11 January 2022
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Voraxaze (glucarpidase)
Adjunctive treatment in patients at risk of methotrexate toxicity
EU/3/02/128
Sponsor: Serb

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance	Carboxypeptidase G2
Other name	--
International Non-Proprietary Name	Glucarpidase
Tradename	Voraxaze
Orphan condition	Adjunctive treatment in patients at risk of methotrexate toxicity
Sponsor's details:	Serb 40 Avenue George V 75008 Paris France
Orphan medicinal product designation procedural history	
Sponsor/applicant	Enact Pharma plc
COMP opinion	13 December 2002
EC decision	3 February 2003
EC registration number	EU/3/02/128
Post-designation procedural history	
Transfer of sponsorship	Transfer from Enact Pharma plc to Protherics Plc – EC decision of 15 December 2004
Sponsor's name change	Name change from Protherics Plc to BTG Management Services Limited – EC letter of 26 March 2015
Transfer of sponsorship	Transfer from BTG Management Services Limited to Protherics Medicines Development Europe B.V. – EC decision of 25 March 2020
Transfer of sponsorship	Transfer from Protherics Medicines Development Europe B.V. to Serb– EC decision of 5 July 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Ondřej Slanař / Ewa Balkowiec Iskra
Applicant	Protherics Medicines Development Europe B.V.
Application submission	12 June 2020
Procedure start	13 August 2020
Procedure number	EMA/H/C/005467
Invented name	Voraxaze
Proposed therapeutic indication	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. Further information on Voraxaze can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/voraxaze
CHMP opinion	11 November 2021

COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Bozenna Dembowska-Baginska / Elisabeth Johanne Rook
Sponsor's report submission	8 September 2020 and 22 April 2021
COMP discussion and adoption of list of questions	7-9 September 2021
Responses to list of questions	29 September 2021
COMP opinion (adoption via written procedure)	15 November 2021

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2002 designation was based on the following grounds:

- for the purposes of orphan designation, it was not considered appropriate to limit the indication to last line patients and a broader indication including all patients at risk of methotrexate toxicity was adopted: adjunctive treatment in patients at risk of methotrexate toxicity (hereinafter referred to as "the condition");
- the condition was estimated to be affecting approximately 0.3 in 10,000 persons in the Community at the time the application was made;
- the condition is life-threatening and chronically debilitating in particular due to the high mortality rate of the proposed condition and the severity of the clinical symptoms;
- although satisfactory methods of treatment of the condition have been authorised in the Community, justifications have been provided that Carboxypeptidase G_2 may be of significant benefit to those affected by the condition.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The sponsor got an orphan designation for adjunctive treatment in patients at risk of methotrexate toxicity.

Doses of 500 mg/m2 or higher given intravenously are defined as high-dose methotrexate (HDMTX) and are used to treat a variety of adult and paediatric cancers, including acute lymphocytic leukaemia (ALL), osteosarcoma, lymphomas and gastric cancer. HDMTX therapy can cause significant toxicity, which not only leads to morbidity and occasional mortality but may also interrupt cancer treatment, potentially leading to inferior anticancer outcomes. Patients with renal function impairment, volume depletion, acidic urine and using certain interacting co-medication are at risk for developing MTX-associated (nephro-) toxicity, due to impaired excretion of MTX. To prevent unacceptable toxicity, it

must be given with rigorously standardized supportive care, which differs across tumour types and treatment protocols. When patients experience delayed methotrexate excretion, without timely recognition and treatment, the prolonged exposure to toxic methotrexate concentrations can lead to significant morbidity and mortality.

Acute kidney injury impairs the renal clearance of methotrexate, resulting in the accumulation of toxic concentrations and an increased risk for additional adverse events. Prolonged renal dysfunction with increased systemic methotrexate exposure can cause myelosuppression, mucositis, hepatotoxicity, and, in severe cases, multiorgan failure. Emesis occurs in 10%–30% of patients receiving HDMTX even when appropriate antiemetics are used; in this subgroup, antiemetics should be escalated to completely control vomiting and additional hydration provided to replace lost fluid. Transient liver toxicity may include reversible chemical hepatitis in up to 60% and hyperbilirubinemia in 25% of courses, respectively. In up to 15% of HDMTX courses, patients report transient disturbances of the central nervous system (CNS), and a subset of these experience significant symptoms, such as cortical blindness, hemiparesis, and seizure.

The COMP designated this condition once in 2002 and there was a large gap between the time of the OD and this assessment of the maintenance of OD (more than 18 years). Marketing Authorisation Application (MAA) at the EMA for this product occurred also earlier in 2009 but was then withdrawn by the sponsor due to unresolved major objections. In 2020, the MAA was resubmitted.

The sponsor argued that the condition is still valid, and MTX toxicity (in the context of HDMTX therapy) is a distinct medical condition, based on its pathophysiological, histopathological and clinical characteristics. The current practice of the COMP is to not designate so-called iatrogenic disorders as an orphan condition. However, given that Orphan Designation for this condition was established by the EC in 2003, the validity of the orphan condition will not be re-assessed, as there have been no changes to classification system or other definitions of the condition. However, the condition is not considered suitable for future orphan designations.

The approved therapeutic indication "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" falls within the scope of the designated orphan condition "Adjunctive treatment in patients at risk of methotrexate toxicity".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The condition can be life-threatening as it is reported in the literature that overall mortality varied from 6.2% to 44.2% and mortality directly attributed to complications due to HDMTX ranged from 0 to 23.3%. Morbidity is associated with myelosuppression, mucositis, hepatotoxicity, gastrointestinal toxicity, nephrotoxicity and neurotoxicity which are more acute and not per se chronically debilitating. In severe cases multiorgan failure can occur which is life-threatening (*ClinicoEconomics and Outcomes Research 2019:11 129–144*).

Number of people affected or at risk

The sponsor has focused their prevalence estimate on patients who would be eligible for glucarpidase therapy in the treatment of high dose methotrexate toxicity namely two populations: those receiving

intrathecal methotrexate and patients with MTX toxicity as a result of delayed elimination. This leads to an overall final incidence estimate of 0.35 in 10,000.

The COMP discussed that the proposed incidence might be an under-estimate as the number of patients who are treated with high dose methotrexate appears to be significantly higher than what is proposed. In addition, the use of high dose methotrexate in the paediatric and adult populations does not appear to have been considered to any great extent. It would appear that the population at risk is much broader, as high and intermediate-high doses of methotrexate in a large number of disorders It has been highlighted in the literature that there is difficulty in quickly identifying the patients who could potentially have nephrotoxicity induced by high dose methotrexate. Many assumptions made by the Sponsor are difficult to verify and it would be helpful to understand how often Voraxaze is distributed and used on a "named patient basis" throughout the EU, and how often Voraxaze is used in the US, to get more insight in the prevalence.

The sponsor reconfirmed the calculation which included three data sources:

For the worst-case scenario, the maximum rate of toxicity from across all studies reporting this outcome was taken. These rates ranged from 0.1% (psoriasis, RA) to 77.8% (osteosarcoma) of patients developing delayed elimination and 0.05% (psoriasis, RA) to 77.8% (osteosarcoma) developing AKI (see sponsors submission addendum for more details). Of note, in both these analyses, a degree of double counting will have occurred, as the patients with delayed elimination overlap with those developing AKI.

However, it is noted that the rate of AKI and delayed elimination might have been underreported in the public literature. In general, safety is rarely systematically reported in the public literature on trials, or details are lacking. MTX is an old product, and adverse events may not be reported in detail, particularly if these are expected and already well-known. Therefore, the most conservative estimate of the sponsor was taken into consideration.

The real-world data from the US that were presented, where the product is marketed since 2013 for a similar indication, are of interest. It may be assumed that there are similarities in the use of MTX among the US and EU, given that MTX is a well-established treatment in oncology and auto-immune disorders. However, it is noted that there are other treatment options like Leucovorin (calcium folinate), and therefore the sales data do not fully represent the prevalence of the condition.

Assuming more conservatively an 100% MTX treatment rates and the highest published incidence and MTX toxicity rates, it was estimated by the sponsor that the most extreme scenario could mean that 3.303 per 10,000 people with Europe will need Voraxaze each year. The COMP accepted a final calculation of 3 per 10,000 as a reasonable prevalence estimate.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Currently in Europe, Leucovorin (calcium folinate) is authorised for use in high dose methotrexate toxicity, for the following wording of the indication: *Calcium folinate is used to diminish the toxicity and counteract the action of folic acid antagonists such as methotrexate in cytotoxic therapy and overdose*

in adults and children. In cytotoxic therapy, this procedure is commonly known as "Calcium Folinate Rescue".

There does not appear to be formal European guidelines for managing high dose methotrexate toxicity, but national guidelines are available in France, Germany, Spain and Italy and International Guidelines (Ramsey L et al, Oncologist 2018;23:52–61) according to the sponsor.

It is noted that successful management requires timely recognition of delayed methotrexate elimination and renal dysfunction. Rising serum creatinine concentration or decreased urine output after HDMTX indicates a medical emergency. Increased hydration, high dose leucovorin, and glucarpidase (when necessary) effectively reduce serum methotrexate concentrations and protect cells from methotrexate, but these measures must be administered as early as possible to prevent further toxicity, facilitate renal recovery, and allow patients to resume HDMTX therapy after normalization of renal function. (*The Oncologist 2016; 21:1471–1482).*

In case of MTX intoxication, dialysis may be applied.

Significant benefit

The sponsor notes that glucarpidase is used on a patient name basis in many European countries in the management of the condition and that the only product authorized is calcium folinate. The use of glucarpidase is recommended for the treatment of the condition in International Guidelines and the sponsor believes that an authorization of the product would improve access and treatment. This is acknowledged by the COMP.

It is recognized that calcium folinate has limitations as while it may help to protect cells at the intracellular level, it may be less effective in case of nephrotoxicity resulting from MTX and/or metabolite precipitation in the kidney (The Oncologist 2018;23:52–61). Leucovorin provides an exogenous source of tetrahydrofolate to replace the intracellular pool inhibited by MTX, but does not reduce the amount of circulating MTX, in contrast to glucarpidase. When MTX concentrations remain high, (nephro-) toxicity may still occur because Leucovorin cannot compete effectively with MTX for transport into cells.

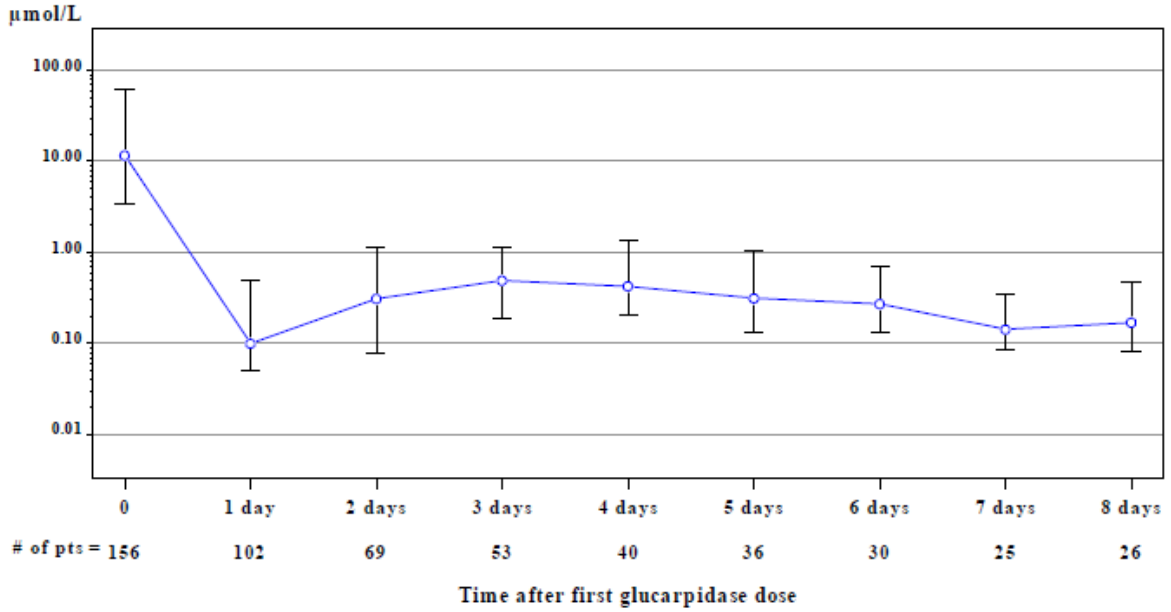
As the treatment of nephrotoxicity is not addressed by calcium folinate, the use of glucarpidase would offer a clinically relevant advantage in treating this aspect of high dose methotrexate toxicity thereby offering a significant benefit in the management of these patients.

The efficacy of glucarpidase has been evaluated in four open-label multi-centre, single-arm, compassionate-use clinical trials in patients with delayed MTX elimination due to renal dysfunction (001, 002, 003 and 006).

Table 1.

001 Germany	Compassionate use, single arm, open label, multicentre	Delayed MTX elimination secondary to MTX-induced renal dysfunction 10–78 years	Efficacy and safety of glucarpidase	IV glucarpidase 50 U/kg; up to 2 doses based on MTX concentration	44 patients
002 Nine countries in North America, Europe, Israel and Australia	Compassionate use, single arm, open label, multicentre	Delayed MTX elimination secondary to MTX-induced renal dysfunction 0–82 years	Efficacy and safety of glucarpidase +/- thymidine	IV glucarpidase 50 U/kg (1–3 doses); IV thymidine 8 g/m^2/day	214 patients
003 13 countries in Europe and Israel	Compassionate use, single arm, open label, multicentre	Delayed MTX elimination secondary to MTX-induced renal dysfunction 0–71 years	Efficacy and safety of glucarpidase	IV glucarpidase 50 U/kg; single dose with optional 2nd dose	69 patients
006 United States, Australia and Canada	Compassionate use, single arm, open label, multicentre	Delayed MTX elimination secondary to MTX-induced renal dysfunction 2–84 years	Efficacy, pharmaco-dynamics and safety of glucarpidase	IV glucarpidase 50 U/kg; single dose with optional 2nd dose based on MTX concentration	149 patients

Figure 1. MTX Concentration within the first eight days following treatment with glucarpidase – central MTX HPLC population (median with 25th and 75th percentiles)



The primary endpoint in the clinical trials was referred to as a 'clinically important reduction (CIR)' in MTX concentration and was based on central HPLC data. A patient was considered to have achieved a CIR if all central MTX plasma concentrations (analyzed by HPLC , high precision liquid chromatography) after the first dose of glucarpidase were ≤1 µmol/L. A CIR was achieved by 61.5% (95% confidence interval [CI]: 54.0% to 68.5%) of patients in the pooled studies population that was sustained for up to 8 days.

Furthermore, from the 410 patients in the pooled Renal Evaluable Population (patients who had at least one post-glucarpidase renal function assessment) who developed serum creatinine common toxicity criteria Grade ≥2 at pre-glucarpidase baseline, 262 (63.9%) recovered to Grade 0 or 1. In the Renal Evaluable Population there was a 3.5-fold increase in mean serum creatinine (sCr) concentration from pre-MTX to pre-glucarpidase baseline (0.79 mg/dL to 2.79 mg/dL). After administration of glucarpidase, sCr continued to rise (mean increase of 0.24 mg/dL over three days), then began to decrease. The mean sCr value at Day 22 was 1.27 mg/dL. For the 258 patients for whom days to recovery could be calculated, the median time to recovery was 12.5 days (range 1–213 days).

Significant benefit versus Leucovorin (calcium folinate)

The sponsor Protherics requested protocol assistance (PA) from the Scientific Advice Working Party (SAWP)/ Committee for Medicinal Products for human use (CHMP) in 2007 (EMEA/H/SA/1013/1/2007/PA/II) and in 2012 (EMEA/H/SA/1013/1/FU/1/2012/PA/II), relating to the uncontrolled study design, and the concern in the original MAA assessment that the clinical benefit of a reduction in plasma MTX was unclear.

In their Scientific Advice, the CHMP agreed that a comparative clinical trial of standard of care versus glyceridase was not feasible. So indirect comparisons to historic data with SoC would be relevant for establishing the clinical relevance of the treatment effect and significant benefit. Not mentioned by the sponsor in the maintenance report, but discussed in the CHMP assessment report, is a comparison with historic controls of patients with high MTX levels at baseline, who were treated with SoC Leucovorin (Flombaum, 1999 (N=13) and Flombaum 2018 (N=88)). The CIR response is 0-18% in the study cohorts by Flombaum, which is considerably lower than reported for Voraxaze (responder rates of about 60%, see table below). The historical data were not reported in sufficient detail to allow matched comparisons. Nevertheless, it may be considered as supportive evidence.

Table 2. Comparison of Central HPLC Cohort and Flombaum (historical control) Cohorts

Measurement	Module 2.7.3	001	002	003	006	Flombaum 1999	Flombaum 2018
Baseline* MTX (µmol/L)	11.7	4.8	24.8	6.4	37.1	16.3	6.9
CIR % (95% CI)	61.5 (54.0, 68.5)	85.7 (68.5, 94.3)	54.8 (44.2, 65.0)	66.7 (48.8, 80.8)	51.9 (34.0, 69.3)	0 (0, 24.7)	19** (11.8, 28.1)

*Median value for the most recent MTX level prior to glucarpidase for the central MTX HPLC population or the 48h MTX level for Flombaum cohorts
** Upper bound based on a calculated 20th percentile of 1.05 µmol/L interpolated from the reported 25th percentile of 1.3 µmol/L, assuming equal distribution for the lowest 25% of patients.
Source: Module 2.7.3 Table 10, Table 1.4.1.1; Study 001 Table 14.2.4, Table 14.7.1; Study 002 Table 14.2.3, Table 14.7.1; Study 003 Table 14.2.1.3, Table 14.6.1; Study 006 Table 14.2.3, Table 14.7.1.

Table 3. Comparison of Local MTX Assay Cohort and Flombaum (historical control) Cohorts

Measurement	Module 2.7.3	001	002	003	006	Flombaum 1999	Flombaum 2018
Baseline* MTX (µmol/L)	12.8	8.0	18.4	10.7	27.3	16.3	6.9
24h MTX ≤1 µmol/L % (95% CI)	57.6 (52.8, 62.2)	69.0 (53.9, 80.9)	46.8 (39.8, 53.9)	60.3 (47.4, 71.9)	52.2 (43.8, 60.5)	0 (0, 24.7)	19** (11.8, 28.1)

*Median value for the most recent MTX level prior to glucarpidase for the Local MTX cohort or the 48h MTX level for Flombaum cohorts
** Upper bound based on a calculated 20th percentile of 1.05 µmol/L interpolated from the reported 25th percentile of 1.3 µmol/L, assuming equal distribution for the lowest 25% of patients
Source: Module 2.7.3 Table 6 and 10, Table 1.4.4.1; Study 001 Table 14.2.4, Table 14.7.1; Study 002 Table 14.2.3, Table 14.7.1; Study 003 Table 14.2.1.3, Table 14.6.1; Study 006 Table 14.2.3, Table 14.7.1.

Not mentioned by the sponsor, but relevant for establishing the Significant Benefit, is that Voraxaze showed efficacy while it was administered on top of standard of care in HDMTX. Consistent with general recommendations, patients were treated with IV hydration, adequate diuresis and alkalinization (to maintain urinary pH >7.5) prior to the start of HDMTX therapy. Calcium folinate was also provided according to SoC in most studies, but with a dose interval of 2-4 hrs after glucarpidase.

The sponsor has provided data which support the effect of glucarpidase on nephrotoxicity induced by high dose methotrexate, an aspect of the condition not treated with the currently authorised product.

4. COMP position adopted on 15 November 2021

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of adjunctive treatment in patients at risk of methotrexate toxicity (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 3 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating in particular due to the high mortality rate of the proposed condition and the severity of the clinical symptoms;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Voraxaze may be of potential significant benefit to those affected by the orphan condition still holds. It has been shown that glucarpidase rapidly induces a reduction in serum MTX concentration below the target of ≤1 µmol/L an aspect of the condition not treated with the currently authorised product.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Voraxaze, carboxypeptidase G2, glucarpidase for adjunctive treatment in patients at risk of methotrexate toxicity (EU/3/02/128) is not removed from the Community Register of Orphan Medicinal Products.