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
Glucarpidase (reduction of toxic plasma methotrexate concentrations; aged 28 days and older)

of 6 October 2022

At its session on 6 October 2022, 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 Glucarpidase as follows:

Glucarpidase

Resolution of: 6 October 2022
Entry into force on: 6 October 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 11 January 2022):

Glucarpidase (Voraxaze) is indicated to reduce toxic plasma methotrexate concentration in adults and children (aged 28 days and older) with delayed methotrexate elimination or at risk of methotrexate toxicity.

Therapeutic indication of the resolution (resolution of 6 October 2022):

See therapeutic indication according to marketing authorisation.

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

Glucarpidase is approved as a medicinal product for the treatment of rare diseases under 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 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) 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 28 days and older with delayed elimination of methotrexate (MTX) or if there is a risk of MTX toxicity</u>

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

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

Study results according to endpoints:[1]

<u>Adults, adolescents and children 28 days and older with delayed elimination of methotrexate (MTX) or if there is a risk of MTX toxicity</u>

Summary of results for relevant clinical endpoints

[1] Data from the dossier assessment of the G-BA (published on 15. July 2022), unless otherwise indicated.

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	The data are not assessable.
Morbidity	n.a.	The data are not assessable.
Health-related quality of life	∅	No data available.
Side effects	n.a.	The data are not assessable.

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
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

PR001-CLN-001, -002, -003 and -006 studies: multicentre, single-arm compassionate use studies of the pivotal target population[2]

PR001-CLN-017 studies: open-label, non-randomised, multicentre pharmacokinetics (PK) study of the pivotal target population[2]

Mortality

Endpoint Study	Glucarpidase	
	N[f]	Patients with event n (%)
Overall mortality		
Deaths ≤ 30 days after glucarpidase treatment		
001	8	1 (12.5)
002	47[a]	6 (12.8)
003	16	2 (12.5)
006	44	2 (4.5)
017	9	0 (0)
Pooled target population	*124*	*11 (8.9)*

[2] Patients who had received a single dose of glucarpidase of 50 U/kg according to the product information and for whom delayed MTX elimination was documented.

Morbidity

Endpoint Study	**Glucarpidase**		
	N	Patients with event n (%)	[95% CI][b]
Clinically important reduction (CIR) of MTX concentration (sensitivity analysis)[q] (presented additionally)			
001 002 003 006 *Pooled target population*	4 25 6 12 *47*	2 (50.0) 14 (56.0) 4 (66.7) 8 (66.7) *28 (59.6)*	[15.0; 85.0][c] [37.0; 73.4][c] [30.0; 90.4][c] [39.1; 86.2][c] *-*[d]
	N	Mean value (SD)	Median (min – max)
Time to reach CIR (in hours)[e] (presented additionally)			
001 002 003 006 *Pooled target population*	5 23 7 16 *51*	50.7 (57.9) 36.6 (64.5) 1.7 (3.7) 32.4 (58.1) *31.9 (57.3)*	33.00 (0.3 – 132.0) 0.25 (0.2 – 192.0) 0.25 (0.2 – 10.0) 0.66 (0.3 – 164.9) *0.25 (0.2 – 192.0)*

Health-related quality of life

The endpoint was not collected in the studies.

Side effects

Endpoint Study	**Glucarpidase**	
	N[f]	Patients with event n (%)
Adverse events (AEs) in total		
001 002 003 006 017 *Pooled target population*	8 47 15 44 9 *123*	8 (100.0) 43 (91,5)[g] 13 (86.7) 38 (86.4) 5 (55.6) *107 (87.0)*
AE severity grade ≥ 3[h,i]		
001 002 003 006 017 *Pooled target population*	8 47 15 44 9 *123*	7 (87.5) 30 (63.8)[j] 7 (46.7) 26 (59.1) 5 (55.6) *75 (61.0)*[k]
Serious adverse events (SAE)		
001	8	6 (75.0)

Endpoint Study	Glucarpidase	
	N[f]	Patients with event n (%)
002	47	21 (44.7)[l]
003	15	8 (53.3)
006	44	17 (38.6)
017	9	1 (11.1)
Pooled target population	*123*	*53 (43.1)*
AEs of special interest[p]		
001	8	-[m]
002	47	5 (10.6)[n]
003	15	-[m]
006	44	3 (6.8)
017	9	-[m]
Pooled target population	*123*	-[o]

a. Separate results are not available for patients who received thymidine and patients who did not receive thymidine.
b. CI according to the Newcombe and Altman method.
c. Patients with a baseline MTX concentration of > 1 measured by central HPLC.
d. Not specified for the pooled analysis.
e. Defined as the period from the first glucarpidase administration to the first post-glucarpidase MTX concentration ≤ 1 µmol/l, with all subsequent MTX concentrations ≤ 1 µmol/l.
f. Safety population
g. Patients, who did not receive thymidine: 32 (88.9%). Patients, who received thymidine: 11 (100.0%).
h. All AE severity grades that had been documented as ≥ 3.
i. For the 001 and 003 studies, the WHO toxicity grade was used for severity grading of the AEs. For the 002 study, CTCAE version 2 was used for the severity grading of AEs before 16.07.2003. After 16.07.2003 for the 002 study, and for the 006 and 017 studies, CTCAE version 3 was used for severity grading of the AEs.
j. Patients, who did not receive thymidine: 21 (58.3%). Patients, who received thymidine: 9 (81.8%)
k. In the statistical recalculation by the pharmaceutical company, 78 (63.4%) cases were reported. This figure does not match the sum of the cases of the individual studies
l. Patients, who did not receive thymidine: 14 (38.9%). Patients, who received thymidine: 7 (63.6%).
m. Data are available for the total population, but no data were presented for the target population.
n. Patients, who did not receive thymidine: 4 (11.1%). Patients, who received thymidine: 1 (9.1%).
o. No calculation possible, as no data on the target population are available for the 001, 003 and 017 studies.
p. Includes hypersensitivity reactions of type I/II/III.
q. Sensitivity analyses for the endpoint CIR of MTX concentration: Analysis of patients who had baseline MTX concentrations of > 1 µmol/l.

Abbreviations:

CIR = clinically important reduction; CTCAE = Common Terminology Criteria for Adverse Events; HPLC = High Performance Liquid Chromatography; CI = confidence interval; MTX = methotrexate N = number of patients evaluated; n = number of patients with (at least one) event; PC = pharmaceutical company; SD = standard deviation; SAE = serious adverse event; AE= adverse event.

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

<u>Adults, adolescents and children 28 days and older with delayed elimination of methotrexate (MTX) or if there is a risk of MTX toxicity</u>

approx. 90 to 440 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 Voraxaze (active ingredient: glucarpidase) at the following publicly accessible link (last access: 22 August 2022):

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

This medicinal product was approved under "special conditions". This means that it was not possible to obtain complete information on this medicinal product due to the rarity of the disease and ethical reasons. The EMA will assess any new information that becomes available on an annual basis, and, if necessary, the summary of product characteristics will be updated.

4. Treatment costs

Annual treatment costs:

Adults, adolescents and children 28 days and older with delayed elimination of methotrexate (MTX) or if there is a risk of MTX toxicity

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Glucarpidase	€ 31,837.60 – € 127,350.40

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 September 2022

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 6 October 2022.

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

Berlin, 6 October 2022

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

Prof. Hecken