT DD MM YYYY Bx

Approved therapeutic indication (according to the marketing authorisation of 30 May 2017):

Brineura is indicated for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency.

1. Extent of the additional benefit of the medicinal product

Cerliponase alfa is approved as a medicinal product for the treatment of a rare disease 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 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medicinal benefit is considered to be already 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).

Extent of the additional benefit:

Non-quantifiable

Study results according to endpoints[1]

	Cerliponase alfa		Historical control cohort		Cerliponase alfa vs historical control cohort[a]	
	N		**N**			**p value**
Mortality						
Deaths (recorded as AE)	None		no data available			
Morbidity						
Proportion of responders (ML scale, primary endpoint)[b]	22	*Responder (slope < 2 points scaled to 48 weeks), n (%)*	22	*Responder (slope < 2 points scaled to 48 weeks), n (%)*	*RR [95% CI]*	p = 0.0009[c]
		22 (100)		10 (45)	2.14 [1.37; 3.36][c]	

1 Data from the single-arm studies 190-201/190-202 (cerliponase alfa) and study 190-901 (historical control cohort) from the benefit assessment of the G-BA.

	Cerliponase alfa		Historical control cohort		Cerliponase alfa vs historical control cohort[a]	
	N		**N**			**p value**
Decrease of the ML/HML scale (original primary endpoint, slope analysis)	22	*scaled to 48 weeks MV (SD) [95% CI]* 0.34 (0.46) [0.13; 0.54]	22	*scaled to 48 weeks MV (SD) [95% CI][d]* 2.0 (1.39) [1.38; 2.62]	*Difference MV (SD) [95% CI]* 1.66 (0.31) [1.02; 2.31][d]	p = < 0.0001[e]
Time to stable decrease of ≥ 2 points or occurrence of value 0 on ML/HML scale (observation time up to 72 weeks)	22	*Median time to event (days):* not achieved	22	*Median time to event (days):* *285*	*HR [95% CI]* 0.10 [0.03; 0.38]	p = 0.0005
Change in the score on the ML-/HML scale		*Change from baseline, MV (SD)*		*Change from baseline, MV (SD)*	no data available	
	22	−0.5 (0.80): Week 49	21	−2.1 (0.51): Week 49		
	22	−0.5 (0.91): Week 73	20	−2.7 (0.67): Week 73		
	17	−0.4 (0.76): Week 89	11	−2.7 (0.86): Week 89		

	Cerliponase alfa (N = 23)	
Morbidity		
Responder rate of the ML scale (primary endpoint, responder analysis)[f]	*Responders (by Week 48)[g] n (%)* 20 (87)	*Responders (by Week 80)[g] n (%)* 20 (87)
ML scale (range 0–6 points)[i]	*Change at Week 73, MV (SD)* −0.4 (0.9)	*Change at Week 97, MV (SD)* −0.6 (0.8)
MLV scale (range 0–9 points)[i, j,k]	−0.6 (1.3)	−0.9 (1.2)
MLVS scale (range 0–12 points)[i, j,l]	0.0 (2.2)	−0.1 (2.4)
Health-related quality of life		
	Study 190-201[m]	Study 190-201/190-202[n]
PedsQL (Parent Report for Toddlers)	*Change from study baseline to Week 49, MV (SD)*	*Change from study baseline to Week 98* **[N = 12]** *MV (SD)*
Physical skills[o]	−6.1 (21.7)	−27.9 (22.4)
Emotional skills[o]	7.7 (26.2)	−0.5 (25.5)

Social skills[o]	7.8 (16.2)	−5.8 (18.3)
Academic skills[o]	6.3 (29.8)[r]	−17 (21.8)[r]
Psychosocial component score[o, p]	7.9 (14.9)	−5.4 (11.1)
Total score[o, q]	2.6 (12.2)	−14.1 (13.1)
Side effects		
	Study 190-201[m], n (%)	*Study 190-201/190-202[n], n (%)*
Adverse events (AE)	24 (100)	24 (100)
AEs of CTCAE grade ≥3	9 (38)	13 (54)
Serious AE (SAE)	16 (67)	19 (79)
AEs leading to study or treatment discontinuation	0	0
AE leading to death	0	0
AEs of special interest ≥ 20%		
MedDRA System Organ Class, Preferred Term[s],	*Study 190-201[m], n (%)*	*Study 190-201/190-202[n], n (%)*
(1) Incidence of hypersensitivity and anaphylactic reactions[t]		
Patients with at least one reported hypersensitivity reaction AE	14 (58)	14 (58)
Immune system disorders	8 (33)	10 (42)
Hypersensitivity reactions	8 (33)	9 (38)
Skin and subcutaneous tissue disorders	5 (21)	5 (21)
(2) Incidence of AEs in temporal relation to the infusions ("temporally-related events", TRE)[u]		
Patients with at least one AE that occurred in temporal relation to the infusion	24 (100)	24 (100)
Gastrointestinal disorders	10 (42)	12 (50)
Vomiting	5 (21)	7 (29)
General disorders and administration site conditions	11 (46)	11 (46)
Pyrexia	11 (46)	11 (46)
Immune system disorders	8 (33)	9 (38)
Hypersensitivity reactions	8 (33)	9 (38)
Infections and infestations	8 (33)	15 (63)
Injury, poisoning, and procedural complications	4 (17)	5 (21)
Metabolism and nutrition disorders	3 (13)	6 (25)
Nervous system disorders	16 (67)	19 (79)
Epileptic seizures	8 (33)	8 (33)
Tremor	3 (13)	6 (25)
Psychiatric disorders	7 (29)	7 (29)
(3) Incidence of AEs related to ICV access[v]		
Patients with at least one AE related to the ICV port	7 (29)	11 (46)
Product problems	n.a.	7 (29)

(4) Incidence of AEs within SOC "Nervous system disorders" and convulsions[w]		
Patients with at least one AE that had occurred within the SMQ convulsions.	23 (96)	23 (96)
Nervous system disorders (SMQ, "convulsions")	23 (96)	23 (96)
Epilepsy	11 (46)	11 (46)
Generalised tonic-clonic seizures	2 (8)	11 (46)
Petit mal epilepsy	2 (8)	7 (29)
Epileptic seizure	14 (58)	14 (58)

a: Matching Method #1 for patients from the Study 190-201/202 on cerliponase and the historical controls: Identical ML/ HML value and the smallest possible age difference (but not more than 12 months), each at baseline.
b: Estimated slope categorised by < 2 and ≥ 2 points on the ML/HML scale/48 weeks.
c: Own calculation. Correction for cells with 0 events by adding 0.5.
d: A t-distribution using the Satterthwaite approximation was used to calculate the CIs.
e: Two-sample t-test with Satterthwaite approximation.
f: Responders were defined as the proportion of patients who did not experience a net decrease in ML score of two or more points or to a value of zero by week 48 (i.e. response is a net decrease of < 2 by week 48, which may include a decrease of ≥ 2 points during the course of the study followed by an increase in score and a resulting overall decrease of no more than 1 point). In contrast, non-responders (or stable decrease) were defined as the proportion of patients whose ML score dropped by two or more points (≥ 2) by week 48 (study day 340 related to the first 300 mg infusion).
g: The responder analysis refers to study day 340 related to the first infusion of 300 mg of Study 190-201.
h: The responder analysis refers to study day 540 related to the first infusion of 300 mg of Study 190-201.
i: Method used = estimation using a time window: In patients who participated in dose escalation, the timing of the first 300 mg infusion did not correspond to that of the first 300 mg dose during the stable dose phase. A time window was therefore defined for these patients. This algorithm was designed used the observation closest in time to the planned observation at each planned examination time during the stable dose phase (the first 300 mg infusion was taken as the starting point).
j: For each individual domain, the functional status is surveyed on a scale from 3 (normal functioning) to 0 (complete loss of functioning).
k: Includes ML scale plus vision (0–9 points).
l: Includes ML scale plus vision and epileptic seizures (0-12 points).
m: Data cut-off: 30 November 2015. All patients in study 190–201 (N = 23, ITT) had completed 48 weeks of treatment with 300 mg cerliponase at this data cut-off.
n: Data cut-off 3 June 2016. Treatment with 300 mg cerliponase for at least 72 weeks (ITT population).
o: Each item was rated on a 5-point Likert scale from 0 (never) to 4 (almost always). The values were converted into a scale from 0–100 as follows: 0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0. The score to be achieved is between 0 and 100. Higher scores indicate a better quality of life.
p: The psychosocial component score is composed of the dimensions emotional competences, social competences, and school competences.
q: Sum of all dimensions: Physical competences, emotional competences, social competences, and school competences
r: There is a patient missing at both Week 49 and Week 98: (Week 49 [N = 22]; Week 98 [N = 11])
s: For patients with more than one AE within a MedDRA (SOC or PT), the most severe event was considered.
t: Hypersensitivity reactions included (1) the broad MedDRA SMQ "Hypersensitivity" or (2) the broad SMQ algorithm "Anaphylactic reactions". No AEs were identified using the SMQ algorithm "Anaphylactic reactions".
u: AEs temporally related to the infusion were defined as AEs occurring after the start of the infusion of the investigational product and within 24 h of starting or restarting the infusion.
v: Subsequently defined as AE of special interest with Amendment 3. The investigators assessed the association with the medical device (ICV access).
w: Status epilepticus, hydrocephalus, and meningitis were defined *a priori* as AEs of special interest. Additional AEs were identified by broad MedDRA query "convulsions" (SMQ).

HML scale = Hamburg Motor/Language scale, HR = hazard ratio, ICV= intracerebroventricular, CI = confidence interval, MedDRA = Medical Dictionary for Regulatory Activities, ML scale = Motor/Language scale, MLV scale = Motor/Language/Vision scale, MLVS = Motor/Language/ Vision/Seizures scale, MV = mean value, n = number of patients with event, N = number of patients evaluated, PedsQL = Paediatric Quality of Life Inventory, PT = Preferred Term, RR = relative risk, SD = standard deviation, SMQ = Standardised MedDRA Queries, SOC = System Organ Classes, SAE = serious adverse event, AE = adverse event

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

approx. 20–40 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 Brineura® (active ingredient: cerliponase alfa) at the following publicly accessible link (last access: 8 November 2017):

http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/004065/WC500229798.pdf

Treatment with cerliponase alfa as well as the administration of cerliponase alfa may be initiated and monitored only by specialists who are experienced in the intracerebroventricular administration of medicinal products.

This medicinal product was approved under “special conditions”. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will assess new information on this medicinal product at a minimum once per year and update the product information where necessary.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs per patient
Cerliponase alfa	€ 747,057.22
Costs for additionally required SHI services:	
Implantation of an intracerebro-ventricular access device, infusion, laboratory examination of the cerebrospinal fluid	Costs are non-quantifiable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 December 2017

II. Entry into force

1. **The resolution will enter into force from the day of its publication on the internet on the website of the G-BA on 21 December 2017.**
2. **The period of validity of the resolution is limited to 1 June 2021.**

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

Berlin, 21 December 2017

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

Prof. Hecken