Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V) Pegzilarginase (hyperargininemia (ARG1-D), ≥ 2 years)

of 4 July 2024

At its session on 4 July 2024, the Federal Joint Committee (G-BA) resolved to amend the 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 by the publication of the resolution of D 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 Pegzilarginase as follows:

Pegzilarginase

Resolution of: 4 July 2024
Entry into force on: 4 July 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 15 December 2023):

Loargys is indicated for the treatment of arginase 1 deficiency (ARG1-D), also known as hyperargininemia, in adults, adolescents and children aged 2 years and older.

Therapeutic indication of the resolution (resolution of 4 July 2024):

See therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Pegzilarginase 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 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The 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) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. 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).

<u>Adults, adolescents and children aged 2 years and older with arginase 1 deficiency (hyperargininemia)</u>

Extent of the additional benefit and significance of the evidence of pegzilarginase:

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

Study results according to endpoints:[1]

Adults, adolescents and children aged 2 years and older with arginase 1 deficiency (hyperargininemia)

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↔	No relevant differences for the benefit assessment, advantage in the clinically relevant laboratory parameter change in arginine concentration
Health-related quality of life	n.a.	The data are not assessable.
Side effects	↔	No relevant differences for the benefit assessment.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

PEACE study: RCT phase over 24 weeks; pegzilarginase vs placebo, each in combination with Individualised Disease Management (IDM)

Mortality

Endpoint	Pegzilarginase + IDM n = 21		Placebo + IDM n = 11		Pegzilarginase vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value
Overall mortality					
	21	0 (0)	11	0 (0)	-

[1] Data from the dossier assessment of the G-BA (published on 15. April 2024), and from the amendment to the dossier assessment from 14 June 2024, unless otherwise indicated.

Morbidity

Endpoint	Pegzilarginase + IDM n = 21			Placebo + IDM n = 11			Pegzilarginase vs placebo
	N	Values at the start of study MV in µM (log scale SD)	Values at week 24 MV in µM (log scale SD)	N	Values at the start of study MV in µM (log scale SD)	Values at week 24 MV in µM (log scale SD)	Changes GLS (generalised least squares) mean [95% CI]; p value
Arginine concentration (primary endpoint; presented additionally)							
	21	354.0 (1.30)	86.4 (1.60)	11	464.7 (1.21)	426.5 (1.31)	0.23 [0.17, 0.33] < 0.0001

Endpoint	Pegzilarginase + IDM n = 21			Placebo + IDM n = 11			Pegzilarginase vs placebo
	N	Baseline MV (SD)	Change from baseline to week 24 LS mean [95% CI]	N	Baseline MV (SD)	Change from baseline to week 24 LS mean [95% CI]	LS mean difference [95% CI]; p value
2MWT (walking distance in metres)							
	19[a]	109.0 (55.76)	7.4 [n.d.]	10	99.9 (49.00)	1.9 [n.d.]	5.5 [-15.6; 26.7]; 0.60
GMFM-D (standing)[b]							
- Pre-specified analysis (with the subject in the placebo arm at 0 to baseline)							
	20	28.0 (9.61)	2.7 [n.d.]	11	26.8 (14.76)	1.3 [n.d.]	1.4 [-1.4; 4.2] 0.3037
- Pre-specified model without subject with missing baseline value							
	21	28.05 (9.61)	2.67 [n.d.]	10	29.5 (12.42)	0.42 [n.d.]	2.25 [-0.37; 4.87] 0.090[c]
- Sensitivity analysis 1: post hoc; without subject with missing baseline value and with adjusted MMRM model due to variance heterogeneity							
	20	28.05 (9.61)	2.70 [0.9; 4.5]	10	29.5 (12.42)	0.40 [-0.3; 1.1]	2.30 [0.38; 4.22] 0.021[d]
							Hedges' g[e]: 0.66 [-0.12; 1.44]
- Sensitivity analysis 2: (post hoc; imputation of the missing baseline value with the average baseline value of all other subjects with a GMFCS level IV (7.25 points)							
	20	28.05 (9.61)	2.69 [n.d.]	11	27.48 (13.56)[f]	0.68 [n.d.]	2.01 [-0.51; 4.52] 0.11[g]

Endpoint	Pegzilarginase + IDM n = 21			Placebo + IDM n = 11			Pegzilarginase vs placebo
	N	Baseline MV (SD)	Change from baseline to week 24 LS mean [95% CI]	N	Baseline MV (SD)	Change from baseline to week 24 LS mean [95% CI]	LS mean difference [95% CI]; p value
- Sensitivity analysis 3: post hoc; imputation of the missing baseline value with the average baseline value of all other subjects (28.5 points)							
	20	28.05 (9.61)	2.68 [n.d.]	11	29.41; (11.79)[h]	-1.22 [n.d.]	3.90 [0.37; 7.43] 0.032[i]
							Hedges' g: 0.81 [0.05; 1.58]
GMFM-E[j] (walking, running, jumping)							
	20[k]	48.3 (19.93)	4.2 [n.d.]	11	46.5 (24.56)	-0.4 [n.d.]	4.6 [-1.1; 10.2]; 0.11
GFAQ[l] **(walking scale)**							
	20[k]	7.9 (2.05)	0.1 [n.d.]	11	7.5 (2.62)	-0.3 [n.d.]	0.4 [-0.3; 1.0]; 0.23

Health-related quality of life

No assessable data on health-related quality of life are available.

Side effects

Endpoint MedDRA system organ classes/ preferred terms/ AEs of special interest	Pegzilarginase + IDM n = 21		Placebo + IDM n = 11		Pegzilarginase vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Total adverse events *(presented additionally*[m]*)*	21	18 (85.7)	11	11 (100)	-
Serious adverse events (SAE)[n]	21	4 (19.0)	11	4 (36.4)	0.52 [0.16; 1.70]; 0.40
Severe adverse events [n,o]	21	1 (4.8)	11	0 (0)	1.64 [0.07; 37.15]; 1.00
Therapy discontinuation due to adverse events	21	0 (0)	11	0 (0)	-
Severe adverse events according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)					
No severe AEs ≥ 5%.					

SAEs according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)
No significant differences
Adverse events of special interest (with statistically significant difference between the treatment arms)
No significant differences

a. The 2MWT should only be carried out from the age of 3. There is at least 1 subject in the pegzilarginasearm who is 2 years old at the start of study. It is unclear why there is no calculation for the change from baseline to week 24 for 1 subject. The returns cannot be traced in full.
b. Range of values 0–39. Higher values correspond to gross motor function.
c. MMRM with visit, study treatment and interaction between visit and study treatment as effects, and baseline value as covariate. Standard covariance structure type = unstructured. No stratified analysis was presented and the pre-specified non-parametric Wilcoxon rank sum test showed no significant difference (p = 0.094).
d. MMRM with visit, study treatment and interaction between visit and study treatment as effects, and baseline value as covariate. Standard covariance structure type = unstructured, but a compound symmetry structure was used here according to the statement. No stratified analysis was presented. Using the Mancl-DeRouen covariance estimator, which is estimated to be equivalent on the basis of the limited information available, a significant effect (p = 0.028) with an effect estimator of 2.25 [0.27; 4.23] and a Hedges´ g of 0.64 [-0.14; 1.41] is shown. For reasons of clarity, the results are not additionally presented in tabular form.
e. The assessability of the Hedges´ g is questioned by the pharmaceutical company in the case of unequal variance.
f. No baseline value was available for 1 subject (with GMFCS level IV). The missing baseline value was imputed as 7.25, which corresponds to the average baseline value of all other subjects with a GMFCS level of IV.
g. The pre-specified non-parametric Wilcoxon rank sum test showed no significant difference (p = 0.15).
h. No baseline value was available for 1 subject (with GMFCS level IV). The missing baseline value was imputed as 28.5, which corresponds to the average baseline value of all other subjects (regardless of treatment arm and GMFCS level).
i. The pre-specified non-parametric Wilcoxon rank sum test showed a significant difference (p = 0.045).
j. Range of values 0–72. Higher values correspond to gross motor function.
k. 1 subject discontinued the study at week 6, which is why 20 subjects were included in the calculation at week 24 in the pegzilarginase arm.
l. Range of values from 1-10. Higher values correspond to better walking ability.
m. Patient relevance of laboratory parameters unclear.
n. In the dossier, non-disease related SAEs that were defined post hoc were reported in 1 subject (compared to 4 subjects in the present case) in the pegzilzilginase arm and in no subject (compared to 4 subjects in the present case) in the placebo arm. The number of subjects with severe AEs is consistent between the two evaluation procedures.
o. The study's own criteria were used for severity grading (mild, moderate, severe).

Abbreviations used: n.c. = not calculable; n.r. = not reached; abbreviations = GFAQ = Gillette Functional Assessment Questionnaire; GLS = Geometric Least Square; GMFM = Gross Motor Function Measure-88; IDM = Individualised Disease Management; CI = confidence interval; log = logarithmised; LS = Least Square; MedDRA = Medical Dictionary for Regulatory Activities; MV = mean value; µM = micromolar; N = number of patients evaluated; n = number of patients with (at least one) event; PT = preferred term; RCT = randomised controlled trial; RR = relative risk; SD = standard deviation; SOC = system organ class; (S)AE = (serious) adverse event; vs = versus

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

Adults, adolescents and children aged 2 years and older with arginase 1 deficiency (hyperargininemia)

Approx. 50 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 Loargys (active ingredient: pegzilarginase) agreed upon in

the context of the marketing authorisation at the following publicly accessible link (last access: 23 May 2024):

https://www.ema.europa.eu/en/documents/product-information/loargys-epar-product-information_en.pdf

Treatment with pegzilarginase should only be initiated and monitored by doctors experienced in treating inherited metabolic disorders.

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for patients and caregivers.

4. Treatment costs

Annual treatment costs:

Adults, adolescents and children aged 2 years and older with arginase 1 deficiency (hyperargininemia)

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pegzilarginase	€ 330,091.53 - € 2,640,732.26

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2024)

Costs for additionally required SHI services: not applicable

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Adults, adolescents and children aged 2 years and older with arginase 1 deficiency (hyperargininemia)

- No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the

medical treatment mandate, nor do they make statements about expediency or economic feasibility.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 4 July 2024.

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

Berlin, 4 July 2024

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

Prof. Hecken