CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125327Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology - BLA Filing Memo

BLA:	**STN 125327/004-006 Original Submission**	**INDs: 11,557; 11,630; 04663**
Product:	**Voraxaze® (Glucarpidase); Lyophilized powder containing 1,000 Units of glucarpidase in single-use vials**	
Sponsor:	**BTG International Inc.**	
Filing Date:	**September 8, 2011**	
Reviewer:	**Lillian Zhang, Ph.D.**	

Background and Mechanism of action: This rolling submission is the original BLA for Voraxaze® (glucarpidase) for the (b) (4) reduction of toxic methotrexate (MTX) levels due to impaired renal function. Voraxaze® is a recombinant bacterial enzyme with a molecular weight of 83 kilo Daltons. Voraxaze® hydrolyzes the N-carboxyl terminal glutamate of folate-related molecules such as MTX by converting MTX to its inactive metabolites 4-deoxy-4-amino-N10-methylpteroic acid (DAMPA) and glutamate. Because both DAMPA and glutamate are metabolized by the liver, treatment with glucarpidase, therefore, provides an alternate route of MTX clearance in patients with impaired renal function who are unable to clear MTX efficiently.

Because of its large molecular size, glucarpidase does not cross the blood-brain barrier or cellular membranes. Therefore, administration of the rescue agent, leucovorin (LV), is still required to counteract the cellular damage caused by MTX.

Formulation: Voraxaze® is supplied as a sterile, white, lyophilized powder in single-use vials. Each vial contains 1,000 Units of glucarpidase that requires reconstitution prior to use with 1 mL of sterile normal saline.

The recommended dose of Voraxaze® is a single intravenous (IV) injection of 50 units/kg, (b) (4)t
(b) (4)

Clinical Studies: Among the nine clinical studies contributed key data to this BLA, four clinical studies (Studies 001, 002, 003 and 006) are used to support efficacy and safety of glucarpidase in patients who received glucarpidase as compassionate use treatment due to delayed MTX elimination in the presence of renal impairment (see Table 1).

Clinical Pharmacology Review

BLA	STN 125327
Submission Type	BLA-NME
Submission Date(s) (Rolling Submission)	11/17/08; 4/30/09; 5/10/10; 9/29/10; 12/16/10; 6/30/11; 7/18/11
Review Classification	Priority (Orphan Indication, Fast Track Designation)
PDUFA Due Date	1/17/12
Brand Name	VORAXAZE®
Generic Name	Glucarpidase
Proposed Indication	For the treatment of toxic plasma methotrexate concentrations due to impaired renal function through the (b) (4) reduction of methotrexate concentrations
Formulation	Lyophilized powder containing 1,000 units of glucarpidase in single-use vials to be reconstituted with 1 mL of sterile normal saline
Proposed Dosing Regimen	A single dose of 50 Units/kg by intravenous injection over 5 minutes, (b) (4) . (b) (4)
Related INDs	11,557; 11,630; 04663
Sponsor	BTG International, Inc.
OCP Reviewer	Lillian H. Zhang, Ph.D.
OCP Team Leader	Hong Zhao, Ph.D.
OCP Division	Division of Clinical Pharmacology 5 (DCP5)
Clinical Division	Division of Oncology Products 2 (DOP2)

List of Tables

List of Figures

1 EXECUTIVE SUMMARY

Glucarpidase is a recombinant bacterial carboxypeptidase that hydrolyzes the carboxyl-terminal glutamate residue from folic acid and classical antifolates such as methotrexate (MTX). The current original BLA submission is for glucarpidase for the proposed indication of the treatment of toxic plasma MTX concentrations due to impaired renal function through the (b) (4) reduction of MTX concentrations.

Efficacy of glucarpidase was studied in a single-arm trial in patients who had markedly delayed MTX clearance secondary to renal dysfunction and received a single dose 50 Units/kg glucarpidase as an intravenous (IV) injection over 5 minutes. The clinical endpoint was defined as the proportion of patients who achieved a rapid and sustained clinically important reduction (RSCIR) in plasma MTX concentration (measured by a chromatographic method) to ≤1 µmol/L at 15 minutes and sustained for up to 8 days following glucarpidase administration. With 22 patients eligible for the efficacy analysis, 10 patients achieved RSCIR [45.5% (95% CI: 26.9, 65.3%)] following glucarpidase injection. The MTX concentration was reduced by ≥97% within 15 minutes in all 22 patients, and was maintained >95% reduction up to 8 days in 20 of the 22 patients. An exploratory analysis identified that the pre-glucarpidase MTX concentration is associated with the likelihood of attaining RSCIR. In the trial, patients with pre-glucarpidase MTX concentrations >100 µmol/L were eligible to receive a second dose of 50 Units/kg 48 hours after the first dose; however no patients achieved RSCIR after the second dose of glucarpidase. Therefore, a second dose of glucarpidase (b) (4) is not recommended. Since none of the patients included in the efficacy dataset had a dose capped at (b) (4) the dose should not be capped at 2,000 units.

Administration of leucovorin (LV) is still necessary to protect normal cells from MTX toxicity because glucarpidase cannot counteract the intracellular antineoplastic effects of high dose MTX. Therapy with LV should be continued according to the LV prescribing information for delayed MTX elimination. Because LV is also a substrate of glucarpidase and a pharmacokinetic interaction between glucarpidase and LV was observed, LV should not be administered within 2 hours before or after glucarpidase injection.

A total of 17% of patients in clinical studies developed anti-glucarpidase antibodies (AGAs). However, an impact of immunogenicity on glucarpidase pharmacodynamics (PD) was not observed in the registration trial. Due to a short elimination half-life ($t_{1/2}$ 5.7 to 9 hours) of glucarpidase relative to the time needed for AGA formation, the impact of immunogenicity on its pharmacokinetics (PK) is not anticipated.

In clinical trials, the most common adverse events (occurring in >1% of patients) associated with glucarpidase were paraesthesia, flushing, nausea and/or vomiting, hypotension and headache.

1.1 RECOMMENDATIONS

This BLA is acceptable from a clinical pharmacology perspective provided that the Applicant and the Agency come to an agreement regarding the labeling language. The Office of Clinical Pharmacology recommends approval of this BLA.

1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS

There are no clinical pharmacology requested PMRs or PMCs.

Signatures:

12/21/2011

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DCP5: Reviewers – **LH Zhang**; TL – **H Zhao**; Division Deputy Director – **B Booth**; Division Director - **A Rahman**

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

***Product Property and Mechanism of Action*:** Glucarpidase recombinantly produced in *Escherichia coli* is a 390-amino acid homodimer protein with a molecular weight of 83 kDa. Glucarpidase converts methotrexate (MTX) to its inactive metabolites 4-deoxy-4-amino-N^{10}-methylpteroic acid (DAMPA) and glutamate. Because both DAMPA and glutamate are metabolized by the liver, glucarpidase provides an alternate non-renal pathway for MTX elimination in patients with renal dysfunction during high-dose (HD) MTX treatment.

***Clinical Study Design*:** Glucarpidase is being developed as a rescue agent to reduce toxic plasma MTX concentrations in patients with renal dysfunction during HDMTX treatment. The proposed dose regimen is a single intravenous injection of 50 Units/kg over 5 minutes, (b) (4) (b) (4) . The efficacy was evaluated in a single arm trial conducted by the National Cancer Institute (NCI) in which the pharmacodynamic (PD) endpoint of achieving and maintaining MTX levels ≤1 μmol/L in a proportion of patients treated with glucarpidase was used as a surrogate for clinical benefit. Following the administration of glucarpidase, plasma MTX concentrations were measured using a chromatographic method (HPLC) at 15 minutes, 1 and 2 hours, and daily for a total of 8 days. As DAMPA (mean $t_{1/2}$ ~ 9 hours) interferes with the immunoassays used to measure MTX concentrations, plasma MTX concentrations within 48 hours following administration of glucarpidase can only be reliably measured by an HPLC method.

***Efficacy Results*:** Among the 149 patients treated with glucarpidase in the trial, the clinical endpoint, RSCIR, was achieved in 10 of the 22 patients [45.5% (95% CI: 26.9, 65.3%] who met the trial inclusion criteria: having a pre-glucarpidase MTX concentration >1 μmol/L and plasma MTX samples measured by the chromatographic method. An exploratory analysis revealed that none of the patients with pre-glucarpidase MTX level >50 μmol/L achieved RSCIR. Of the 12 patients who failed to achieve RSCIR, five patients (22.7%) attained a transient plasma MTX concentration of ≤1 μmol/L; but had a rebound with the median time to reach a plasma MTX concentration >1 μmol/L after attainting a level of ≤1 μmol/L occurring between 2 and 3 days, and the median increase of plasma MTX concentration from their nadir of 1.4 μmol/L (0.34 to 2.5 μmol/L). Among six patients who met the protocol specified second dose criteria (pre-1st dose glucarpidase MTX concentrations >100 μmol/L) received a second 50 Units/kg dose of glucarpidase administered 48 hours after the first dose; however, none of the patients who met the (b) (4) second dose criteria (MTX concentrations >1 μmol/L after the first dose) achieved RSCIR. Therefore, the (b) (4) second dose is not supported by the efficacy data submitted. In addition, none of the patients in the efficacy dataset was dosed cap to 2,000 Units per dose.

***Pharmacokinetics*:** Glucarpidase pharmacokinetics (PK) were studied in healthy subjects in the absence of MTX and PK data was collected in only two patients with HDMTX treatment. Following single administration of glucarpidase 50 Units/kg, the serum concentration of glucarpidase declined in a monophasic manner with clearance comparable between the two patients and the healthy subjects except that the half-life appeared shorter in the patients (~3.5 hours by the enzymatic method, ~3.0 hours by ELISA) than that observed in the healthy subjects (~5.6 hours by the enzymatic method, ~9.0 hours by ELISA).

Renal Impairment: No dose adjustment for glucarpidase in patients with renal impairment is necessary. Following an intravenous injection of glucarpidase 50 Units/kg in subjects with severe renal impairment (creatinine clearance <30 mL/min) in the absence of MTX, the mean PK parameters were similar to those observed in healthy subjects except for a longer $t_{1/2}$ of 8.2 hours as compared to 5.6 hours in healthy subjects by the enzymatic assay.

Concomitant Leucovorin (LV) Therapy: LV, an active, chemically reduced derivative of folic acid, is used to counteract the cellular damage caused by HDMTX. As glucarpidase does not cross the cellular membranes, in clinical practice glucarpidase would almost invariably be given to patients concomitantly receiving LV as a rescue agent for HDMTX therapy. Therapy with LV should be continued according to its prescribing information for delayed MTX elimination; however, LV should not be administered within 2 hours before or after a dose of glucarpidase due to its PK interaction with glucarpidase. In a study of cancer patients receiving HDMTX and LV rescue regimen, administration of 50 Units/kg glucarpidase 2 hours before LV reduced $AUC_{0\text{-}3h}$ of (6S)-LV by 33% and C_{max} by 52%, and also reduced $AUC_{0\text{-}3h}$ of LV active metabolite, (6S)-5-methyl-tetrahydrofolate, by 92% and C_{max} by 93%.

Immunogenicity: In clinical studies, 16 of 96 evaluable patients (16.7%) had treatment-emergent anti-glucarpidase antibodies (AGAs) detected at one or more time points ranging from day 7 to month 7 following exposure to glucarpidase. Twelve of the 16 patients who developed AGAs had received a single dose of glucarpidase and the remaining four patients had received two doses of glucarpidase. However, an impact of immunogenicity on glucarpidase PD was not observed in the registration trial as a ≥97% reduction in plasma MTX concentration at 15 minutes occurred in all of the 22 patients included in the efficacy dataset. In addition, an impact of immunogenicity on glucarpidase PK is not anticipated due to a short $t_{1/2}$ of glucarpidase relative to the time needed for AGA formation.

Safety profile: Overall, glucarpidase-related toxicities appear to be mild to moderate in severity. The most common related adverse events (occurring in >1% of patients) associated with glucarpidase were paraesthesia, flushing, nausea and/or vomiting, hypotension and headache.

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTITES

What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

The clinical development of glucarpidase in the United States (US) began in 1992. It was initially supplied on a compassionate-use basis by NCI under a Special Exception Program (NSC #641273; IND 4663). The manufacturer for the initial clinical supply of glucarpidase was the Center for Applied Microbiology and Research [CAMR; United Kingdom (UK)].

In 2002, glucarpidase was acquired by Enact Pharma, which continued to supply the product via the NCI on a compassionate-use basis. In 2003, Protherics took over the development of glucarpidase and subsequently transferred manufacture of glucarpidase, using a re-derived Master Cell Bank, to two contract manufacturing organizations, Eurogentec SA for the formulated bulk product and Cangene Corporation for the finished product. In June 2004, the NCI began supplying glucarpidase manufactured by Protherics' contractors under a new NSC #732443 (IND 11630). Protherics was acquired by BTG International in 2008, and BTG has

continued the development of glucarpidase since then. Manufacture of the finished product was moved to Cangene bioPharma Inc. (CBI; US) in 2009. BTG continues to supply glucarpidase on a compassionate use basis under IND 11557.

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology review?

VORAXAZE contains an enzyme, glucarpidase, that is recombinantly produced in *Escherichia coli*. Glucarpidase is a 390-amino acid homodimer protein with a molecular weight of 83 kDa. VORAXAZE is supplied as a sterile, preservative-free, lyophilized powder in single-use vials. Each vial contains 1,000 Units of glucarpidase requiring reconstitution with 1 mL of sterile normal saline prior to use. Each potency unit corresponds to the enzymatic cleavage of 1 µmol/L of MTX per minute at 37°C.

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Glucarpidase is a recombinant bacterial carboxypeptidase that hydrolyzes the carboxyl-terminal glutamate residue from folic acid and classical antifolates such as MTX. MTX is primarily excreted via the renal route. Delayed elimination of MTX in patients suffering from renal dysfunction can result in fatal MTX toxicity. Glucarpidase converts MTX to its inactive metabolites 4-deoxy-4-amino-N^{10}-methylpteroic acid (DAMPA) and glutamate. Because both DAMPA and glutamate are metabolized by the liver, glucarpidase provides an alternate non-renal pathway for MTX elimination in patients with renal dysfunction during HDMTX treatment.

The proposed indication of glucarpidase is for the treatment of toxic plasma MTX concentrations due to impaired renal function through the (b) (4) reduction of MTX concentrations.

2.1.3 What are the proposed dosage and route of administration?

Glucarpidase is proposed to be given as a single intravenous injection of 50 Units/kg over 5 minutes, (b) (4)

(b) (4)

(b) (4)

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The efficacy claim of glucarpidase in the proposed patient population was supported by the data from a single-arm, open-label, multicenter, compassionate use trial PR001-CLN-006 conducted

by NCI. In this submission, the Applicant also submitted reports for glucarpidase compassionate-use trials PR001-CLN-001, PR001-CLN-002, and PR001-CLN-003 to provide additional supportive efficacy and safety information. Trial 002 was conducted by NCI prior to BTG's involvement, and trials 001 and 003 were primarily European studies. Patients in these three trials received glucarpidase manufactured using CAMR Lot 004 that was made by CAMR for the initial clinical supply of glucarpidase. In Trial 006, patients received glucarpidase manufactured using lots that were made by Protherics and are representative of the proposed commercial product. Since CAMR Lot 004 did not demonstrate bioequivalence to the proposed commercial lot in a PK study in rabbits, studies utilizing the CAMR Lot 004 product are not considered by the FDA as providing evidence of the efficacy or safety of glucarpidase in this application. Therefore, this review only focuses on Trial 006 hereafter. The design feature of Trial 006 is summarized in the table below:

Table 1 Summary of Study Design of Trial PR001-CLN-006

Study Description	Single arm, open label, multicenter, compassionate use
Objectives	Efficacy and safety
Patient Population	HDMTX treated patients experiencing delayed MTX elimination due to impaired renal function
Treatment	• Glucarpidase 50 Units/kg single dose IV over 5 minutes; • Patients with plasma MTX concentrations >100 μmol/L immediately prior to the 1st glucarpidase dose were eligible for a 2nd dose of 50 Units/kg; • Starting from November 2005, the maximum total dose of glucarpidase was capped at 2000 U, irrespective of body weight.
No. of Patients	• N = 184 total enrolled; • N = 149 in safety population; • N = 27 with plasma MTX concentrations measured by a central chromatographic method

The primary objective of the study was to evaluate the effect of glucarpidase in reducing toxic plasma MTX concentrations. Plasma samples collected at 15 minutes, 1 and 2 hours, and daily up to 8 days following glucarpidase administration were measured for MTX concentrations using a chromatographic (HPLC) method. As DAMPA (mean $t_{1/2}$ ~ 9 hours) interferes with the immunoassays used to measure MTX concentration in most clinical laboratories, plasma MTX concentrations within 48 hours following administration of glucarpidase can only be reliably measured by an HPLC method.

The protocol specified that patients continue receiving intravenous hydration, urinary alkalinization and leucovorin (LV), and that LV administration be adjusted to assure it is not administered within 2 hours before or after glucarpidase due to an observed PK drug-drug interaction between glucarpidase and LV (see in Section 2.4.2.5).

Additional Clinical Trials

Table 2 summarizes five additional clinical trials that provide data on PK, drug interactions, immunogenicity and safety of glucarpidase.

Table 2 Other Clinical Trials Contributing Data to the BLA

Study No	Study description, Population	Objectives	Treatment	No. of Subjects
Completed Pharmacokinetic and Interaction Studies				
PR001-CLIN-005	Phase 1, open label, single site, PK study Healthy subjects or subjects with impaired renal function	Glucarpidase PK	Single IV glucarpidase 50 U/kg	N = 8 healthy subjects N = 4 subjects with severely impaired renal function
PR001-CLIN-010	Phase 1, two-period, randomized, double blind, placebo controlled crossover study Healthy male subjects	Effect of glucarpidase on the PK of LV	Single IV glucarpidase 50 U/kg or placebo; LV q6hr x 5 doses IV 150 mg/m^2	N = 6
PR001-CLIN-017	Phase 1, open label, 2-arm multicenter interaction study Patients receiving HDMTX Arm A Delayed MTX elimination Arm B Normal MTX elimination	Effect of glucarpidase on the PK of LV	Arm A IV glucarpidase 50 U/kg plus LV Arm B LV	N = 11 Arm A N = 9 Arm B
Terminated Controlled Intervention Study				
PR001-CLIN-012	Phase 2, randomized, blinded, placebo controlled crossover study with an unblended compassionate use arm Patients treated with high dose MTX and LV	Effect of glucarpidase on successful advancement to next chemotherapy cycle at the scheduled time	IV glucarpidase 50 U/kg or placebo	Randomized: N = 4 enrolled; N = 2 treated Compassionate use: N = 5 (glucarpidase PK available in 2 patients)
Ongoing Uncontrolled Intervention Study				
PR001-CLIN-016	Open label, single arm, multicenter expanded access study Delayed MTX elimination due to MTX induced renal dysfunction	To provide compassionate use access to glucarpidase	Single IV glucarpidase 50 U/kg	N = 141 no PK sampling, provide safety, immunogenicity data

For simplicity, the last three characters of each trial's ID are used to represent the trial hereafter.

2.2.2 *What is the basis for selecting the clinical endpoint or surrogate and how are they used to assess efficacy in the pivotal clinical study? What is the clinical outcome in terms of efficacy and safety?*

Primary Clinical Endpoint: The primary clinical endpoint in Trial 006 was defined as the proportion of patients who achieved a rapid and sustained clinically important reduction (RSCIR) in plasma MTX concentration, defined as an attainment of plasma MTX concentration ≤1 μmol/L by a central laboratory chromatographic method (HPLC) at 15 minutes and sustained up to 8 days following glucarpidase administration.

Toxic plasma MTX concentrations due to its delayed elimination in patients with renal dysfunction post HDMTX treatment are potentially fatal. In clinical practice, concentrations of MTX ≤1 μmol/L are considered below the level associated with severe MTX toxicity. Therefore, the proposed pharmacodynamic (PD) endpoint is considered as a reasonable surrogate for clinical benefit.

As the majority of the patients in the trial received a single dose of glucarpidase, the results presented below refer to the data obtained following the 1st dose administration of glucarpidase. The effectiveness of the 2nd dose of glucarpidase is discussed in Section 2.2.3.

The Applicant's efficacy analysis is based on data from a total of 27 patients who had at least 1 post-glucarpidase MTX concentration measured by an HPLC method following glucarpidase administration. FDA's analysis excludes five patients who either did not meet the inclusion criteria for the trial or had a pre-glucarpidase MTX concentration ≤1 μmol/L. The primary efficacy results analyzed by the FDA and the Applicant are presented in Table 3. Based on the FDA analysis, 45.5% of patients achieved a RSCIR after treatment with a single dose of glucarpidase.

Table 3 Summary of the Primary Efficacy Results

	FDA Assessment	Applicant Assessment
No. of Patients	22	27
Patients Achieving RSCIR n [% (95% CI)]	10 [45.5 (26.9, 65.3)]	14 [51.9 (34.0, 69.3)]

Secondary Efficacy Endpoint: The secondary clinical endpoint is rebound of plasma MTX concentration following glucarpidase administration. Rebound was defined by the Applicant as an increase in MTX concentration following a post-glucarpidase decrease in plasma MTX concentration, where:

- The post-Voraxaze MTX concentration at time t_n was >2 times the nadir post-glucarpidase MTX concentration prior to time t_n; *and*
- The increase of MTX concentration at time t_n from the nadir prior to t_n was >1 μmol/L.

Based on the clinical relevance, the FDA simplified the definition of rebound as plasma MTX concentration became >1 μmol/L after attaining a level of ≤1 μmol/L following glucarpidase administration. Results of rebound analysis performed by the FDA are shown in the table below:

Table 4 Summary of the Secondary Efficacy Results

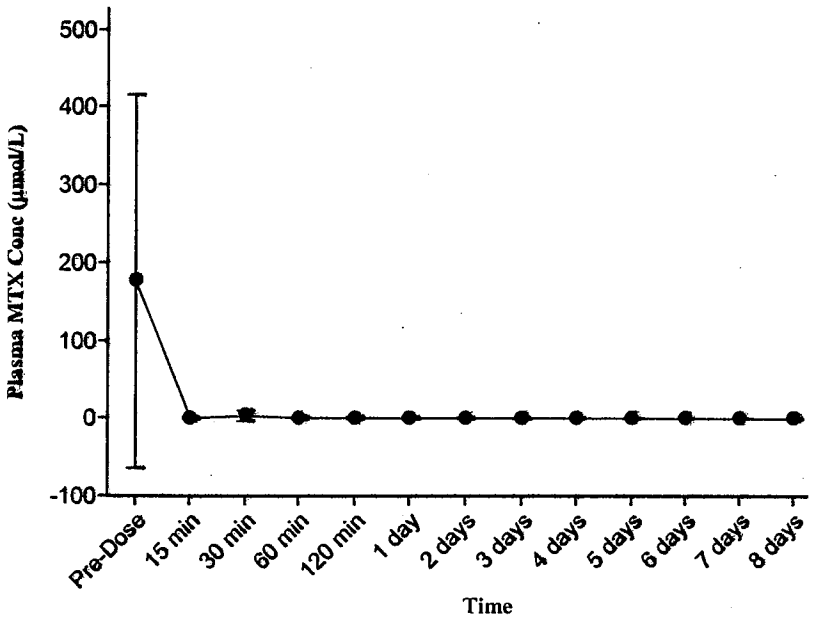
Proportion of patients with rebound (95 CI%)	22.7 % (10.1%, 43.4%)
Median increase of MTX concentration from nadir (Min, Max)	1.4 (μmol/L) (0.3, 2.5)
Median time to rebound (Min, Max)	63.3 (hrs) (2.0, 194.3)

Five (22.7%) of the 12 patients who failed to achieve RSCIR attained a transient plasma MTX concentration of ≤1 μmol/L. In these 5 patients, the median time for rebound occurred between 2 and 3 days and the median increase of plasma MTX concentration from their nadir was 1.4 μmol/L (0.3 to 2.5 μmol/L).

Exploratory Analyses

Percent Reduction in Plasma MTX Concentrations over Time: Plasma MTX concentrations were reduced by ≥97% within 15 minutes in all 22 treatment-evaluable patients, and maintained >95% reduction up to 8 days in 20 of the 22 patients following the first dose administration of 50 Units/kg glucarpidase (see Figure 1).

Figure 1 Mean Plasma MTX Concentration (SD) *vs* Time Profile



Based on the limited number of patients in the efficacy dataset, the reviewer conducted an exploratory analysis assessing the potential factors including age, body weight, tumor type, MTX dose administered, total first dose of glucarpidase, pre-glucarpidase plasma MTX concentration, and pre-glucarpidase creatinine clearance on the achievement of RSCIR. Among those factors, age, tumor type, and pre-glucarpidase MTX concentration showed the trend in affecting the achievement of RSCIR.

Age and Tumor Type: In Study 006, the most common underlying cancers were osteogenic sarcoma (50%) and acute lymphoblastic leukemia (ALL) or lymphoma (45%). The majority of the osteogenic sarcoma patients were children. Patients with osteogenic sarcoma received a higher median dose of MTX and had a higher pre-glucarpidase MTX concentration than those

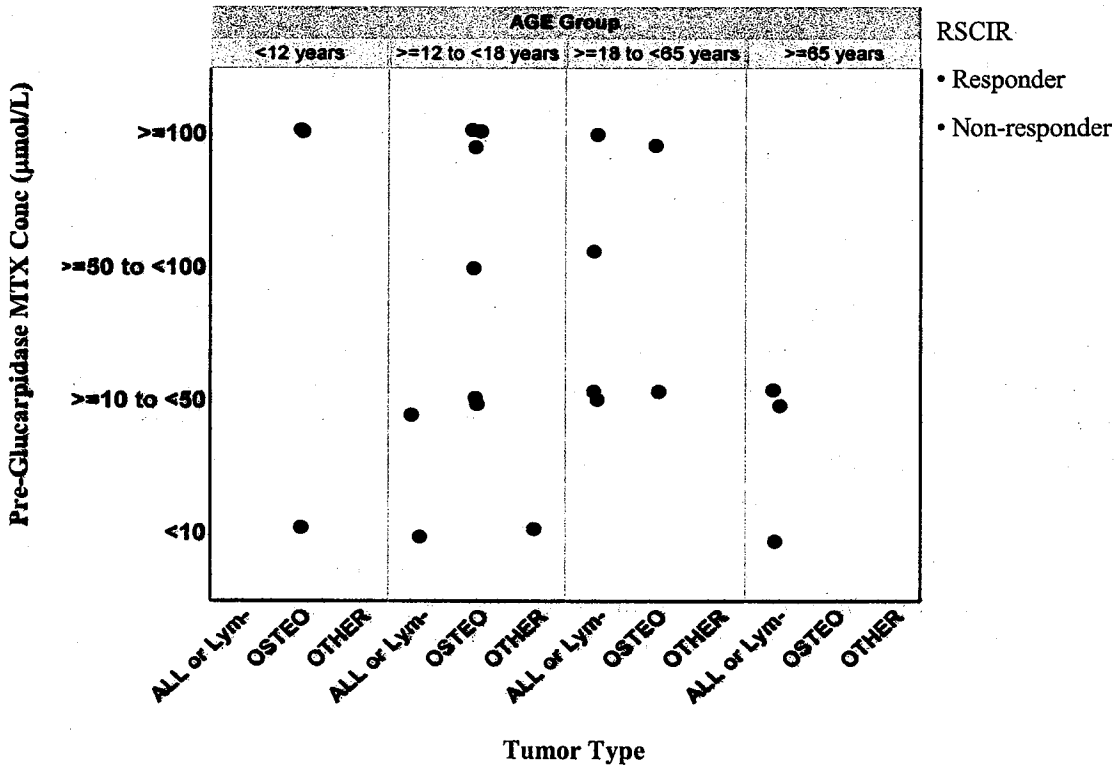
for ALL or lymphoma patients (Table 5).

Table 5 Baseline Characteristics

Tumor Type	Age Group n (%)		Median MTX Dose (g/m^2) (Min, Max)	Median Pre-Glucarpidase MTX Conc. (µmol/L) (Min, Max)
Osteogenic sarcoma (N=11)	<12	3 (13.6)	12.0 (2.0, 20)	361.7 (8.1, 708.3)
	≥12 to <18	6 (27.2)		
	≥18 to <65	2 (9.1)		
	≥65	0		
ALL or Lymphoma (N=10)	<12	0	5.9 (2.9, 5.0)	28.9 (3.9, 286.2)
	≥12 to <18	2 (9.1)		
	≥18 to <65	5 (22.7)		
	≥65	3 (13.6)		
Other (N=1)	≥12 to <18	1 (4.5)	12	8.57

Key factor affecting RSCIR achievement: Since majority of the pediatric patients had osteogenic sarcoma with a higher pre-glucarpidase MTX concentration, pediatric patients had a lower rate of achieving RSCIR (25%, 3/12) than those ≥18 years (70%, 7/10) (Figure 2). On the other hand, as shown in Figure 2, none of the patients with a pre-glucarpidase MTX concentration >50 µmol/L achieved a RSCIR regardless of age and tumor type, while 10 of 13 patients with a pre-glucarpidase MTX concentration ≤50 µmol/L achieved a RSCIR. This exploratory analysis suggests that the pre-glucarpidase MTX concentration is the key factor affecting the achievement and attainment of a RSCIR and is associated with the likelihood of attaining a RSCIR following glucarpidase injection.

Figure 2 RSCIR – Age and Tumor Type



As presented in Table 6, all nine patients who had pre-glucarpidase MTX concentrations >50 µmol/L had a >95% reduction in MTX concentrations for up to 8 days following the initial injection of glucarpidase although none of them achieved a RSCIR.

Table 6 Results of an Exploratory Analysis following Glucarpidase Administration

Pre-Glucarpidase MTX Conc. (µmol/L)	No. of Patients	Patients Achieving RSCIR n (%)	Patients with > 95% Reduction in MTX Conc. up to 8 Days n (%)
>1 to ≤ 50	13	10 (77%)	11 (84.6%)
> 50 to ≤ 100	2	0	2 (100%)
> 100	7	0	7 (100%)

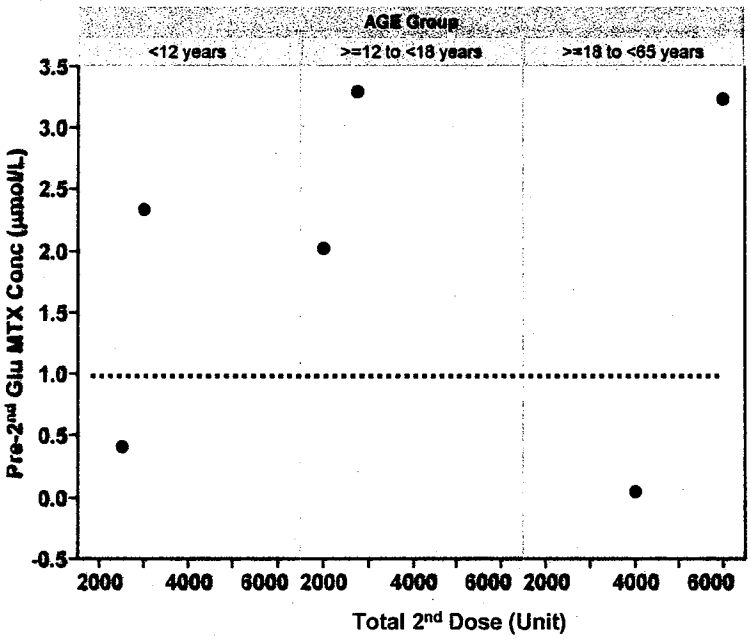
Safety

The analysis of glucarpidase safety is complicated by the lack of controlled data and the presence of baseline toxicities in patients due to prolonged toxic MTX exposure. Overall, glucarpidase-related toxicities appear to be mild to moderate in severity. In clinical trials, the most common adverse events (occurring in >1% of patients) associated with glucarpidase were paraesthesia, flushing, nausea and/or vomiting, hypotension and headache.

2.2.3 Is the 2nd dose effective to achieve RSCIR?

As protocol specified, in Trial 006 any patients with pre-1st dose glucarpidase MTX concentrations >100 µmol/L were eligible to receive a 2nd dose of glucarpidase. Among the 22 patients in the efficacy dataset, six of seven eligible patients received a 2nd dose of 50 Units/kg glucarpidase administered 48 hours after the first dose. Among them, two patients achieved a RSCIR but their pre-2nd dose glucarpidase MTX concentrations were already ≤1 µmol/L. The other four patients with pre-2nd dose glucarpidase MTX concentrations >1 µmol/L did not achieve a RSCIR following the 2nd dose of glucarpidase (see Figure 3).

Figure 3 RSCIR Following the 2nd Dose of Glucarpidase



(b) (4)

2.2.4 *What is the basis of the dose selection?* (b) (4)

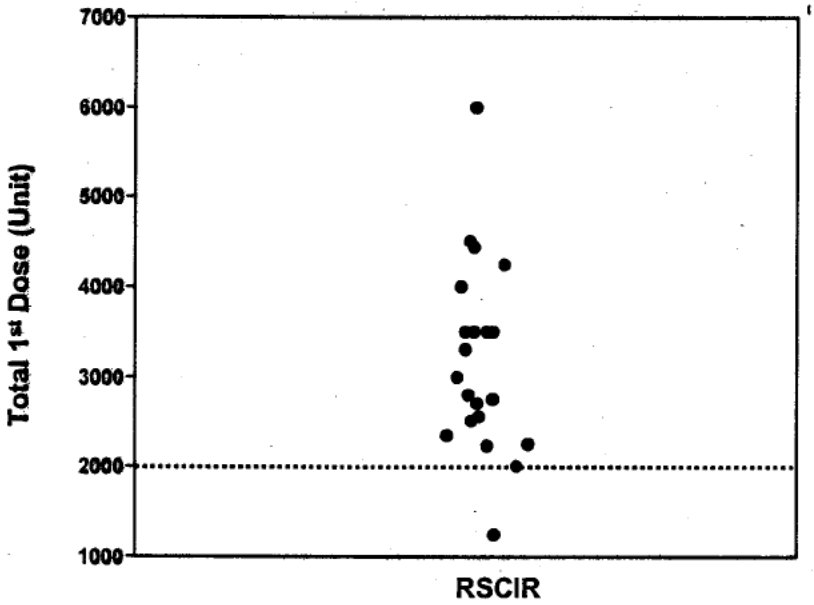
The dosing regimen, 50 Units/kg administered intraveneously over a 5-minute period, was originally selected for the NCI sponsored Trial 002 based upon theoretical considerations with respect to glucarpidase enzymatic activity. In the trial, a marked reduction in plasma MTX concentrations was observed. The Applicant states that the dose of 50 U/kg selected was also based on the results of a nonclinical study in which there was some evidence that the rate of decrease of MTX concentration was greater in the Rhesus monkeys treated with the higher doses of glucarpidase (15 and 50 U/kg *vs* 5 U/kg). In Trial 006, the efficacy and safety of glucarpidase at this dose was demonstrated.

Trial 006 was conducted by NCI between years 2004 and 2007. Due to product availability, per protocol amendment, starting from November 2005, the maximum single dose of glucarpidase, irrespective of body weight, was capped at 2,000 Units per dose. (b) (4)

Figure 4 below illustrates the total first dose of glucarpidase received by the 22 patients in the efficacy dataset in Trial 006, in which patients received glucarpidase at 50 U/kg. None of the patients was dose capped to 2,000 Units although two patients received a total dose of ≤ 2,000 Units because of their low body weight. Figure 4 also shows that there were non-responders even at a total dose greater than 2,000 Units. (b) (4)

(b) (4)

Figure 4 Total Dose Administered in the Efficacy Dataset (50 U/kg, N = 22)



2.2.5 *Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

Glucarpidase concentrations in serum samples were measured by an ELISA method and an enzymatic assay to assess its PK parameters. Plasma concentrations of MTX and its metabolite, DAMPA were measured by a high-performance liquid chromatographic (HPLC) method. The performance of the bioanalytical methods is reviewed in Section 2.6.

2.2.6 *Exposure-response*

The available data does not allow for assessment of the relationships between exposure and efficacy or safety because PK data for glucarpidase after a single dose was not collected in the registration trial 006.

2.2.7 *Does glucarpidase prolong the QTc interval?*

Electrocardiogram (ECG) data were collected in two clinical trials: Trial 005 in healthy subjects and subjects with impaired renal function at screening and study completion; and Trial 010 in healthy subjects at screening, 32 hours post glucarpidase, and at the post-study visit 5-7 days. No ECG abnormality was observed in either of these two trials. There are no glucarpidase related cardiac toxicities observed in clinical trials.

2.2.8 *Pharmacokinetic (PK) characteristics of the drug and its major metabolites*

2.2.8.1 *What are the PK parameters of the drug in healthy subjects and in patients?*

Glucarpidase

The PK of glucarpidase following single administration was evaluated in an open-label, single site trial in eight healthy subjects (Study 005). In the trial, healthy subjects (≥ 18 years old, mean body weight 88.3 kg) received glucarpidase as a single IV injection of 50 Units/kg in the absence of MTX. Serum samples were collected at pre-dose and up to 96 hours following the injection. Serum glucarpidase activity levels were measured by an enzymatic assay and serum total glucarpidase concentrations were measured by an ELISA method. The mean serum concentration *vs.* time profiles following singe IV injection of 50 Units/kg glucarpidase are depicted in Figure 5. The serum PK parameters determined using the two assays are presented in Table 7. The PK parameters of glucarpidase derived from serum glucarpidase activity levels and from serum total glucarpidase concentrations were similar except that a longer elimination $t_{1/2}$ and a larger volume of distribution derived with serum total glucarpidase concentrations.

Figure 5 **Mean Serum Glucarpidase Concentration-Time Profiles in Healthy Subjects Following Single 50 Units/kg IV Injection on a Normal Scale and a Semi-log Scale**

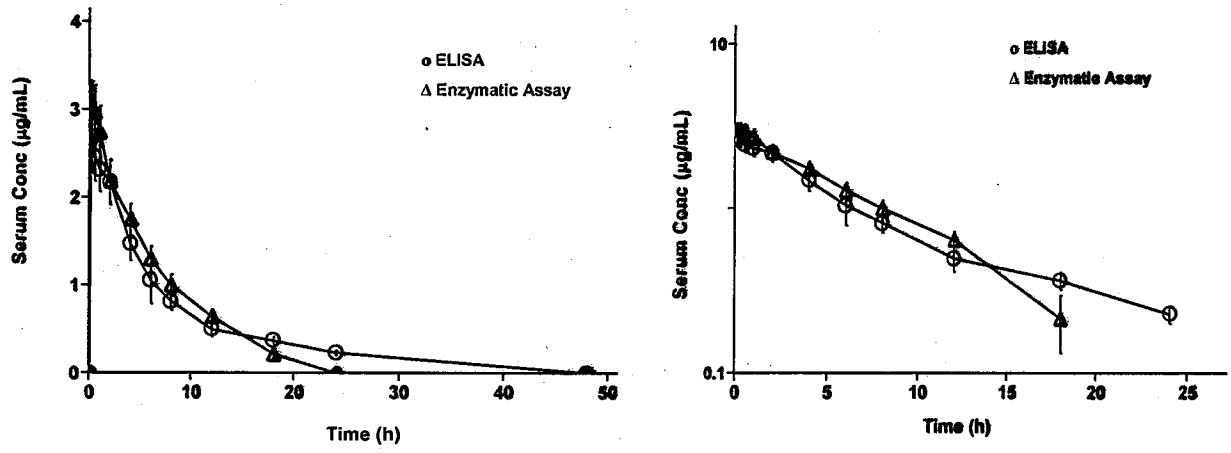


Table 7 **PK Parameters of Glucarpidase Following Single IV Administration of 50 Units/kg in Healthy Subjects**

PK Parameter	ELISA Method Mean (SD)	Enzymatic Method Mean (SD)
C_{max} (µg/mL)	3.1 (0.8)	3.3 (0.8)
$AUC_{0-\infty}$ (µg*h/mL)	23.4 (6.9)	23.3 (7.2)
$t_{1/2}$ (h)	9.0 (3.2)	5.6 (0.7)
Cl (mL/min)	7.5 (1.6)	7.5 (1.2)
V_d (L)	5.0 (1.3)	3.6 (0.5)

The PK of glucarpidase in patients were evaluated in a terminated randomized, blinded phase 2 trial (Study 012) and data were only available in two osteogenic sarcoma patients with normal renal function, Patients-001 and -003 with ages of 18 and 16 years and body weights of 54.4 and 66 kg, respectively. Both of them received HDMTX and two glucarpidase doses (50 Unit/kg) 24 hour apart. Glucarpidase PK samples were collected at pre-dose and up to 24 hours following the first injection. Serum samples were analyzed for total glucarpidase concentrations by ELISA and for enzyme activity by an enzymatic assay. The PK parameters of glucarpidase obtained after the first dose in these two patients are shown below:

Table 8 PK Parameters of Glucarpidase Following Single IV Administration of 50 Units/kg in Patients

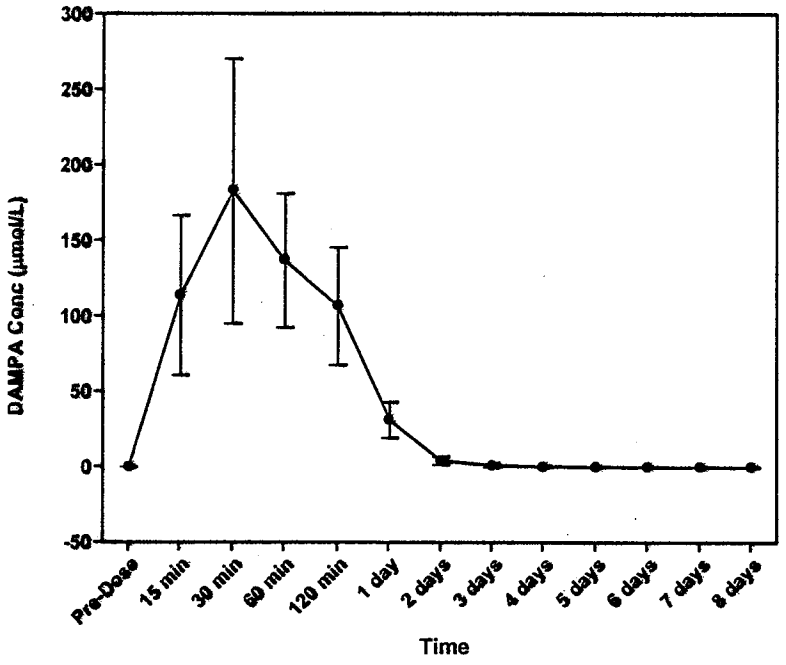
PK Parameter	ELISA Method		Enzymatic Method
	Patient-001	Patient-003	Patient-001
C_{max} (µg/mL)	2.4	2.5	3.1
$AUC_{0-\infty}$ (µg*h/mL)	13.3	12.8	13.0
$t_{1/2}$ (h)	3.6	3.3	3.0
Cl (mL/min)	7.4	9.1	7.6
V_d (L)	2.3	2.6	1.9

In two patients with normal renal function treated with HDMTX, total glucarpidase elimination $t_{½}$ were shorter (3.3 h and 3.6 h) than that in healthy subjects. Total glucarpidase AUC_{0-inf} values for patients were approximately 43% lower than that for healthy subjects. The lower AUC_{0-inf} could be attributed to lower body weight of the two patients relative to the normal subjects which, in turn, resulted in lower glucarpidase doses. The clearance of glucarpidase was similar between the patients and the healthy subjects. The PK parameters derived from serum glucarpidase enzymatic levels was only available in one patient. The limited PK data available in patients does not allow for a statistical comparison between patients and health subjects.

DAMPA

DAMPA is a minor metabolite of MTX in the absence of glucarpidase, but is the major metabolite of MTX following administration of glucarpidase. In Trial 006, plasma concentrations of DAMPA were also measured by an HPLC method. The mean concentration *vs.* time profile is depicted in Figure 6:

Figure 6 Mean Plasma Concentration-Time Profile for DAMPA following Single Administration of Glucarpidase



The mean maximum plasma DAMPA concentration, 183 μmol/L, occurred at 30 min following glucarpidase administration. The mean $t_{1/2}$ was approximately 9 hours.

2.2.8.2 Does the mass balance study suggest renal or hepatic as the major route of elimination?

No mass balance study has been conducted for glucarpidase. Mass balance studies are not generally performed for biologic products because they are degraded into amino acids that then recycled into other proteins.

2.2.8.3 What are the characteristics of drug metabolism?

Metabolism studies are not generally performed for biologic products because they are degraded into amino acids that are then recycled into other proteins.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

No formal studies have been conducted to assess the effect of age, gender, race, body weight, or hepatic function on the PK and/or response of glucarpidase. Glucarpidase PK were not evaluated in the registration trial 006. As pointed out earlier, analyses of response or efficacy by each factor are complicated and confounded by several factors. Thus, the existence of the confounding factors and the limited number of patients in the efficacy dataset, do not allow for the evaluation of the impact of these factors (age, gender, body weight, race) on response.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly

Of the 22 patients in the efficacy dataset from Trial 006, 3 patients were ≥ 65 years old and all of them with the pre-glucarpidase MTX concentration <50 μmol/L achieved a RSCIR in plasma MTX concentration.

2.3.2.2 Pediatric patients

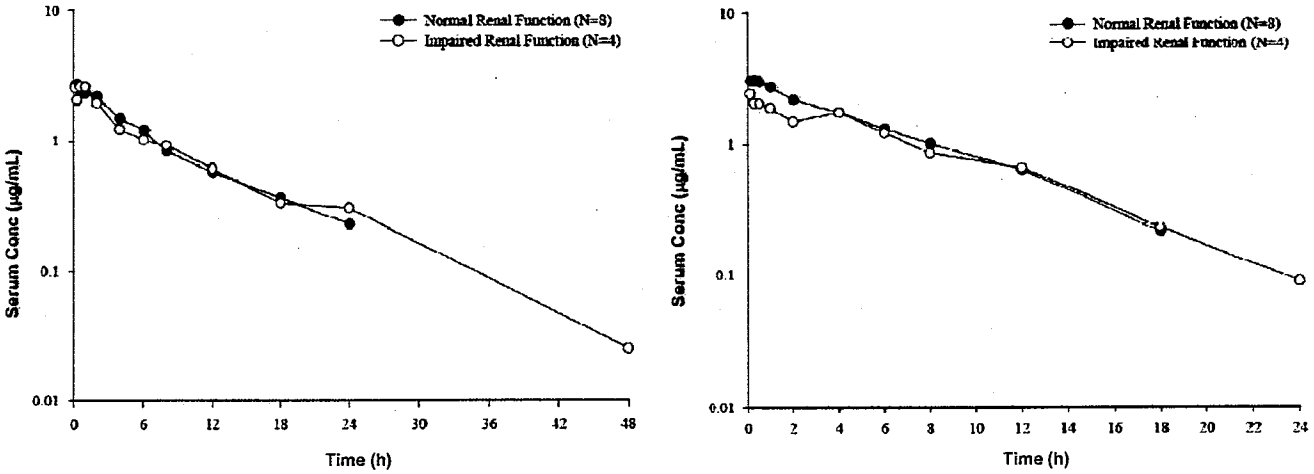
Of the 22 patients in the efficacy dataset, 12 were pediatric patients with age ranging from 5 to 16 years. Three of the six pediatric patients with the pre-glucarpidase MTX concentration ≤50 μmol/L achieved a RSCIR in plasma MTX, while none of the six pediatric patients with pre-glucarpidase MTX concentration >50 μmol/L achieved a RSCIR.

2.3.2.3 Renal impairment

The impact of renal impairment on the PK of glucarpidase was evaluated in Trial 005 in four patients with severe renal impairment (creatinine clearance <30 mL/min). Following an IV dose

of 50 Units/kg glucarpidase in the absence of MTX, serum concentrations of glucarpidase appeared to decline in a monophasic manner in both renal impaired patients and healthy subjects (Figure 7). The clearance was 7.7 mL/min in patients with renal impairment by either ELISA or the enzymatic method. This value is comparable to that for healthy subjects (7.5 mL/min). Overall, the mean PK parameters in patients with renal impairment were similar to those in healthy subjects except that subjects with severe renal impairment had a longer $t_{1/2}$ of 8.2 hours as compared to that in healthy subjects (5.6 hours) by the enzymatic assay. Results from this trial suggest that dose adjustment for glucarpidase is not necessary in patients with impaired renal function.

Figure 7 Mean Concentration Time Profile of Serum Glucarpidase Using the ELISA Method (left) or the Enzymatic Method (right)



2.3.2.4 Hepatic impairment

No specific studies of glucarpidase in patients with hepatic impairment have been conducted. Glucarpidase is an enzyme that is eliminated by catabolism not by hepatic metabolism via cytochrome P450 enzymes, thus hepatic impairment study is considered unnecessary.

2.3.2.5 What pregnancy and lactation use information is there in the application?

Glucarpidase belongs to pregnancy category C. It is not known whether glucarpidase can cause fetal harm when administered to a pregnant woman, or whether it can affect reproduction capacity. There is no information on the excretion of glucarpidase in the milk of humans or animals in the application.

2.3.2.6 Other factors that are important to understand the drug's efficacy and safety

Immunogenicity: The immunogenicity of glucarpidase was assessed using a validated bridging enzyme-linked immunosorbent assay (ELISA) for determination of anti-glucarpidase antibodies (AGAs). A pooled analysis of immunogenicity data from three trials, 012, 016 and 017, in patients treated with HDMTX and glucarpidase was performed.

Of the 96 patients in these trials, 16 patients (16.7%) had treatment-emergent AGAs at one or more time points ranging from day 7 to month 7 following exposure to 50 Units/kg glucarpidase (see Table 9 below). Twelve of the 16 patients who developed AGAs had received a single dose

of glucarpidase and four of the patients had received two doses of glucarpidase. Neither the PD (plasma MTX concentrations) nor the PK (glucarpidase concentrations) data were collected in these patients. However, in the efficacy dataset, there was no impact of immunogenicity on glucarpidase PD as a ≥97% reduction in plasma MTX concentration was observed at 15 min in all patients. In addition, an impact of immunogenicity on glucarpidase PK is not anticipated due to a short $t_{1/2}$ (5.6 to 9 hours) of glucarpidase relative to the time needed for AGA formation.

Table 9 Summary of Anti-glucarpidase Antibody Results in Clinical Trials

Study No.	Incidence (Timepoint)	PD (MTX Conc. Testing)
017	1/9 (week 4-6)	MTX plasma conc. only collected up to 3 hours following glucarpidase dosing
012 (terminated)	1/5 (month 3)	Not tested
016 (ongoing)	14/82 (day 7-10 to month 5-7)	Not tested

(b) (4)

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

No dedicated studies were conducted to evaluate the impact of extrinsic factors on the PK and/or PD of glucarpidase. Given that glucarpidase is an enzyme and is intravenously administered, the influence of extrinsic factors on dose-exposure and/or response is anticipated to be minimal, if any.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

No *in vitro* metabolic screening was conducted given that glucarpidase is an enzyme.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

No given that glucarpidase is an enzyme.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes? Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

No given that glucarpidase is an enzyme.

2.4.2.4 Are there other metabolic/transporter pathways that may be important?

No. As biologics are degraded into amino acids that then recycled into other proteins, classical biotransformation studies performed for small molecule drugs are generally not needed for biologics.

2.4.2.5 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Due to its large molecular size, glucarpidase does not cross the cellular membranes. Therefore, glucarpidase cannot counteract the intracellular antineoplastic effects of HDMTX, and administration of leucovorin (LV) is still necessary to protect normal cells from MTX toxicity.

LV is an active, chemically reduced derivative of folic acid. It is a mixture of the diastereoisomers of the 5-formyl derivative of tetrahydrofolic acid (THF). The biologically active compound of the mixture is the (-)-*l*-isomer [(6S)-LV]. After administration, (6S)-LV is rapidly metabolized to its active metabolite (6S)-5-methyl tetrahydrofolate [(6S)-5-MeTHF]. LV is used to counteract the cellular damage caused by HDMTX. The labeling recommended doses range from 15 mg (10 mg/m^2) either orally or parenterally every 6 hours to 150 mg (100 mg/m^2) every 3 hours intravenously depending on the timing and extent of renal excretion of MTX and on the presence of renal functional impairment, with individual clinicians employing higher doses to take into account higher doses of MTX or clinical circumstances (see Table 10).

Table 10 Labeling Recommended Guideline for LV Dosage and Administration

Clinical Situation	Laboratory Findings	LV Dosage and Duration
Normal MTX Elimination	Serum MTX level approximately 10 μM at 24 hours after administration, 1 μM at 48 hours, and less than 0.2 μM at 72 hours.	15 mg PO, IM, or IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of MTX infusion).
Delayed Late MTX Elimination	Serum MTX level remaining > 0.2 μM at 72 hours, and > 0.05 μM at 96 hours after administration.	Continue 15 mg PO, IM, or IV q 6 hours, until MTX is < 0.05 μM.
Delayed Early MTX Elimination and/or Evidence of Acute Renal Injury	Serum MTX level ≥ 50 μM at 24 hours, or ≥ 5 μM at 48 hours after administration, OR; a 100% or greater increase in sCr level at 24 hours after MTX administration (e.g., an increase from 0.5 mg/dL to a level of 1 mg/dL or more).	150 mg IV q 3 hours, until MTX level is < 1 μM; then 15 mg IV q 3 hours until MTX level is < 0.05 μM.

As in clinical practice, glucarpidase would almost invariably be given to patients concomitantly receiving LV as a rescue agent for HDMTX therapy, the potential for an PK interaction between

glucarpidase and LV was examined in a pilot study in healthy subjects (Trial 010) and in patients receiving HDMTX (Trial 017).

Trial 010

It was a double-blind, placebo-controlled, randomized, 2-period crossover PK trial in healthy subjects. Each eligible adult subject was randomized to one of the two treatment periods:

Treatment A: intravenous injection of glucarpidase (50 U/kg) over 5 minutes + intravenous injection of LV (150 mg/m^2) over 2.5 minutes
Treatment B: intravenous injection of placebo + intravenous injection of LV (150 mg/m^2) over 2.5 minutes

In each study period, subjects received single intravenous infusion of glucarpidase or placebo together with five intravenous injections of LV, administered with 6-hour intervals (q6h) at 2 (Dose 1), 8, 14, 20 and 26 (Dose 5) hours after the glucarpidase or placebo injection. Each study period was separated by a washout period of 14 days. A total of six subjects were enrolled and completed the study.

Blood samples were taken for the analysis of (6S)-LV, (6S)-5-MeTHF, (6R)-LV, and (6R)-5-MeTHF [the inactive metabolite of (6R)-LV] at pre-dose and up to 6 hours post first and fifth LV doses. Blood samples for glucarpidase were collected at pre-dose and up to 26 hours after glucarpidase administration and were analyzed by ELISA.

Table 11 presents statistical results of the PK parameters for the biologically active folates, (6S)-LV and its active metabolite (6S)-5-MeTHF, following the first and fifth doses of LV when given with glucarpidase or placebo.

Table 11 Summary of LV PK parameters Following Doses 1 and 5 of LV by the Two Treatments

PK parameter*	Glucarpidase + LV (n = 6)		Placebo + LV (n = 6)		Ratio of geo-mean (90% CI) (Glucarpidase + LV) / (Placebo + LV)	
	Dose 1	Dose 5	Dose 1	Dose 5	Dose 1	Dose 5
(6S)-LV						
C_{max} (µmol/L)	31.8 (34.5)	26.5 (50.5)	35.0 (58.5)	38.9 (47.7)	0.909 (0.670, 1.23)	0.679 (0.501, 0.922)
$AUC_{0-\tau}$ (µmol*hr/L)	10.9 (30.3)	16.3 (26.4)	20.7 (39.5)	20.9 (36.0)	0.528 (0.431, 0.648)	0.782 (0.638, 0.958)
t_{max} (h)	0.07 (0.05, 0.08)	0.08 (0.05, 0.18)	0.06 (0.05, 0.17)	0.07 (0.05, 0.08)		
(6S)-5-MeTHF						
C_{max} (µmol/L)	<1.0 (0)	1.6 (16.1)	2.0 (82.8)	3.2 (128)	--	0.490 (0.151, 1.59)
$AUC_{0-\tau}$ (µmol*hr/L)	NC	5.4 (28.4)	9.6 (34.3)**	19.8 (35.8)**	--	0.255 (0.162, 0.401)
t_{max} (h)	NC	2.00 (1.50, 3.00)	3.00 (1.50, 3.00)	1.50 (1.50, 2.00)		

*t_{max} values are median (range), all others are geometric mean (CV%); ** n=5
NC = Not calculated, (6S)-5-MeTHF concentrations were below the limit of quantification in all subjects

Administration of LV 2 hours (Dose 1) after a single 50 U/kg glucarpidase injection resulted in a 47% and 9% reduction in (6S)-LV $AUC_{0-\tau}$ and C_{max}, respectively, and a profound effect on (6S)-5-MeTHF with all its plasma concentrations being below the limit of quantification (1.0 μmol/L). When LV was administered 26 hours (Dose 5) after a single dose of 50 U/kg glucarpidase, (6S)-LV exposure ($AUC_{0-\tau}$) was decreased by 22% and C_{max} decreased by 32%, and $AUC_{0-\tau}$ and C_{max} of (6S)-5-MeTHF decreased by 75% and 51%, respectively. These results indicate that both (6S)-LV and (6S)-5-MeTHF are substrates of glucarpidase and administration of glucarpidase can reduce their exposures.

The PK parameters of glucarpidase in the study in the presence of the LV doses were comparable to the previously reported data in healthy subjects in the absence of LV (Study 005), with serum concentration declined in a monophasic manner and a mean $t_{1/2}$ of 7.1 hours.

Study 017

It was an open-label, nonrandomized, multicenter PK study in patients treated with HDMTX and LV. Based on the results of Study 010 in healthy subjects, the main purpose of this study was to determine the effect of glucarpidase on the PK of LV and its active metabolite in patients when both agents were administered together.

Each eligible patient was assigned to one of the following groups based on his/her plasma MTX concentration and renal function:

- Treatment Group with Glucarpidase (Arm A)
    - Patients with inadequate renal function and delayed MTX clearance received HDMTX followed by intravenous injection of LV, then a single glucarpidase (50 U/kg) injection, then followed by injection of LV again based upon the pre-glucarpidase MTX concentrations in accordance with LV product labeling
- Control Group (Arm B)
    - Patients with adequate renal function and without delayed MTX clearance received HDMTX followed by intravenous injection of LV

Based on the results of Study 010, patients in Treatment Group were not to receive LV within 2 hours after glucarpidase dosing. Patients were also required to receive LV at the dose recommended for patients with delayed early MTX elimination and/or evidence of acute renal injury, (i.e., 100 mg/m^2 or 150 mg q3h). Control Group patients were to receive ≥15 mg (or 10 mg/m^2) q6h of LV but no more than 25 mg/m^2 q6h.

The overall study design, dosing interval between glucarpidase and LV, and the amount of LV received is illustrated in Figure 8:

Figure 8 Study Design

Treatment Group
Patients with renal impairment and delayed MTX clearance
HDMTX + LV ——→ Glucarpidase ——→ LV
median 2.2 hours mean dose 186.6 mg

Control Group
Patients with normal renal function and without delayed MTX clearance
HDMTX + LV
mean dose 17.4 mg

The LV dose after glucarpidase for Treatment Group and the first LV dose after MTX for Control Group were designated as the reference LV doses.

The PK samples were collected at pre-reference LV dose, 5 and 30 minutes, 1, 2, and 3 hours after the reference LV dose for the assessment of (6S)-LV, (6S)-5-MeTHF, (6R)-LV, and (6R)-5-MeTHF.

The PK parameters for (6S)-LV, (6R)-LV, and (6S)-5-MeTHF are presented in Table 12. Plasma concentrations of (6R)-5-MeTHF were below the lower limit of quantification (0.01 µmol/L) for all samples. Therefore PK parameters were not computed for this analyte.

Table 12 Summary of PK Parameters for Treatment Group and Control Group

PK Parameter*	Treatment Group (N=8)	Control Group (N=9)
6S-LV		
AUC_{0-3h} (µmol*h/L)	6.4 (122.5)	1.1 (62.5)
C_{max} (µmol*h/L)	8.7 (119.8)	2.1 (65.1)
T_{max} (h)	0.34 (0.08, 3.22)	0.50 (0.05, 0.70)
6S-5-MeTHF		
AUC_{0-3h} (µmol*h/L)	0.47 (116.7)	0.69 (40.8)
Cmax (µmol*h/L)	0.20 (129.1)	0.32 (40.8)
Tmax (h)	2.04 (0.35, 3.00)	1.00 (0.05, 1.25)
6R-LV		
AUC_{0-3h} (µmol*h/L)	146.5 (105.2)	8.9 (19.1)
Cmax (µmol*h/L)	66.9 (112.8)	5.6 (24.7)
Tmax (h)	0.46 (0.08, 3.22)	0.50 (0.05, 0.70)

*t_{max} values are median (range), all others are geometric mean (CV%)

To compare the differences between the treatment and control group, the PK parameters were dose-normalized by the LV dose since the doses of LV employed in the two groups were different. The Applicant's dose-normalized PK parameters using the LV dose in the unit of

mg/m^2 (see Table 13). However, the distribution of body surface area (BSA) between the two groups was not balanced with a higher median BSA seen in the treatment group (see Figure 9). Therefore, the dose-normalized PK parameters for the biologically active folates, (6S)-LV and (6S)-5-MeTHF, were recalculated by the reviewer using the total LV dose in the unit of mg (see Table 14).

Table 13 LV Dose-Normalized PK Parameters by Group

Analyte Parameter	Arm A			Arm B		
	n	Mean ± SD (% CV)	% CV change[a]	n	Mean ± SD (% CV)	% CV change[a]
(6S)-LV						
$AUC_{0\text{-}3}/D_{LV}$ (µmol*h/L/(mg/m^2))*10^2	8	10.02±4.83 (48.24)	-24.45	9	9.79±5.18 (52.87)	-11.04
C_{max}/D_{LV} (µmol/L/(mg/m^2))*10^2	8	17.33±17.28 (99.71)	-13.11	9	18.79±9.75 (51.87)	-8.98
C_3/D_{LV} (µmol/L/(mg/m^2))*10^2	6[b]	9.42±20.97 (222.55)	2.14	1[b]	0.46	
C_0/D_{LV} (µmol/L/(mg/m^2))*10^2	8	0.09±0.14 (154.86)	-3.97	9	0.00±0.00	
(6R)-LV						
$AUC_{0\text{-}3}/D_{LV}$ (µmol*h/L/(mg/m^2))*10^2	8	211.51±74.58 (35.26)	-44.78	9	68.67±7.78 (11.33)	-35.03
C_{max}/D_{LV} (µmol/L/(mg/m^2))*10^2	8	97.02±35.49 (36.58)	-37.67	9	43.21±6.37 (14.73)	-31.10
C_3/D_{LV} (µmol/L/(mg/m^2))*10^2	8	75.78±37.22 (49.12)	-29.36	9	16.42±3.03 (18.46)	-4.65
C_0/D_{LV} (µmol/L/(mg/m^2))*10^2	8	48.65±21.22 (43.62)	-15.32	9	0.04±0.12 (300.00)	0.00
(6S)-5MeTHF						
$AUC_{0\text{-}3}/D_{LV}$ (µmol*h/L/(mg/m^2))*10^2	8	1.04±1.15 (110.50)	18.88	9	5.55±1.69 (30.53)	-14.19
C_{max}/D_{LV} (µmol/L/(mg/m^2))*10^2	8	0.43±0.44 (104.06)	15.02	9	2.54±0.65 (25.66)	-21.86
C_3/D_{LV} (µmol/L/(mg/m^2))*10^2	8	0.35±0.37 (105.77)	4.18	9	1.44±0.58 (40.12)	-10.77
C_0/D_{LV} (µmol/L/(mg/m^2))*10^2	8	0.17±0.14 (83.05)	-2.89	9	0.05±0.07 (159.58)	4.16

Source: Table 10 in Clinical Study Report for Study 017

Figure 9 BSA Distribution Between Treatment and Control Groups

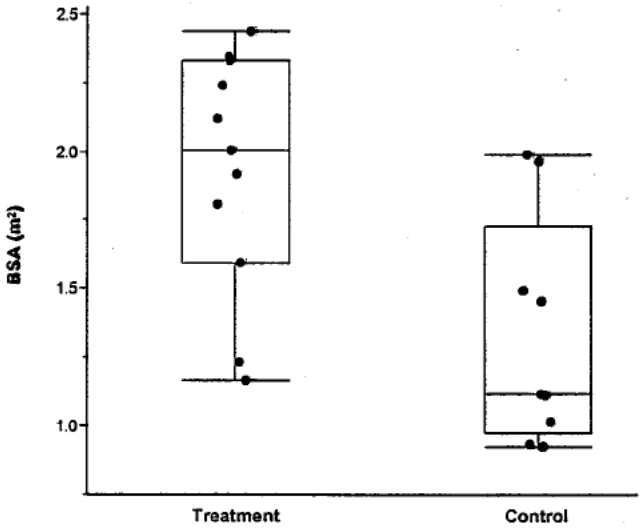


Table 14 Summary of Statistical Analysis of Dose-Normalized PK Parameters for Active Folates (Reviewer's Analysis)

LV-Dose Normalized PK Parameter	Treatment (N=8)	Control (N=9)	Ratio of geo-mean (90% CI) Treatment /Group
$AUC_{0\text{-}3h}$ (nmol*h/L)/(mg)	45.7 (69.9)	67.8 (68.9)	0.67 (0.39 – 1.15)
C_{max} (nmol/L)/(mg)	61.8 (132.9)	128 (74.5)	0.48 (0.23 – 0.99)
$AUC_{0\text{-}3h}$ (nmol*h/L)/(mg)	3.3 (120.6)	41.5 (51.0)	0.08 (0.04 – 0.15)
C_{max} (nmol/L)/(mg)	1.4 (124.2)	19.2 (51.1)	0.07 (0.04 – 0.14)

PK parameters: geometric mean (CV%)

Individual dose-normalized $AUC_{0\text{-}3h}$ and C_{max} and the magnitude of change in these parameters compared to the control for 6S-LV and 6S-5-MeTHF are illustrated in figures 10 and 11.

Figure 10 Comparison of Dose-Normalized $AUC_{0\text{-}3h}$ and C_{max} for 6S-LV between Treatment and Control Groups

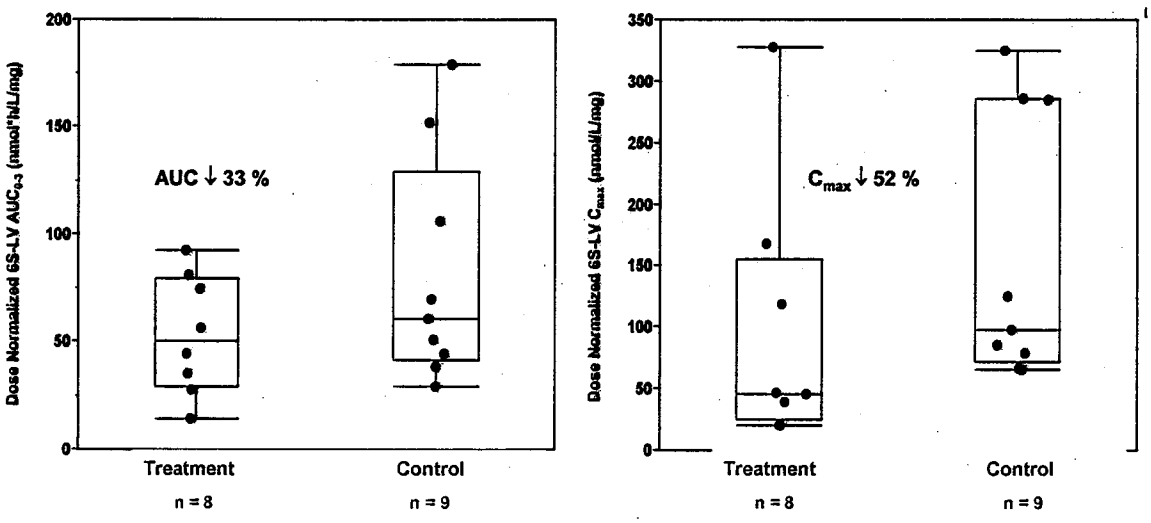
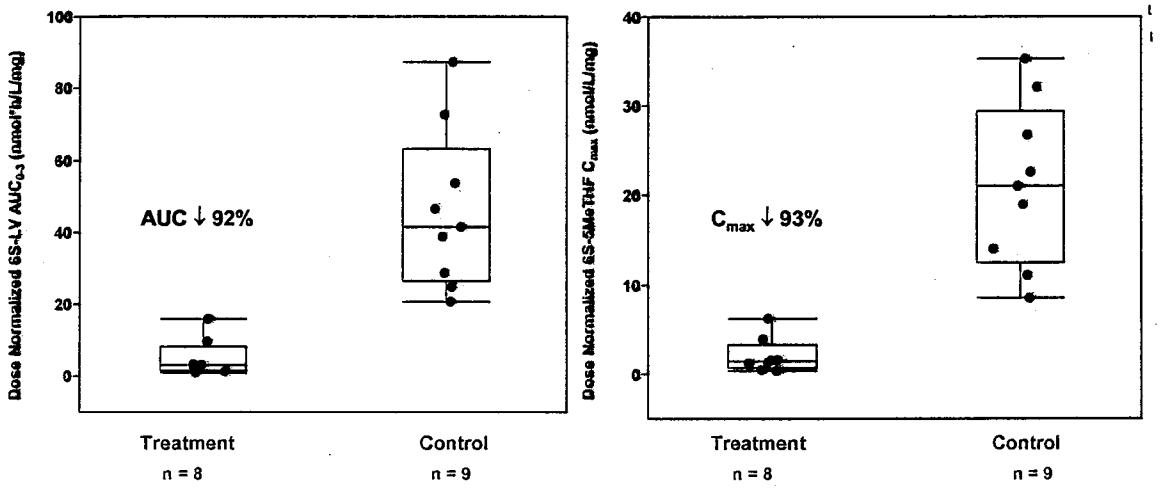


Figure 11 Comparison of Dose-Normalized AUC_{0-3h} and C_{max} for 6S-5-MeTHF between Treatment and Control Groups



These results suggest that single administration of 50 Units/kg glucarpidase 2 hours before LV reduced both (6S)-LV and (6S)-5-MeTHF exposures. The impact was more profound for (6S)-5-MeTHF. Despite of these findings, dose adjustment for LV is not necessary because of the following reasons: a) in clinical practice, the dose of LV is guided by the plasma MTX concentrations not by LV's exposure; b) following glucarpidase administration, a rapid and sustained reduction in plasma MTX concentrations occurs; c) the leucovorin dose will still be based on the patient's pre-glucarpidase MTX concentration for 48 hours after glucarpidase administration; d) in addition, after glucarpidase administration, LV dosing will not be stopped and will continuously be given every 3 hours until MTX level below the LV treatment threshold according to the rescue dosing regimen. Therefore, the FDA recommends that continue therapy with LV according to the leucovorin prescribing information for delayed MTX elimination and do not administer LV within 2 hours before or after a dose of glucarpidase.

2.4.2.6 What other co-medications are likely to be administered to the target patient population?

Besides LV, various chemotherapies are likely to be administered to the target patient population.

2.4.2.7 Are there any other in vivo drug-drug interaction (DDI) studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Not applicable because glucarpidase is a therapeutic enzyme given by intravenous route.

2.5.2 *What is the composition of the to-be-marketed formulation?*

VORAXAZE is supplied as a sterile, preservative-free, lyophilized powder in single-use vials. Each vial contains 1,000 Units of glucarpidase, lactose monohydrate, Tris-HCl and zinc acetate dehydrate. The composition of the drug product is presented in Table 15.

Table 15 Glucarpidase Drug Product Composition

Ingredient	Function	Reference	Quantity
Glucarpidase	Active	In-house	1000 Units
Lactose monohydrate	(b) (4)	Ph. Eur. / NF	10 mg (1%)
Tris-HCl (b) (4)		Tris(hydroxymethyl)aminomethane Ph. Eur. / USP	(b) (4)
Zn^{2+}		Zinc Acetate dihydrate (Ph. Eur. / USP)	

2.5.3 *What moieties should be assessed in bioequivalence studies?*

Not applicable.

2.5.4 *What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?*

Not applicable.

2.5.5 *Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?*

Not applicable.

2.6 ANALYTICAL SECTION

2.6.1 *Were the active moieties identified and measured in the clinical pharmacology studies?*

Yes. In clinical trials, the active moieties: glucarpidase (for PK), MTX (for efficacy) and its inactive metabolite, DAMPA, LV (co-administered medication) and its associated active metabolites were all determined by validated bioanalytical methods.

2.6.2 *What bioanalytical procedures and methods were used to determine drug concentrations? Are they acceptable for this BLA?*

MTX & DAMPA

For Trial 006, plasma concentrations of MTX and DAMPA were determined by a validated HPL)-UV method at (b) (4) Briefly, this method involved the extraction of MTX and DAMPA from aliquots of human plasma (1 mL) mixed with hydrochloric acid (100 µL, 1 N, used to inactivate glucarpidase) using conditioned (methanol-water-sodium phosphate buffer: 0.1 M, pH 6.8) Bond Elut C-18 (b) (4) columns. The (b) (4) columns were washed with

sodium phosphate buffer (0.1 M, pH 6.8). MTX and DAMPA were eluted from the (b) (4) columns with methanol and the eluates were evaporated to dryness under nitrogen. The residues were reconstituted in 200 µl mobile phase (0.1 M sodium phosphate buffer pH 6.8-methanol 80% / 20% v/v) and aliquots (50 µL) were injected onto a NovaPak, C-18 µ 8 in Waters 8 x 10 RCM with Waters C-18 µ Bondpak guard column. MTX and DAMPA are chromatographed isocratically and detected by UV at 303 and 313 nm, respectively. A summary of the method validation is presented in Table 16.

The following description of deficiencies based on Office of Scientific Investigations (OSI) inspection and resolutions with respect to method performance and samples handling are focused on MTX, as MTX is the active moiety for efficacy determination.

- Inadequate use of QC samples during analysis of plasma samples to accept or to reject analytical run

For MTX, the calibration standards ranged from 0.05 µM to 10.0 µM. The accuracy and precision of the method were validated using QC samples at concentrations of 1 µM, 2.5 µM and 10.0 µM; no QC sample at LLOQ (0.05 µM) was used. However, during method validation, at MTX concentration of 0.05 µM, the mean peak AUC was 7.8x (range from 6.4 to 9.7x) over baseline plasma with a precision of 16.5 % (CV) and accuracy of 14.7% (RMS %RE). During analysis of patient samples, QC samples at 0.5 µM and 5.0 µM were used. A qualitative assessment of the line (e.g. based on R correlation coefficient) and location of patient sample concentrations within the calibration range was made to accept or to reject the run.

- Absence of stability data

Plasma samples received at (b) (4) were stored at -80 °C till analyzed, but no specific sample stability studies were conducted at (b) (4) During drug development, the Applicant has conducted stability studies for MTX in plasma and samples using HPLC. The results suggest that MTX in plasma was stable up to 517 days stored at -70°C, for at least 24 hours at room temperature, and through 5 freeze/thaw cycles at *ca* -80°C. The extracted samples using (b) (4) procedure with different organic solvents were stable for at least six days stored at 4 °C.

Glucarpidase

Enzymatic Assay

In trials 050, 010, and 012, the enzymatic activity of glucarpidase in human serum samples was determined using an enzyme-substrate spectrophotometric method. The cleavage of the substrate MTX is monitored by UV absorbance at 320 nm against time. The rate of change in absorbance is directly related to the activity of glucarpidase. An excess of substrate leads to a linear graph of the plot of increasing absorbance against time. The reference glucarpidase was dissolved in physiological saline first to make a stock solution and then the stock solution was diluted as appropriate using blank human serum to obtain a series of calibration standard solutions and QC samples. Working MTX solution was prepared by dissolving a known amount of MTX in Assay Buffer (100mM Tris, 0.26mM Zinc acetate, pH7.4). An aliquot of working MTX solution was dispensed into cuvettes containing assay buffer, calibration standard solutions, QC samples or serum glucarpidase samples collected from the clinical studies. The absorbance of each mixture was determined using a UV-spectrophotometer at 320 nm. By comparing the gradients (Abs/min) of control reactions against parallel reactions containing accurately known concentrations of glucarpidase, the activity and concentration of the enzyme in unknown test samples can be calculated. A summary of the method validation is presented in Table 16.

ELISA-1

An ELISA was used in trials 005 and 010 to determine the total glucarpidase protein concentration in human serum. Wells of 96-well microtiter plates were first coated with goat IgG raised to rabbit IgG (Fc). Appropriately diluted rabbit IgG anti-glucarpidase was incubated with serially diluted standards, controls or samples which had been mixed with a constant amount of biotin-labeled glucarpidase. Following incubation, rabbit anti-glucarpidase/glucarpidase complexes were captured by the goat anti-rabbit antibody coated on the microtiterplate. Unlabelled glucarpidase in standards, controls and samples competed with the biotin-labeled glucarpidase to bind to the rabbit IgG anti-glucarpidase. Bound biotin-glucarpidase was detected by addition of streptavidin alkaline phosphatase reagent. Addition of alkaline phosphatase chromogenic reagent resulted in a colorimetric response that was measured by optical density measurements at 490 nm. The QC acceptance criterion was that QC results should be within 30% of the nominal concentration. A summary of the method validation is presented in Table 16.

ELISA-2

Another quantitative ELISA was used in trial 012 to determine the total glucarpidase protein concentration in human serum. Rabbit IgG anti-glucarpidase antibody was coated on a flat bottomed 96-well immunoplate at 2 µg/mL and then blocked using a non-specific protein (PBS/0.05% Tween-20). Glucarpidase reconstituted to 2.5 mg/mL, used to prepare standards and QC sample, was then added to designated sample wells. The assay was visualized by the subsequent addition of goat anti-glucarpidase IgG:HRP, followed by the chromogenic substrate tetramethylbenzidine (TMB). On addition of hydrochloric acid, the product of this reaction was detected with a spectrophotometer at 450 nm (reference 630 nm). The concentration of glucarpidase in samples was then calculated from a calibration curve. The QC acceptance criterion was that QC results should be within 25% of the nominal concentration. A summary of the method validation is presented in Table 16.

LV & 5-MeTHF

Chiral HPLC Fluorescence – Trial 010

A chiral HPLC fluorescence method was used in Trial 010 for the measurement of plasma (6R)-LV, (6S)-LV, (6R)-5-MeTHF and (6S)-5-MeTHF. The method involved the extraction of LV and 5-MeTHF from aliquots of human heparinized plasma mixed with hydrochloric acid (1 M) using conditioned methanol, water and sodium phosphate buffer C18 Strata extraction cartridges. The cartridge sorbents were washed with sodium phosphate buffer. LV and 5-MeTHF are eluted from the extraction cartridges with methanol and the eluates were evaporated to dryness under nitrogen. The residues were reconstituted in sodium phosphate buffer (200 µL, 0.1 M, pH 6.5, containing ascorbic acid 0.1%, w/v) and aliquots (20 µl) were injected onto a Chirobiotic T (250 x 4.6 mm) analytical column. (6R)-LV, (6S)-LV, (6R)-5-MeTHF and (6S)-5-MeTHF were detected by fluorescence, following post-column photo-derivitization, with an excitation wavelength of 286 nm and an emission wavelength of 363 nm. A summary of method validation for the biologically active moieties (6S)-LV and (6S)-5-MeTHF is presented in Table 17.

Chiral HPLC Fluorescence – Trial 017

The preparation and extraction of plasma samples prior to analysis were the same as that used in Trial 010. After extraction, the residues were reconstituted in phosphate buffer (200 µL, 0.1 M,

pH 6.5, containing ascorbic acid (0.1%, w/v) and cysteine (0.05%, w/v)) and aliquots (10 µL) were injected onto a X-Bridge 3.5 µm, 50 x 4.5 mm, analytical reverse phase column, a timed portion of the eluate from this column was directed onto a Chirobiotic T (250 x 4.6 mm) analytical chiral column. (6R)-LV, (6S)-LV, (6R)-5-MeTHF and (6S)-5-MeTHF were chromatographed isocratically and detected by fluorescence, (following post column photo-derivatization for LV analysis), with an excitation wavelength of 286 nm and an emission wavelength of 363 nm. The summary of method validation for (6S)-LV and (6S)-5-MeTHF is presented in Table 17.

Table 16 Summary of Bioanalytical Method Validation for MTX, DAMPA and Glucarpidase in Clinical Studies

Trial No.	PR001-CLN-006	PR001-CLN-006	PR001-CLN-005 PR001-CLN-010 PR001-CLN-012	PR001-CLN-005 PR001-CLN-010	PR001-CLN-012
Analyte	MTX	DAMPA	Glucarpidase	Glucarpidase	Glucarpidase
Matrix	Human plasma	Human plasma	Human resume	Human serum	Human serum
Detection Method	HPLC/UV	HPLC/UV	UV	ELISA	ELISA
Standard Curve Range	0.05 – 10.0 µM	0.1 – 10.0 µM	0.012 – 0.061 µg/mL	0.5 – 750 ng/mL	2 – 100 ng/mL
Regression Type	Linear analysis with 1/x weighting	Linear analysis with 1/x weighting	Linear analysis with 1/x weighting	Linear analysis with 1/x weighting	Linear analysis with 1/x weighting
QC Samples					
Conc.	0.5, 1.0, 2.5, 5.0 10.0 µM	0.5, 1.0, 2.5, 5.0 10.0 µM	0.029, 0.043, 0.057 µg/mL	75, 125, 250, 500 and 750 ng/mL	2, 5, 25, 50 and 75 ng/mL
Precision (≤%CV)					
Intra-Assay	8.3	9.6	14.7	6.8	12.3
Inter-Assay	6.3	28.6	15.2	28.0	20.3
Accuracy (≤ ± %deviation)					
Intra-Assay	13.7	11.9	4.7	13.9	7.5
Inter-Assay	9.3	10.1	1.8	17.2	9.9
Stability					
Bench Top	--	--	48 h @ 25 °C	48 h @ 25 °C	24 h @ RT
Long Term	--	--	12 weeks @-70 °C	12 weeks @-70 °C	--
Freeze/Thaw	--	--	3 cycles @-70 °C	--	6 cycles @-70°C

Table 17 Summary of Bioanalytical Method Validation for LV and 5-MeTHF in Clinical Studies

Trial No.	PR001-CLN-010		PR001-CLN-017	
Analyte	(6S)-LV	(6S)-5-MeTHF	(6S)-LV	(6S)-5-MeTHF
Matrix	Human plasma			
Detection Method	Chiral HPLC fluorescence			
Standard Curve Range	0.5 to 10 µmol/L	0.5 to 10 µmol/L	0.050 to 10.0 µmol/L	0.010 to 2.00 µmol/L
Regression Type	Linear analysis with $1/x^2$ weighting	Linear analysis with $1/x^2$ weighting	Linear analysis with $1/x^2$ weighting	Linear analysis with $1/x^2$ weighting
QC Samples Conc.	0.5, 1.5, 4 and 8 µmol/L		0.050, 0.150, 2.50 and 8.00 µmol/L	0.010, 0.030, 0.500 and 1.60 µmol/L
Precision (≤%CV)				
Intra-Assay	11.7	6.4	4.3	6.8
Inter-Assay	11.2	9.2	4.0	4.7
Accuracy (≤ ± %deviation)				
Intra-Assay	11.0	15.2	10.7	8.7
Inter-Assay	7.8	8.0	8.0	6.7
Stability				
Bench Top	2 h @ 22 °C	2 h @ 22 °C	8 days @ 4 °C	8 days @ 4 °C
Long Term	155 days @-70 °C	155 days @-70 °C	92 days @-70 °C	92 days @-70 °C
Freeze/Thaw	3 cycles @-70 °C	3 cycles @-70 °C	3 cycles @-70 °C	3 cycles @-70 °C

3 DETAILED LABELING RECOMMENDATIONS

Changes that were sent to the Applicant are presented below. Only relevant clinical pharmacology sections are included. ~~Strikethroughs~~ indicate content taken out by the Agency and contents in BLUE are the revisions made by the Agency.

7 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

4. APPENDIX - OCP FILING REVIEW FORM

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

BLA Number	STN 125327	**Brand Name**	Voraxaze®
DCP Division (I, II, III, IV, V)	V	**Generic Name**	Glucarpidase
Medical Division	Oncology/DOP2	**Drug Class**	A recombinant bacterial enzyme that hydrolyzes the carboxyl-terminal glutamate residue from folic acid and classical antifolates
OCP Reviewer	Lillian Hua Zhang, Ph.D.	**Indication**	For the (b) (4) reduction of toxic methotrexate (MTX) concentrations due to impaired renal function
OCP Team Leader	Hong Zhao, Ph.D.	**Dosage Form**	Lyophilized powder containing 1,000 Units of glucarpidase in single-use vials, which should be reconstituted with 1 mL of normal saline prior to use.
Date of Submission	November 17, 2008; April 30, 2009; May 10, 2010; September 29, 2010; December 16, 2010; June 30, 2011; July 18, 2011	**Dosing Regimen**	A single dose of 50 Units/kg, (b) (4) (b) (4) by bolus intravenous injection over 5 minutes. (b) (4)
Due Date of OCP Review	December 20, 2012	**Route of Administration**	Intravenous (IV)
Priority Classification	Priority	**Sponsor**	BTG International Inc.
PDUFA Due Date	January 17, 2012		

Clinical Pharmacology Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			19 Bioanalytical validation reports and 31 Bioanalytical data reports
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	1		PR001-CLN-005
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	1		PR001-CLN-012
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	x	3		PR001-CLN-010 (effect of glucarpidase on leucovorin PK in healthy subjects) PR001-CLN-017 (effect of glucarpidase on leucovorin PK in patients receiving MTX) PR001-NCL-PK004 (effect of glucarpidase on the PK of leucovorin in the presence of MTX in rabbits)
In-vitro:	x	3		PR001-NCL-PK006 PR001-NCL-PK007 PR001-NCL-PK008

in-silico				
Subpopulation studies -				
ethnicity:				
gender:				
geriatrics:				
renal impairment:	x	1		PR001-CLN-005
hepatic impairment:				
pediatrics:				
PD:				
Phase 2:	x	4		PR001-CLN-006, PR001-CLN-002, PR001-CLN-001, PR001-CLN-003
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Compatibility	x	1		1845/016 in rabbits (an earlier batch of glucarpidase produced by CAMR used in the initial clinical studies compared to the glucarpidase manufactured by Eurogentec and Cangene).
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
QTC studies:				
In-Vitro Release BE				
(IVIVC):				
Bio-wavier request based on BCS				
CS class				
Other CPB Studies				
Biliary Elimination				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments

	"X" if yes	Comments
Application fileable?	X	
Comments sent to firm?	X	Please submit the central HPLC bioanalytical study report(s) for clinical studies PR001-CLIN-002, PR001-CLIN-001, and PR001-CLIN-003 and provide the corresponding acceptance criteria for selectivity, accuracy, and precision of the assay run.
QBR questions (key issues to be considered)	**Any Key questions to be addressed during the review?**	
Other comments or information not included above	**Actions:** 1. The above comment was sent to the sponsor on September 2, 2011. 2. A request was submitted to OSI on August 12, 2011 for an inspection of the (b) (4) where a central HPLC assay was performed on blood samples from the efficacy/safety studies, PR001-CLN-006 and PR001-CLN-002.	
Primary reviewer Signature and Date	**Lillian Hua Zhang, Ph.D.**	
Secondary reviewer Signature and Date	**Hong Zhao, Ph.D.**	

': HFD-150 (CSO – **E Laughner;** MTL – **S Demko;** MO – **P Dinndorf**)
HFD-860 (Reviewer – **LH Zhang;** DDD - **B Booth;** DD - **A Rahman**)

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
	eria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	To-be-marketed product was used in the pivotal clinical trial.
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	N/A. IV Formulation
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
	Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)				
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		x		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	N/A. Orphan Drug
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

Comment:
Please submit the central HPLC bioanalytical study report(s) for clinical studies PR001-CLIN-002, PR001-CLIN-001, and PR001-CLIN-003 and provide the corresponding acceptance criteria for selectivity, accuracy, d precision of the assay run.

Actions:

1. The above comment was sent to the sponsor on September 2, 2011.
2. A request was submitted to OSI on August 12, 2011 for an inspection of the (b) (4) where a central HPLC assay was performed on blood samples from the efficacy/safety studies, PR001-CLN-006 and PR001-CLN-002.

Signatures

Lillian H. Zhang, Ph.D. Reviewer Division of Clinical Pharmacology 5	Hong Zhao, Ph.D. Team Leader Division of Clinical Pharmacology 5

Cc: DOP2: CSO – **E Laughner**; MTL – **S Demko**; MO – **P Dinndorf**
DCP-5: Reviewer – **LH Zhang;** TL – **H Zhao;** Deputy DD - **B Booth**
DD - **A Rahman**

APPEARS THIS WAY ON ORIGINAL.

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

BLA Number	STN 125327	Brand Name	Voraxaze®
DCP Division (I, II, III, IV, V)	V	Generic Name	Glucarpidase
Medical Division	Oncology/DOP2	Drug Class	A recombinant bacterial enzyme that hydrolyzes the carboxyl-terminal glutamate residue from folic acid and classical antifolates
OCP Reviewer	Lillian Hua Zhang, Ph.D.	Indication	For the (b) (4) reduction of toxic methotrexate (MTX) concentrations due to impaired renal function
OCP Team Leader	Hong Zhao, Ph.D.	Dosage Form	Lyophilized powder containing 1,000 Units of glucarpidase in single-use vials, which should be reconstituted with 1 mL of normal saline prior to use.
Date of Submission	November 17, 2008; April 30, 2009; May 10, 2010; September 29, 2010; December 16, 2010; June 30, 2011; July 18, 2011	Dosing Regimen	A single dose of 50 Units/kg (b) (4) (b) (4) by bolus intravenous injection over 5 minutes.
Due Date of OCP Review	December 17, 2012	Route of Administration	Intravenous (IV)
Priority Classification	Priority	Sponsor	BTG International Inc.
PDUFA Due Date	January 17, 2012		

Clinical Pharmacology Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			19 Bioanalytical validation reports and 31 Bioanalytical data reports
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	1		PR001-CLN-005
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	1		PR001-CLN-012
Dose proportionality -				
fasting / non-fasting single dose:				

fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	x	3		PR001-CLN-010 (effect of glucarpidase on leucovorin PK in healthy subjects) PR001-CLN-017 (effect of glucarpidase on leucovorin PK in patients receiving MTX) PR001-NCL-PK004 (effect of glucarpidase on the PK of leucovorin in the presence of MTX in rabbits)
In-vitro:	x	3		PR001-NCL-PK006 (inhibition of DAMPA on CYP isozymes) PR001-NCL-PK007 (induction of DAMPA on CYP isozymes) PR001-NCL-PK008 (effect of leucovorin and its active metabolite 5-MeTHF on the enzymatic degradation of MTX by glucarpidase in human plasma)
in-silico				
Subpopulation studies -				
ethnicity:				
gender:				
geriatrics:				
renal impairment:	x	1		PR001-CLN-005
hepatic impairment:				
pediatrics:				
PD:				
Phase 2:	x	4		PR001-CLN-006, PR001-CLN-002, PR001-CLN-001, PR001-CLN-003
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Compatibility	x	1		1845/016 in rabbits (an earlier batch of glucarpidase produced by CAMR used in the initial clinical studies compared to the glucarpidase manufactured by Eurogentec and Cangene).
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
QTC studies:				
In-Vitro Release BE				
(IVIVC):				

Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Biliary Elimination				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments

	"X" if yes	Comments
Application fileable?	X	
Comments sent to firm?	X	Please submit the central HPLC bioanalytical study report(s) for clinical studies PR001-CLIN-002, PR001-CLIN-001, and PR001-CLIN-003 and provide the corresponding acceptance criteria for selectivity, accuracy, and precision of the assay run.
QBR questions (key issues to be considered)	Any Key questions to be addressed during the review?	
Other comments or information not included above	**Actions:** 1. The above comment was sent to the sponsor on September 2, 2011. 2. A request was submitted to OSI on August 12, 2011 for an inspection of the (b) (4) where a central HPLC assay was performed on blood samples from the efficacy/safety studies, PR001-CLN-006, PR001-CLN-002, PR001-CLN-001, PR001-CLN-003.	
Primary reviewer Signature and Date	Lillian Hua Zhang, Ph.D.	
Secondary reviewer Signature and Date	Hong Zhao, Ph.D.	

CC: HFD-150 (CSO – E Laughner; MTL – S Demko; MO – P Dinndorf)
HFD-860 (Reviewer – LH Zhang; DDD - B Booth; DD - A Rahman)

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	To-be-marketed product was used in the pivotal clinical trial.
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	N/A. IV Formulation
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		x		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	N/A. Orphan Drug

16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
7	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

Comment:

Please submit the central HPLC bioanalytical study report(s) for clinical studies PR001-CLIN-002, PR001-CLIN-001, and PR001-CLIN-003 and provide the corresponding acceptance criteria for selectivity, accuracy, and precision of the assay run.

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Signatures

Lillian Hua Zhang, Ph.D. 9/8/11
Reviewer
Division of Clinical Pharmacology 5

Hong Zhao, Ph.D. 9/8/2011
Team Leader
Division of Clinical Pharmacology 5

Cc: DBOP: CSO – E Laughner; MTL – S Demko; MO – P Dinndorf
DCP-5: Reviewer – LH Zhang; TL – H Zhao; Deputy DD - B Booth
DD - A Rahman

TABLE 1. Clinical Studies to Support Efficacy

Study No	Study description, population	Objectives	Treatment and Number of Doses	No. of patients with MTX PK sampling
PR001-CLIN - 006 (pivotal)	Compassionate use, single arm, open label, multicenter Delayed MTX elimination due to MTX induced renal dysfunction (184 registered, 149 in safety population)	Efficacy and safety	IV glucarpidase 50 U/kg; single dose with optional 2nd dose based on MTX concentration	N = 27 (Central HPLC assay, n = 19 PK paramter values available) N = 124 (Local Assay, n = 107 PK paramter values available)
PR001-CLIN-002	Compassionate use, single arm, open label, multicenter Delayed MTX elimination due to MTX induced renal dysfunction (262 registered, 214 in safety population)	Efficacy and safety	IV glucarpidase 50 U/kg (1-3 doses)	N = 84 (Central HPLC assay, n = 66 PK paramter values available) N = 188 (Local Assay, n = 115 PK paramter values available)
PR001-CLIN-001	Compassionate use, single arm, open label, multicenter Delayed MTX elimination due to MTX induced renal dysfunction (44 registered and in safety population)	Efficacy and safety	IV glucarpidase 50 U/kg; up to 2 doses based on MTX concentration	N = 28 (Central HPLC assay, n = 10 PK paramter values available) N = 42 (Local Assay, n = 38 PK paramter values available)
PR001-CLIN-003	Compassionate use, single arm, open label, multicenter Delayed MTX elimination due to MTX induced renal dysfunction (82 registered, 69 in safety population)	Efficacy and safety	IV glucarpidase 50 U/kg; single dose with optional 2nd dose based on MTX concentration	N = 30 (Central HPLC assay, n = 66 PK paramter values available) N = 58 (Local Assay, n = 21 PK paramter values available)

Dose selection

In all of the clinical studies of glucarpidase, the recommended dose was 50 U/kg. The sponsor states that drug availability prompted imposition of a dose cap of 2,000 Units per dose at certain times during the conduct of the major glucarpidase clinical studies, Studies 006 and 002.

Efficacy

The primary efficacy endpoint used in Studies 006, 002, 001 and 003 was the proportion of patients with a clinically important reduction (CIR) in MTX concentration based on the central laboratory HPLC assay. A CIR was defined as a reduction in MTX concentration to ≤1 μmol/L at all post-glucarpidase time points, as measured by central laboratory HPLC assay. The key secondary efficacy endpoint includes change from baseline in MTX concentration and rebound of MTX concentration.

Based on the sponsor's analysis, a CIR in MTX concentration was achieved by 104 of 169 (61.5%) patients in the pooled Central MTX HPLC Population (95% CI: 54.0% to 68.5%). The median time to the first post-glucarpidase MTX concentration ≤1 μmol/L with all subsequent MTX concentrations ≤1 μmol/L was 15 minutes (0.25 hours). In the Central MTX HPLC Population, the median baseline MTX concentration was 11.68 μmol/L. After the first dose of glucarpidase, median MTX concentrations at all time points through Day 8 were <1 μmol/L (range 0.06 to 0.49 μmol/L), which represents a median reduction from baseline of 98.8% at the first measurement (median of 15 minutes after glucarpidase administration) to 98.6% at the last measurement (median of 40.25 hours after glucarpidase administration). 19.4% of patients met the criteria for rebound of MTX concentration. The median absolute increase in MTX concentration from the nadir to the highest rebound value was 1.6 μmol/L, and the median time to the highest rebound value was 64 hours after the first dose of glucarpidase.

Safety

The most common treatment-emergent adverse events (TEAEs) were renal disorder (27%), stomatitis and nausea (26%, each), vomiting (25%), diarrhea (16%), and blood creatinine abnormal (10%). The most common severe AEs were renal disorder (6%), stomatitis (4%), and neutrophil count abnormal (3%). Severe (Grade ≥3) events were reported in 55% of patients, life-threatening (Grade 4) events were reported in 30% of patients, and fatal (Grade 5) events were reported in 15% of patients. The sponsor states that these events are consistent with prolonged exposure to high concentrations of MTX and AEs most likely related to glucarpidase are hypersensitivity reactions, acute infusion reactions (AIR), paresthesia, flushing, headache, and possibly hypertension.

Additional Clinical Studies

Table 2 summarizes five additional studies (Studies 005, 010, 012, 016, and 017) that provide data on PK, drug interactions, and immunogenicity of glucarpidase.

TABLE 2. Other Clinical Studies Contributing Data to the BLA

Study No	Study description, population	Objectives	Treatment	No. of Subjects
Completed Pharmacokinetic and Interaction Studies				
PR001-CLIN-005	Phase 1, open label, single site, PK study Healthy subjects or subjects with impaired renal function	PK evaluation of glucarpidase	IV glucarpidase 50 U/kg; single dose	N = 8 (healthy subjects) N = 4 (subjects with impaired renal function)
PR001-CLIN-010	Phase 1, Two-period, randomized, double blind, placebo controlled crossover study Healthy male subjects	Effect of glucarpidase on PK of LV	IV glucarpidase 50 U/kg or placebo: single dose IV LV 150 mg/m^2 q 6 hr x 5 doses	N = 6

PR001-CLIN-017	Phase 1, open label, 2-arm multicenter interaction study Patients receiving high dose MTX Arm A Delayed MTX elimination Arm B Normal MTX elimination	Effect of glucarpidase on PK of LV	Arm A IV glucarpidase 50 U/kg plus LV Arm B LV	N = 11 (Arm A) N = 9 (Arm B)
Terminated Controlled Intervention Study				
PR001-CLIN-012	Phase 2, randomized, blinded, placebo controlled crossover study with an unblended compassionate use arm Patients treated with high dose MTX and leucovorin	Effect of glucarpidase on successful advancement to next chemotherapy cycle at the scheduled time	IV glucarpidase 50 U/kg or placebo	Randomized: 4 enrolled, 2 treated Compassionate use: 5 patients (PK of glucarpidase available in 2 patients)
Ongoing Uncontrolled Intervention Study				
PR001-CLIN-016	Open label, single arm, multicenter expanded access study Delayed MTX elimination due to MTX induced renal dysfunction	To provide compassionate use access to glucarpidase	IV glucarpidase 50 U/kg; Single dose	141 (no PK sampling but provide immunogenicity data)

Immunogenicity

A pooled analysis of immunogenicity data from three studies, Studies 012, 016 and 017, was performed by the sponsor. Of the 96 patients in these studies with at least one antibody evaluation after administration of glucarpidase, 16 patients (16.7%) had treatment-emergent anti-glucarpidase antibodies (AGA) at one or more time points. Twelve of the 16 patients who developed AGA had received a single dose of glucarpidase and four of the patients had received two doses of glucarpidase.

Intrinsic Factors

The effect of intrinsic factors on MTX and DAMPA (a major metabolite of MTX) PK parameters was evaluated by the sponsor in a combined study analysis using descriptive statistics. Central assay MTX and DAMPA PK data from Studies 001, 002, 003 and 006 were analyzed by subgroups according to age, gender, tumor type, pre-glucarpidase MTX concentration, pre-glucarpidase calculated creatinine clearance (CrCl) and hepatic impairment. According to the sponsor's analysis, the extent of MTX decrease following glucarpidase administration was not dependent on age, gender, tumor type, pre-glucarpidase MTX concentration, pre-glucarpidase calculated CrCl or hepatic impairment. The extent of the increase in mean DAMPA concentration was also independent of these factors.

In Vitro Evaluation

The sponsor conducted *in vitro* studies to evaluate the potential inhibitory and induction effect of DAMPA on human cytochrome P450. The sponsor also investigated the influence of leucovorin on the kinetics of the degradation of MTX by glucarpidase in human plasma *in vitro*.

Recommendation: The Office of Clinical Pharmacology/Division of Pharmaceutical Evaluation 5 finds that BLA STN 125327 is fileable.

Comment:

Please submit the central HPLC bioanalytical study report(s) for clinical studies PR001-CLIN-002, PR001-CLIN-001, and PR001-CLIN-003 and provide the corresponding acceptance criteria for selectivity, accuracy, and precision of the assay run.

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Signatures

Lillian Hua Zhang, Ph.D.	Hong Zhao, Ph.D.
Reviewer	Team Leader
Division of Clinical Pharmacology 5	Division of Clinical Pharmacology 5

Cc: DBOP: CSO – **E Laughner**; MTL – **S Demko**; MO – **P Dinndorf**
DCP-5: Reviewer – **LH Zhang**; TL – **H Zhao**; Deputy DD - **B Booth**
DD - **A Rahman**