Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) 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

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V). Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a paragraph 1 sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). According to Section 35a paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the active ingredient glucarpidase in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 April 2022. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 12 April 2022.

Glucarpidase to reduce toxic plasma methotrexate concentrations in adults and children (aged 28 days and over) with delayed methotrexate elimination or at risk of methotrexate toxicity is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the marketing authorisation studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 15 July 2022 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G22-14) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for the marketing authorisation considering their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of glucarpidase.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Glucarpidase (Voraxaze) according to product information

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.

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of glucarpidase is assessed as follows:

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

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

Justification:
For the benefit assessment, the pharmaceutical company submits data from the four prospective, open-label, non-randomised, multicentre, single-arm compassionate use PR001-CLN-001, -002, -003 and -006 studies and one open-label, non-randomised, multicentre pharmacokinetics (PK) -017 study. The studies were conducted between 1993 and 2009. Patients of different ages who had impaired methotrexate (MTX) elimination after therapy with high dose (HD)-MTX due to MTX-induced renal failure or intrathecal overdose were enrolled in the studies. Among others, an elevated methotrexate (MTX) serum concentration, depending on the duration of the previous MTX infusion (e.g., > 5 µmol/l or > 10 µmol/l at least 42 hours after the start of the MTX infusion or > 50 µmol/l 24 hours after MTX administration in patients with osteosarcomas) or an intrathecal MTX overdose (≥ 50 mg MTX) and renal failure (e.g., sCr[2] > 1.5 times the ULN[3] or CrCl[4] of ≤ 60 ml/m²/min) were defined as inclusion criteria. The sub-population relevant for the benefit assessment ("target population") in the five studies included those patients who had received a single dose of glucarpidase of 50 units/kg according to the product information and for whom delayed methotrexate elimination was documented. In the 001, 002, 003 and 006 studies, calcium folinate administration was to be discontinued 2 and 4 hours before and after glucarpidase administration, respectively; further administration of calcium folinate during the course of the study was allowed in all studies. In addition, in the 002 study, all patients were to receive a concomitant administration of thymidine; however, this was changed with the amendment of November 2003 and the administration of thymidine was no longer planned. The primary efficacy endpoint in the 001, 002, 003 and 006 studies was the clinically important reduction (CIR) in plasma methotrexate concentration (measured by HPLC).

In the 001, 002, 003 and 006 studies, the patients were between 5 and 84 years old (median 17 years). The median methotrexate concentration at baseline was 12.8 µmol/l (0.05 to 500 µmol/l). Patients in the target population in the studies received a dose of glucarpidase between 48 and 52 units/kg approximately 2 to 10 days after methotrexate administration (median 50 units/kg after 3 days). According to the product information, glucarpidase should optimally be administered within 60 hours after the start of the high-dose methotrexate infusion.

[2] sCr = serum creatinine
[3] ULN = upper limit of normal
[4] CrCl = creatinine clearance

About 90% of the patients in the pooled target population received leucovorin. Haemodialysis was the most common rescue treatment used in about 13% of patients.

No data are available for comparative assessment due to the single-arm design of the studies. Thus, quantification of the extent of the additional benefit is not possible on the basis of the data presented.

Mortality

Deaths were recorded in the 001, 002, 003, 006 and 017 studies as part of the safety analysis (safety population). In the studies, 11 deaths occurred up to and including 30 days after glucarpidase treatment (approximately 9% of patients in the pooled target population).
For the additional recording of deaths after day 30, there is no sufficient operationalisation in the study documents and it remains unclear whether and over what period the patients enrolled in the studies were followed up.

Morbidity

Morbidity endpoints were only collected in the 001, 002, 003 and 006 studies.

Clinically important reduction (CIR) of methotrexate concentration

In the 001, 002, 003 and 006 studies, a clinically important reduction was defined as a methotrexate concentration of ≤ 1 µmol/l (measured by HPLC[5]) and retrospectively determined as the primary endpoint of all studies. The endpoint was considered to have been reached, as defined in the studies, when a plasma or serum methotrexate concentration ≤ 1 µmol/l was reached after administration of glucarpidase. All subsequent plasma or serum samples also had to show ≤ 1 µmol/l, so that, conversely, no renewed increase in methotrexate concentration > 1 µmol/l (a so-called "rebound") occurred. In addition, the time to the first post-glucarpidase methotrexate concentration ≤ 1 µmol/l was recorded in the studies.

Sensitivity analyses of the primary endpoint were performed in all studies, which included only patients who had baseline methotrexate concentrations of > 1 µmol/l (approximately 85% patients in the pooled target population). Although there is no validation for the choice of the baseline methotrexate concentration value of ≤ 1 µmol/l for achieving a CIR, it is assumed that the choice of this concentration results from the definition of delayed methotrexate elimination (e.g., 1 µmol/l after 48 hours after administration of methotrexate[6]) and thus, there is an increasing risk of methotrexate toxicity. Overall, the operationalisation of the sensitivity analysis of the endpoint "CIR of methotrexate concentration" therefore appears suitable to show a clinically important reduction of methotrexate concentration in plasma or serum by glucarpidase administration.
In the sensitivity analysis, about 60% of the patients achieved a CIR of the methotrexate concentration by treatment with glucarpidase. The methotrexate concentration is a laboratory parameter and is used as part of the diagnosis and for follow-up. The methotrexate concentration in patients in the present therapeutic indication is usually elevated in the toxic range. The clinically important reduction in methotrexate concentration is considered a clinically significant parameter in the present therapeutic indication and is presented

[5] HPLC = High Performance Liquid Chromatography
[6] A generally valid definition of delayed methotrexate elimination does not exist. In a review from 2006, threshold values for systemic methotrexate concentrations were derived from studies on HD-MTX: Widemann BC, Adamson PC. Understanding and managing methotrexate nephrotoxicity. Oncologist 2006;11(6):694-703.

additionally. In the median, the patients of the pooled target population reached the CIR after 0.25 h (or on average after approx. 32 h).
Since the clinical significance of the endpoint "time to reach CIR" or its possible conclusions about the further clinical course of the patients is unclear, the endpoint is only presented additionally.

The secondary endpoint assessed CIR measured by local immunoassays. As there is interference between methotrexate (MTX) and a metabolite when determining the MTX concentration with standard immunoassays, the detection of the MTX concentration by HPLC is preferable to evaluation by immunoassays up to 48 hours after glucarpidase administration. Therefore, the results of the secondary endpoint are not presented here.

Change in methotrexate concentration and change in sCr values

The endpoint of methotrexate concentration was determined in the studies at several time points before and after administration of glucarpidase by HPLC and local immunoassays and the change in methotrexate concentration after administration of glucarpidase compared to baseline was determined.
Both MTX and sCr concentrations are laboratory parameters and not per se patient-relevant. Therefore, the endpoints "change in MTX concentration" and "change in sCr values" are not used for the benefit assessment.

Rebound of the MTX concentration

In the studies, the endpoint "rebound of MTX concentration" was operationalised as the number of patients who experienced a renewed increase in MTX concentration (defined as 2-times the minimum MTX concentration or increase in MTX concentration above 1 µmol/l post-glucarpidase) after a decrease in MTX concentration after glucarpidase administration.
A rebound of the MTX concentration in patients who had reached a threshold value defined as clinically relevant is already indirectly covered by the presentation of the primary endpoint of the 001, 002, 003 and 006 studies "CIR of the MTX concentration", as this endpoint also only included patients who were also able to maintain this value after reaching the threshold value of ≤ 1 µmol/l. Against this background, the endpoint "rebound of MTX concentration" is not used for the benefit assessment.

Quality of life
Data on quality of life were not assessed in the studies.

Side effects
Adverse events (AEs) and serious adverse events (SAEs) were recorded in the 001, 002, 003 and 006 studies in the period between glucarpidase administration and 30 days after glucarpidase administration. In the 017 study, AEs were recorded up to 7 days after the last glucarpidase dose and SAEs up to 30 days after the last glucarpidase dose in patients receiving glucarpidase (study arm A).
About 61% of patients had AEs of severity grade ≥ 3 and about 43% of patients had SAEs. The AEs of special interest were type I hypersensitivity reactions in three patients (002 and 006 studies) and type III hypersensitivity reactions in two patients (002 study). In the 001, 003 and 017 studies, no data on these endpoints are available on the target population. The study documents show that in the pooled total population (safety population) of the 001, 002, 003, 006 and 017 studies, AEs of special interest (type I to III hypersensitivity reactions) occurred in 31 (6.4%) of the patients.

Overall assessment

Based on the pivotal target population of the single-arm PR001-CLN-001, 002, 003, 006 and 017 studies, results for mortality, morbidity and side effects are available for glucarpidase to reduce toxic plasma methotrexate concentrations in adults, adolescents and children 28 days of age and older with delayed elimination of methotrexate or at risk of methotrexate toxicity.

No data are available for comparative assessment due to the single-arm design of the studies. Thus, quantification of the extent of the additional benefit is not possible on the basis of the data presented.

In the overall assessment, a non-quantifiable additional benefit is identified for glucarpidase to reduce toxic plasma methotrexate concentrations in adults, adolescents and children aged 28 days and older with delayed elimination of methotrexate or at risk of methotrexate toxicity, since the scientific data does not allow quantification.

Significance of the evidence

For the 001, 002, 003, 006 and 017 studies presented, there is a high risk of bias at study level due to the single-arm, open-label study design, thus not allowing a comparative assessment.

Against this background, the reliability of data is classified under the "hint" category.

2.1.3 Summary of the assessment

In the present benefit assessment of the new medicinal product Voraxaze with the active ingredient glucarpidase, the therapeutic indication assessed here is "adults, adolescents and children aged 28 days and older with delayed elimination of methotrexate or at risk of medicinal product toxicity". Voraxaze was approved under "exceptional circumstances" as an orphan drug.

The 5 single-arm PR001-CLN-001, 002, 003, 006 and 017 studies are considered for the benefit assessment of glucarpidase.

Data on mortality, morbidity and adverse events are available; data on quality of life were not collected.

No data are available for comparative assessment due to the single-arm design of the studies. Thus, quantification of the extent of the additional benefit is not possible on the basis of the data presented.

In summary, for glucarpidase to reduce toxic plasma methotrexate concentrations in adults, adolescents and children 28 days of age and older with delayed elimination of methotrexate or at risk of methotrexate toxicity, a hint for a non-quantifiable additional benefit is derived since the scientific data does not allow quantification.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance.

The stated range of approx. 90 to 440 patients is subject to uncertainties. The range is considered to be likely underestimated, as there are uncertainties in particular regarding the

number of clinics with a need for glucarpidase estimated by the pharmaceutical company and the estimated number of cases per clinic.

2.3 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.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 September 2022).

The recommended dose of glucarpidase is a single dose of 50 units per kilogram (kg) of body weight (bw) as an intravenous (IV) bolus injection over 5 minutes.

For calculating the dosing range depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight of a child under 1 year = 7.6 kg and of adults = 77.0 kg).[7]

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Glucarpidase	Children under 1 year			
	Single dose	1	1	1
	Adults			
	Single dose	1	1	1

[7] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Glucarpidase	Children under 1 year				
	0.38 ml = 380 units	380 units	1 x 1,000 units	1	1 x 1,000 units
	Adults				
	3.85 ml = 3,850 units	3,850 units	4 x 1,000 units	1	4 x 1,000 units

Costs:
In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Glucarpidase 1,000 units	1 PSI	€ 33,764.37	€ 1.77	€ 1,925.00	€ 31,837.60
Abbreviations: PSI = powder and solvent for solution for injection					

LAUER-TAXE® last revised: 15 September 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g., regular laboratory services such as blood count tests) that do not exceed the standard

expenditure in the course of the treatment are not shown.

No additionally required SHI services are taken into account for the cost representation.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 12 April 2022, the pharmaceutical company submitted a dossier for the benefit assessment of glucarpidase to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15 July 2022 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 5 August 2022.

The oral hearing was held on 22 August 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 27 September 2022, and the draft resolution was approved.

At its session on 6 October 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	12 July 2022	Information of the benefit assessment of the G-BA
Working group Section 35a	17 August 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	22 August 2022	Conduct of the oral hearing
Working group Section 35a	31 August 2022 14 September 2022 21 September 2022	Consultation on the dossier assessment by the

		G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	27 September 2022	Concluding discussion of the draft resolution
Plenum	6 October 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 6 October 2022

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

Prof. Hecken