Resolution

Gemeinsamer Bundesausschuss

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

of 19 December 2019

At its session on 19 December 2019, 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 DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

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

Pegvaliase

Resolution of: 19 December 2019
Entry into force on: 19 December 2019
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 3 May 2019):

Pegvaliase is indicated for the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 µmol/l) despite prior management with available treatment options.

1. Extent of the additional benefit of the medicinal product

Pegvaliase 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. According to Section 35a, paragraph 1, sentence 11, 1st half of the sentence 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).

Patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 µmol/l) despite prior management with available treatment options

Extent of the additional benefit of pegvaliase indicating the significance of the evidence:

Hint for a non-quantifiable additional benefit because the scientific data basis does not allow quantification.

Study results according to endpoints:[1]

[1] Data from the dossier evaluation by the G-BA (published on 1 October 2019) unless indicated otherwise.

Study 165-302: Phase III study with 4 study sections, Section 2: randomised, placebo-controlled, double-blind “discontinuation”

Study 165-301: Non-controlled phase III study

Mortality

Endpoint	**Pegvaliase (any dose)**	
	N	*Patients with event n (%)*
Deaths		
Study 165-301	261	1 (0.4)
Study 165-302	215	0 (0)
n: number of patients with (at least one) event; N: number of patients evaluated		

Morbidity

Endpoint	**Pegvaliase 20 mg/day**		**Low dose placebo**		**Pegvaliase 40 mg/day**		**High dose placebo**		**Pegvaliase vs placebo**
	N	*Mean (SD)*	*N*	*Mean (SD)*	*N*	*Mean (SD)*	*N*	*Mean (SD)*	*Difference of LS mean [95% CI][1], p value[2]*
Phenylalanine concentration in blood in µmol/l									
Study 165-302, Section 2									
Baseline	34	629.1 (574.6)	15	616.4 (527.0)	32	529.3 (567.9)	14	508.2 (363.7)	-
Week 8	34	635.2 (576.5)	15	1507.4 (358.1)	32	661.1 (642.0)	14	1164.4 (343.3)	-
Change from baseline at week 8	34	−15.4 (242.3)	15	934.9 (580.7)	-				−879.7 [−1101.5; −657.8] < 0.0001
Change from baseline at week 8	-				32	109.2 (318.7)	14	599.0 (507.4)	−559.5 [−800.4; −318.6] < 0.0001

1) Mixed model for repeated measurements considering the following factors: Treatment group, rounds, interaction of treatment and rounds as well as phenylalanine concentration at baseline.
2) No indication as to which test was performed was identified.

CI: confidence interval, LS: least squares, N: number of patients evaluated, SD: standard deviation

Endpoint	Pegvaliase (any dose)		
	N	*Mean (SD)*	*Change since baseline Mean (SD)*
Phenylalanine concentration in blood in µmol/l			
Study 165-301			
Baseline	261	1232.7 (386.4)	-
Week 8	247	1,198.2 (402.4)	−37.8 (237.8)
Week 12	240	928.0 (527.5)	−312.1 (466.5)
Week 16	210	875.7 (534.2)	−355.8 (474.8)
Week 20	183	807.5 (534.2)	−403.7 (505.8)
N: number of patients evaluated, SD: standard deviation			

Health-related quality of life

No quality of life data was collected

Side effects

Endpoint	Pegvaliase 20 mg/day		Low dose placebo		Pegvaliase 40 mg/day		High dose placebo		Pegvaliase vs placebo
	N	*Patients with event n (%)*	*N*	*Patients with event n (%)*	*N*	*Patients with event n (%)*	*N*	*Patients with event n (%)*	*Effect estimator*
Study 165-302, Section 2									
AE	34	27 (79.4)	15	14 (93.3)	32	28 (87.5)	14	13 (92.9)	n.a.
AE CTCAE grade ≥ 3	34	0	15	0	32	2 (6.3)	14	0	n.a.
SAE	34	0	15	1 (6.7)	32	2 (6.3)	14	0	n.a.
AE that led to discontinuation of the study medication	34	0	15	0	32	0	14	0	n.a.
Endpoint	**Pegvaliase (any dose)**								

	N	*Patients with event n (%)*
AE		
Study 165-301	261	260 (99.6)
Study 165-302	215	209 (97.2)
AE CTCAE grade ≥ 3		
Study 165-301	261	39 (14.9)
Study 165-302	215	30 (14.0)
SAE		
Study 165-301	261	26 (10.0)
Study 165-302	215	26 (12.1)
AE that led to discontinuation of the study medication		
Study 165-301	261	29 (11.1)
Study 165-302	215	12 (5.6)
CTCAE: Common Terminology Criteria for Adverse Events, n.s.: not specified, n: number of patients with (at least one) event; N: number of patients evaluated, SAE: serious adverse event(s), AE: adverse event(s)		

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

Approx. 435 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 Palynziq® (active ingredient: pegvaliase) at the following publicly accessible link (last access: 7 November 2019):

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

Treatment with pegvaliase should be initiated and monitored only by physicians who are experienced in the treatment of patients with phenylketonuria.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/patient
Pegvaliase	€ 170,759.78 – € 512,279.33
Additionally required SHI services	different for each individual patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 December 2019

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 19 December 2019.

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

Berlin, 19 December 2019

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

Prof. Hecken