CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125327Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125327
Priority or Standard	Priority
Submit Date(s)	Rolling submission Initial submission 10/17/08
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Division / Office	DOP2/OHOP
Reviewer Name(s)	Patricia Dinndorf, M.D.
Medical Team Leader	Suzanne Demko, PA-C
Division Director	Patricia Keegan, MD
Review Completion Date	12/19/11
Established Name	Glucarpidase
(Proposed) Trade Name	Voraxaze
Therapeutic Class	Enzyme
Applicant	BTG
Formulation(s)	Lyophilized powder 1,000 Units per vial
Dosing Regimen	50 Units/kg IV push over 5 minutes
Indication(s)	Toxic plasma methotrexate concentrations due to impaired renal function.
Intended Population(s)	Patients who develop delayed methotrexate clearance due to impaired renal function

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical recommendation for this biologic license application (BLA) 125357 for Voraxaze (glucarpidase) is approval. The indication is for the treatment of toxic plasma methotrexate (MTX) concentrations due to impaired renal function. Controlled trials for this indication were not feasible. The evaluation of efficacy was based on a pharmacodynamic endpoint.

The pharmacodynamic efficacy endpoint supporting this application is the proportion of subjects with an elevated methotrexate level prior to glucarpidase administration who demonstrate a rapid and sustained methotrexate level ≤ 1μmol/L after glucarpidase therapy. The analysis of this endpoint was carried out in a subset of patients entered on an National Cancer Institute (NCI) sponsored study with central laboratory high performance liquid chromatography (HPLC) measurement of post glucarpidase plasma methotrexate concentration. Glucarpidase was administered at a dose of 50 Units/kg. There were 22 patients eligible for the efficacy analysis. Ten patients achieved a response [45.5% (95% CI: 26.9, 65.3%)] after a single dose of glucarpidase. The percent reduction of methotrexate concentration was an exploratory endpoint. In 20 of 22 patients the methotrexate concentration was reduced and maintained greater than 95% from baseline pre-glucarpidase level up to 8 days.

Of note, glucarpidase therapy failed to prevent fatal methotrexate toxicity in 3% of patients. Among the 290 patients, included in the safety population, who received glucarpidasethere there were 8 deaths consistent with the sequelae of methotrexate toxicity within 30 days of glucarpidase exposure not related to progressive disease.

The safety evaluation of glucarpidase was complicated because it was not feasible to conduct controlled trials for this indication. The population suffers from extensive baseline toxicity. Patients with delayed methotrexate clearance develop life threatening complications including hematopoietic suppression, renal dysfunction/failure, hepatic dysfunction/failure, mucositis, and infections.

In the safety population the most common adverse events related to gucarpidase administration were parasthesia, flushing, nausea and/or vomiting, hypotension and headache. All adverse reactions were grade 1 or 2 except one episode flushing categorized as grade 3.

1.2 Risk Benefit Assessment

The toxicity profile of glucarpidase supports approval of glucarpidase for the indication of treatment of toxic plasma methotrexate concentrations due to impaired renal function.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no specific recommendations for postmarket risk evaluation and mitigation.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no specific recommendations for clinical postmarket requirements or commitments. There will be a postmarket requirement to evaluate the efficacy of intrathecally administered glucarpidase to prevent the central nervous system damage of an overdose of intrathecal methotrexate in an animal model.

2 Introduction and Regulatory Background

High dose methotrexate is a standard component of therapy for a number of malignant conditions. Methotrexate is predominantly metabolized through the kidney. If a patient develops renal insufficiency or renal failure after administration of high dose methotrexate they are at risk for severe possibly life-threatening toxicity due to persistent levels of methotrexate.

Glucarpidase is a recombinant enzyme cloned from *Pseudomonas* stain RS-16. Glucarpidase is an enzyme that metabolizes methotrexate to non toxic metabolites. Glucarpidase hydrolyzes the terminal glutamate residue from folates and folate analogs including methotrexate. This hydrolysis of the terminal glutamate residue converts methotrexate to the inactive metabolites glutamate; 2,4-diamino-N10-methylpteroic acid (DAMPA); and 7-hydroxy DAMPA These inactive metabolites are eliminated by the liver.

Glucarpidase is intended to rescue patients with potentially severe methotrexate toxicity due to renal dysfunction or failure. It is not feasible to prospectively study glucarpidase in a randomized placebo controlled trial for this indication. Delayed methotrexate clearance related to renal insufficiency is an emergency situation that occurs unpredictably, and it would not be ethical to withhold this antidote from a patient with potentially life-threatening methotrexate intoxication in order to study glucarpidase in a controlled trial setting.

Plasma levels of methotrexate lower than 1 µmol/L are considered below the level associated with severe toxicity. Below this level the methotrexate toxicity can be successfully ameliorated with leucovorin and hydration. Therefore a dose and schedule of glucarpidase that reliably results in rapid and sustained plasma levels of methotrexate below this threshold in patients with renal compromise and toxic plasma levels of methotrexate due to delayed methotrexate clearance represents a pharmacodynamic endpoint that is judged to be a valid surrogate endpoint.

DAMPA interferes with the measurement of methotrexate concentration using immunoassays resulting in an erroneous measurement which overestimates the methotrexate concentration. Due to the long half-life of DAMPA ($t_{1/2}$ of approximately 9 hours), measurement of methotrexate using immunoassays is unreliable for up to 48 hours following glucarpidase administration. The plasma methotrexate levels that support the efficacy of glucarpidase were measured in a central laboratory using an HPLC methodology.

Another important issue regarding the reliability of the pharmacodynamic data used to support this application is the potential of glucarpidase to result in *ex vivo* clearance of plasma methotrexate levels. The applicant conducted spiking experiments in whole blood and plasma to evaluate *ex vivo* metabolism of methotrexate by glucarpidase.

These confirmed the sample handling specifications were adequate to prevent the *ex vivo* metabolism of plasma methotrexate by glucarpidase.

2.1 Product Information

Generic Name:	Glucarpidase
Trade Names:	Voraxaze
Pharmacological Category:	Enzyme
New Molecular Entity:	Yes
Drug Class:	Recombinant Enzyme
Route of Administration:	Intravenous
Dose and Regimen:	50 Units/kg intravenous bolus administration over 5 minutes
Population Studied:	Patients with delayed methotrexate clearance
Proposed Indication:	(b) (4) reduction of toxic plasma methotrexate concentrations due to impaired renal function

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no drugs currently available that eliminate methotrexate when methotrexate clearance is delayed. Methotrexate is primarily cleared through the kidneys. High dose methoterexate is administered with vigorous hydration, alkalinization of the urine, and rescue with leucovorin. Patients are monitored with serial creatinine levels, methotrexate levels, and urinalyses. Hydration is adjusted to maintain a dilute urine specific gravity and high urine output. Bicarbonate is administered to maintain an alkaline urine pH. Leucovorin calcium is administered at a dose and schedule determined by dose and schedule of methotrexate. If methotrexate clearance is delayed then the dose and schedule of the leucovorin calcium is augmented until the methotrexate levels falls below 1 µmol/L. Patients generally continue standard leucovorin rescue until the methotrexate level is less than 0.05 to 0.1 µmol/L.

Leucovorin calcium protects normal cells from methotrexate toxicity but does not alter the clearance of methotrexate. If a patient develops renal failure after receiving high dose methotrexate the only approach to clearing methotrexate is extracorporeal removal, specifically dialysis.

2.3 Availability of Proposed Active Ingredient in the United States

This agent is not marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

There are no pharmacologically related products of this class.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 1: Regulatory History of Glucarpidase

1992	IND 4663 NCI ▪ This IND was for glucarpidase manufactured as CAMR lot 004 ▪ IND inactivated 10/12/06
2003	Protherics acquired rights to glucarpidase
3/18/04	Original Submission of IND 11557 - Hold Teleconference with Protherics, Inc. IND 11557 was placed on full clinical hold. The following issues related to the endpoint to establish efficacy of glucarpidase were discussed. ▪ There were no study objectives specified. ▪ There was no plan for the analysis of the data. During this conversation FDA asked Protherics what clinical endpoints they planned to study. Protherics stated they planned to look at methotrexate levels. FDA counseled Protherics they would need to demonstrate durability of the response without rebound.
4/14/04	IND 11630 NCI ▪ Protocol for IT overdose and a Special Exception Protocol using "Protherics Product" ▪ IND Inactivated May 11, 2007
4/13/04	Type B End of Phase 2 meeting Protherics presented their development plan for glucarpidase. The following was the discussion concerning endpoints: ▪ (b) (4) f t ▪ FDA informed Protherics that justification of a predictive relationship between a specific methotrexate level and the incidence and severity of specific toxicities was required. The following agreement were reached: ▪ The manufacturing data presented are inadequate to confirm biochemical comparability between the lot of material used for the earlier clinical trials (CAMR lot 004) and the lot intended for bridging pharmacokinetic (PK) and pharmacodynamic (PD) studies and for the commercial product. ▪ Protherics' clinical pharmacological data are inadequate for confirming comparability of the CAMR product with the commercial product.

11/9/04	Teleconference Discussion of the deficiencies in data available from NCI compassionate IND to support application. ▪ FDA stated that the primary efficacy endpoint should be a determination of the success rate in methotrexate level reduction to a level that is correlated with clinical benefit.
7/21/05	Type C meeting The surrogate endpoint of clinical benefit was discussed. ▪ Achieving and maintaining methotrexate levels below 1µmol/L in a proportion of patients treated was proposed as a surrogate endpoint of clinical benefit. ▪ The FDA consulted a special government employee consultant inSepetember 2005. The consultant agreed that achieving and maintaining a methotrexate level below 1 µmol/L at 48 hours or longer was a reasonable surrogate for clinical benefit.
12/5/05	FDA Advice Letter ▪ The application must contain the final study report (FSR) of a PK study in 8 subjects with normal renal function and 4 subjects with impaired renal function [Trial 005] ▪ The application must contain the FSR of a trial comparing the PK characteristics of CAMR lot 004 and the commercial in rabbits in order to establish this product was bioequivalent if data from studies using the CAMR lot 004 were to be used to support safety and efficacy in the BLA. ▪ The clinical efficacy of glucarpidase based on data from the NCI study conducted under IND 11630 [Trial 006] may be limited by several deficiencies.
4/28/06	Pre-BLA Meeting Protherics proposed the following: ▪ Use the data from the 68 patients enrolled on the NCI study conducted under IND 11630 [PR001-CLN-006] between July 2004 and November 2005 to support this application. ▪ Of these 68 patients there were 27 with adequate data available for their proposed efficacy evaluation. The FDA had the following comments regarding the Statistical Analysis Plan (SAP) Protherics submitted: ▪ FDA agreed to that the primary analysis population would include patients with plasma methotrexate levels determined by HPLC and plasma methotrexate >1 µmol/L in their last sample before receiving glucarpidase. ▪ The FDA agreed to the primary objective of the "Estimate the

	proportion of patients who achieve a durable, clinically important reduction (CIR) in plasma methotrexate concentration, defined as a reduction of plasma methotrexate ≤ 1 µM in all post-glucarpidase samples." ▪ The analysis should be to determine the point estimate of response rate and determination of the confidence intervals around the observed proportion of eligible patients with sustained post glucarpidase methotrexate levels ≤ 1 µmol/L measured by HPLC. ▪ A subgroup analysis should be conducted on groups based on baseline methotrexate levels, (such as patients with > 1, >10, or > 100 µmol/L immediately prior to treatment. ▪ The FDA agreed to the primary endpoint of "Maximum plasma methotrexate determined by HPLC analysis in any post-glucarpidase sample."
6/30/06	Revised SAP submitted to IND 11557 as amendment 27. ▪ The sponsor has changed their primary analysis to a 95% confidence interval (Newcombe-Altman method) for the proportion of patients that satisfy a CIR. ▪ FDA Statistician agreed the change was acceptable.
(b) (4)	(b) (4)
12/5/07	Fast Track Designation Granted (b) (4) reduction in toxic methotrexate levels in patients who experience delayed methotrexate clearance due to impaired renal function."
11/17/08	BLA 125327 ▪ Rolling eCTD submission with Module 1 (FDA Regional Information), 2 (Common Technical Document Summaries), and 4 (Nonclinical Study Reports) ▪ Module 5 (Clinical Study Reports) submitted 5/11/09 ▪ eCTD files deleted because the application was unacceptable due to major defects overall and in the electronic files 5/18/10 ▪ Modules 1, 2, and 4 replaced 5/18/10 ▪ Module 3 (Quality) submitted 9/29/10 ▪ Resubmission of module 4 on 12/16/11 ▪ Revised Module 5 and amended Module 3 submitted 6/30/11 ▪ Notification the submission complete with schedule to allow pre-approval inspection of production 7/18/11

3/31/11	Name Change Protherics Inc. acquired by BTG International Inc.

2.6 Other Relevant Background Information

A formulation of glucarpidase, CAMR lot 004, was extensively studied under IND 4663 and in Europe in 2 studies, Berlin [Trial 001] and Bonn [Trial 003]. The applicant was not able to demonstrate that the agent was comparable to the gluparpidase product under review in this BLA. Specifically the application contains a Final Study Report for a PK study in rabbits titled "Pharmacokinetics of Voraxaze™ (glucarpidase) following a Single Intravenous Administration in the Male Rabbit" to compare CAMR lot 004 with the commercial product. The study failed to confirm the CAMR lot 004 glucarpidase and the commercial product were bioequivalent. [eCTD 4.2.2.2 PR001-NCL-PK-1845-016 – Pharmamcokinetics of . . . ; 4.2.2.2.1 Legacy Study Report; Study PR001-NCL-PK001/1845 –Study Report page 23/133]

REVIEWER COMMENT:
Studies utilizing the CAMR lot 004 product will not be considered as providing substantial evidence of the safety or efficacy for glucarpidase in this application.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Audits
The Division of Scientific Investigations (DSI) did not audit clinical sites. The nature of the indication for this product precluded study in a prospective randomized trial. No single site contributed more than one or two subjects responsible for the analysis supporting the efficacy of this agent. Glucarpidase was administered to patients who developed renal compromise after receiving high dose methotrexate on an emergent basis. In Trial 006, the trial that includes the data to support efficacy of this agent there were 68 subjects treated in 55 centers in the US, Australia, and Canada. It is unlikely that a DSI audit of a few centers result in additional information concerning the quality of data.

Division of Bioequivalence and GLP Compliance (DBGC) from the Office of Scientific Investigations (OSI) audited the bioanalytical portion of Trial 002 and Trial 006 on 9/27/11 and 9/30/11. The analytical portions of these studies were conducted by the (b) (4)

DBGC concluded Trial 002 was not conducted in a manner that confirms the validity of results to support a BLA. This study evaluated the CAMR lot 004 product. The results of this study will not be used to support the efficacy of glucarpidase in this application. BTG has not confirmed that the CAMR lot 004 product was comparable to glucarpidase being evaluated in this application. See section 2.6.

DBGC concluded that methotrexate concentrations above 0.5 µmol/L from Trial 006 were adequate to support the application. Pharmacodynamic data from a subset of patients enrolled on Trial 006 will be used to support the efficacy of this product.

Review of the Application
The clinical report forms (CRFs) of the 27 subjects from Trial 006 included in the efficacy evaluation were reviewed.

- The CRFs were evaluated to confirm that the subjects met the eligibility criteria for the trial, that is the protocol specified degree of toxic methotrexate concentration and degree of renal dysfunction. One subject, 0236, was identified who did not meet the criteria. This patient was enrolled based on a erroneous methotrexate level reported to be 500 µmol/L which was actually 50 µmol/L. This level was within the standard methotrexate clearance curve, and the patient did not have any evidence of renal dysfunction.

- The CRFs were evaluated to determine if the date and time of the pre and post glucarpidase samples included in the main evaluation of efficacy were adequately documented. Several subjects were missing the sample log from the CRF, but BTG provided these upon request submitted 10/24/11. This documentation was satisfactory.
- The CRFs of the 22 subjects included in the main evaluation of efficacy were reviewed to determine if the dose and time of administration of methotrexate and glucarpidase were correctly reported in the xpt datasets. The data in the xpt datasets was determined to be correct in most cases. Although the total methotrexate dose for body surface area was incorrectly reported on Dataset ADEX column EXDOSEN for subject 233 (2.9 g/m^2 correct 1.4 g/m^2), subject 245 (19.2 g/m^2 correct 12 g/m^2), subject 255 (20 g/m^2 correct 12 g/m^2) this did not preclude evaluation of the endpoint.

REVIEWER COMMENT: The data submitted to support this application is adequate to evaluate the efficacy endpoint of "the proportion of patients who achieve a durable clinically important reduction in plasma methotrexate concentration, defined as a reduction of plasma methotrexate ≤ 1 µmol/L in all post-glucarpidase samples."

3.2 Compliance with Good Clinical Practices

The cover page of the study reports for PR001-CLN-pro005 (Trial 005), PR001-CLN-006 (Trial 006), PR001-CLN-pro010 (Trial 010) , PR001-CLN-011, PR001-CLN-PRO012, PR001-CLN-016 (Trial 016), PR001-CLN-017 (Trial 017) included the following declaration: This study was performed in compliance/accordance with Good Clinical Practices.

3.3 Financial Disclosures

Section 1.3.4. includes form 3454 attests (option 2) the applicant is submitting studies sponsored by a party other than the applicant. No financial compensation was given to any of the investigators.

A list of investigators for the NCI sponsored study PR001-CLN-006 is provided.

A letter from Sherry S. Ansher, Ph.D., Associate Chief of Agreement Coordination Group, Regulatory Affairs Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis. This letter stated: "The National Cancer institute (NCI), as a federal government agency, cannot provide an equity interest to its investigators. Furthermore, all funding for studies conducted under NCI sponsorship is provided to the institution in the form of a grant or contract. Individual investigators do not receive money from the NCI except for salaries and bonuses that comprise their ordinary compensation as government employees.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The final reports for the manufacturing site inspection and product review were not available at the time this review was completed. At this time review was completed, there were no CMC problems identified that will preclude approval of this application. There will be CMC post marketing commitments.

4.2 Clinical Microbiology

Not applicable for this application.

4.3 Preclinical Pharmacology/Toxicology

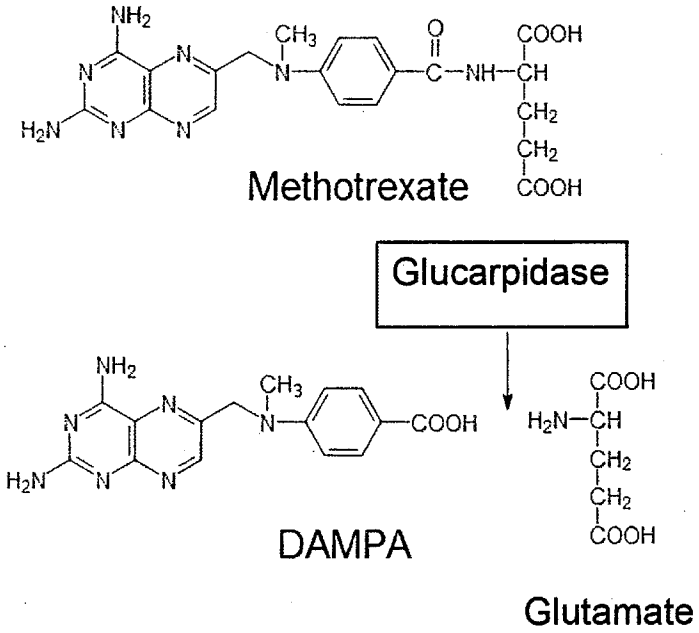
The final reports of the preclinical pharmacology toxicology were not available at the time this review was completed. At the time review was completed, there were no pharmacology toxicology studies missing that will preclude approval of this application. The applicant will be required to perform an animal study of intrathecal methotrexate overdose treated with glucarpidase.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Glucarpidase is a recombinant enzyme cloned from *Pseudomonas* stain RS-16. Glucarpidase is an enzyme that metabolizes methotrexate to non toxic metabolites. Glucarpidase hydrolyzes the terminal glutamate residue from folates and folate analogs including methotrexate. This hydrolysis of the terminal glutamate residue converts methotrexate to the inactive metabolites glutamate; 2,4-diamino-N10-methylpteroic acid (DAMPA); and 7-hydroxy DAMPA These inactive metabolites are eliminated by the liver.

Figure 1: Glucarpidase Reaction with Methotrexate



4.4.2 Pharmacodynamics

See section 6.1.4 for the pharmacodynamic evaluation of glucarpidase.

4.4.3 Pharmacokinetics (copied from Clinical Pharmacology Review)

Pharmacokinetics

Glucarpidase pharmacokinetics were studied in healthy subjects in the absence of methotrexate and pharmacokinetic data was collected in only two patients with high dose methotrexate 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 healthy subjects except that the half-life appeared shorter in patients (~3.5 hours by the enzymatic method, ~3.0 hours by enzyme-linked immunosorbent assay (ELISA)) than that observed in healthy subjects (~5.6 hours by the enzymatic method, ~9.0 hours by ELISA).

Pharmacokinetics Renal Impairment:

Following an intravenous injection of glucarpidase 50 Units /kg in subjects with severe renal impairment (creatinine clearance <30 mL/min) in the absence of methotrexate, the mean pharmacokinetic 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. No dose adjustment for glucarpidase in patients with renal impairment is necessary.

Pharmacokinetics Concomitant Leucovorin Therapy:
Leucovorin, an active, chemically reduced derivative of folic acid, is used to counteract the cellular damage caused by high dose methotrexate. As glucarpidase does not cross the blood-brain barrier or cellular membranes, in clinical practice glucarpidase would almost invariably be given to patients concomitantly receiving leucovorin as a rescue agent for high dose methotrexate therapy. Therapy with leucovorin should be continued according to its prescribing information for delayed methotrexate elimination; however, leucovorin should not be administered within 2 hours before or after a dose of glucarpidase due to its pharmacokinetic interaction with glucarpidase.

In a study of cancer patients receiving a high dose methotrexate and leucovorin rescue regimen, an intravenous administration of 50 Units/kg glucarpidase 2 hours before leucovorin reduced (6S)-Leucovorin AUC_{0-3h} by 33% and C_{max} by 54%, and also reduced leucovorin active metabolite, (6S)-5-methyl-tetrahydrofolate, AUC_{0-3h} by 92% and C_{max} by 93%.

5 Sources of Clinical Data

BTG submitted a final clinical study report on Trial 006 and an interim clinical study report on Trial 016. These trials provided the data that supported the clinical efficacy and safety evaluation of glucarpidase in this application. Clinical study reports were submitted for 4 PK and drug interaction studies, Trial 005, Trial 010, Trial 012 and Trial 017.

BTG included FSRs for Trial 001, Trial 002, and Trail 003. These trials were conducted with glucarpidase manufactured as CAMR lot 004. The commercial product evaluated in this BLA was manufactured (b) (4) (b) (4) BTG was not able to demonstrate that CAMR lot 004 was biochemically equivalent to commercial product. Because the products were not demonstrated to be biochemically equivalent, data from Trial 001, Trial 002, and Trail 003 can not be considered as substantial evidence supporting the safety or efficacy of glucarpidase in this application. However, the clinical experience with the CAMR lot 004 provides an additional level of comfort regarding the safety profile of glucarpidase for this indication. The FSRs for Trial 001, Trial 002, and Trail 003 provide safety information for 327 patients.

5.1 Tables of Studies/Clinical Trials

Table 2: Major Trials Supporting Efficacy and Safety in Application

Major Studies Supporting Safety and Efficacy of Glucarpidase in this Application				
Sponsor / Conducted	**Population**	**Dose Glucarpidase**	**Efficacy**	**Safety**
Title: Trial 006 "Special Exception Protocol for the Use of Carboxypeptidase-G2 for MTX Toxicity"				
NCI IND 11630 Jun 2004 to Apr 2007	Severely delayed MTX 2° to renal dysfunction	50 U/kg IV; 2nd dose 48 hr if baseline MTX > 100 µmol/L. Nov 2005 max 2000 U	Eligible patients enrolled July 2004 and Nov 2005 n = 22	Total enrolled n = 184 Safety Population n = 149
Title: Trial 016 "An Open-label Treatment Protocol for the Use of Voraxaze as Adjunctive Treatment for Patients Experiencing or at Risk of Methotrexate Toxicity"				
BTG IND 11557 May 2007 to Oct 2010 (ongoing)	Severely delayed MTX 2° to renal dysfunction	50 U/kg IV	NA	Total enrolled n = 244 Total dosed n = 171 Safety Population n = 141

Table 3: PK and Drug Interaction Trials in Application

PK and Drug Interaction Trials				
Sponsor / Conducted	**Trial Design**	**Population**	**Dose Glucarpidase**	**Safety**
Title: Trial 005 "A Trial to Determine the Pharmacokinetics of Glucarpidase (Voraxaze) in Subjects with Normal and Impaired Renal Function"				
BTG IND 11557 / Jul to Oct 2004	Phase 1 PK trial to evaluate renal effect	Subjects with normal (n = 8) or impaired (n = 4) renal function	50 U/kg IV	Safety for 12 subjects not complicated by MTX toxicity
Title: Trial 010 "Investigation of the Effect of Glucarpidase on Leucovorin Pharmacokinetics in Healthy Male Subjects"				
BTG in UK / Mar to Apr 2006	Randomized crossover double blind glucarpidase/ placebo with leucovorin	Healthy males (n= 6) co-administerd with leucovorin 150 mg/m2 q 6 hrs x 5	50 U/kg IV (glucarpidase or placebo)	Safety for 6 subjects not complicated by MTX toxicity
Title: Trial 012 Randomized, Blinded, Placebo-controlled Trial of High Dose Methotrexate with Leucovorin Rescue (HDMTX-LV) with or without Glucarpidase in Osteosarcoma.				
BTG at MD Anderson Oct 2008 to Mar 2009 Closed early due to poor accrual	Randomized crossover ± glucarpidase after MTX with leucovorin	Osteosarcoma patients Compare toxicity and ability to start nest course of therapy on schedule	2 doses of glucarpidase 50 U/kg, 24 hours apart versus placebo	Safety for 7 patients exposed to glucarpidase; 2 of 4 in the randomized arm and 5 in compassionate arm
Title: Trial 017 "An Open-label Study to Assess the Pharmacokinetics of Leucovorin in Patients Receiving High Dose Methotrexate, with or without Voraxaze Treatment"				
BTG IND 11557 / Jul 2008 to Jul 2009	Comparison PK leucovorin in normal versus delayed MTX clearance	Patient receiving HDMTX (n=11) Arm A delayed MTX Arm B normal MTX	Arm A 50 U/kg IV plus leucovorin Arm B leucovorin	

Table 4: Trials in Related Product CAMR Lot 004

Legacy Trials Utilizing CAMR Lot 004 Glucarpidase Safety Data of Limited Usefulness			
Sponsor / Conducted	**Population**	**Dose Glucarpidase**	**Safety**
Title: Trial 001 "Study of Recombinant Carboxypeptidase G2 (CPG2) for the Management of Patients with Delayed Methotrexate (MTX) Clearance or Intrathecal MTX Overdosage" [Berlin]			
Conducted in 29 German Centers / Jan 2000 to Aug 2003	Severely delayed MTX 2° to renal dysfunction	50 U/kg IV; 2nd dose if baseline MTX > 0.1 µmol/L at 24 hrs	Total enrolled n = 45 Safety Population n = 44
Title: Trial 002 "A Trial of Carboxypeptidase-G2 (CPG2) for the Management of Patients with Methotrexate Toxicity and Renal Dysfunction"			
NCI IND 4663 / Nov 1993 to May 2004	Severely delayed MTX 2° to renal dysfunction	50 U/kg IV (1 to 3 doses) Feb 2002 max 2000 U (Thymidine for some)	Total enrolled n = 263 Safety Population n = 214
Title: Trial 003 "A trial of Carboxypeptidase-G2 (CPG2) for the Management of Patients with Methotrexate Toxicity and Renal Dysfunction" [Bonn]			
Conducted in 13 non US Countries / Mar 1997 to Mar 2002	Severely delayed MTX 2° to renal dysfunction	50 U/kg IV 2nd dose if > 1 log decrease but remained MTX > 1 µmol/L	Total enrolled n = 82 Safety Population n = 69

5.2 Review Strategy

The clinical efficacy review of glucarpidase in this application is based on a subset of patients included in Trial 006. A summary of the subset of patients from Trial 006 used to support efficacy is presented in section 6.1 below.

The clinical safety review of glucarpidase in this application will focus on 2 studies Trial 006 and Trial 016. Trial 006 and Trial 016 are summarized in sections 5.3.1 Trial 006 and 5.3.2 Trial 016 below.

Supplementary safety information is included in the pharmacokinetic and drug interaction studies. The safety of volunteer subjects enrolled on the PK and drug interaction studies without methotrexate, Trial 005 and Trial 010 are noteworthy because they isolate drug reactions of glucarpidase from methotrexate. Trial 005 and Trial 010 are summarized in section 5.3.3 Trial 005 and 5.3.4 Trial 010 below. Trial 012

and Trial 017 PK trials in patients receiving methotrexate are also summarized in sections 5.3.5 Trial 012 and 5.3.6 Trial 017 below.

Trial 001, Trial 002, and Trial 003 were conducted using glucarpidase manufactured as CAMR lot 004. BTG failed to verify that this material was comparable to the commercial product.. These trials include safety information on 327 patients who received glucarpidase. Trials are summarized in sections 5.3.7 Trial 001 CAMR Lot 004, 5.3.8 Trial 002 CAMR Lot 004, and 5.3.9 Trial 003 CAMR Lot 004 below

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Trial 006

Schema

Table 5: Trial 006 "Special Exception Protocol for the Use of Carboxypeptidase-G2 for MTX Toxicity"

Study Design	Open Label, Nonrandomized, Compassionate Use Protocol
Trial Opened to Subject Entry:	June 2004
Trial Closed to Entry:	April 2007
Dose and Route:	Glucarpidase 50 Units/kg intravenous (IV) push over 5 minutes; Second dose glucarpidase at 48 hours for patients with base line methorexate level > 100 µmol/L; In November 2005 the dose was capped to 2000 Units maximum regardless of weight
Indication:	Markedly delayed methotrexate clearance due to renal failure/dysfunction
Planned enrollment:	Not stated
Actual enrollment:	184 enrolled; 149 with safety data submitted; 27 with samples sent for plasma methotrexate evaluations after glucarpidase treatment
Terminated early (YES/NO):	No

Study Objectives:

Primary:

To confirm the efficacy of glucarpidase by evaluating methotrexate plasma concentrations following glucarpidase administration (as measured by the HPLC method) while providing access to glucarpidase on a compassionate basis for patients experiencing methotrexate toxicity and who have no other treatment options.

Secondary:

To demonstrate a sustained reduction in plasma methotrexate following glucarpidase administration, to collect additional data on methotrexate toxicities and safety, and to assess the development of antibodies to glucarpidase.

Eligibility Criteria:
Inclusion Criteria:
Osteosarcoma Patients

- Plasma methotrexate level greater than 50 µmol/L at 24 hr, greater than 5 µmol/L at 48 hr, or greater than 2 standard deviations above the mean methotrexate excretion curve at greater than 12 hours following methotrexate administration
- Abnormal renal function greater than 2-fold increase in serum creatinine above pretreatment level.

Patients with Other Diagnoses

- Plasma methotrexate level greater than 10 µmol/L for more than 42 hours after start of methotrexate infusion or greater than 2 standard deviations above the mean methotrexate excretion curve at least 12 hours following methotrexate administration
- Abnormal renal function defined by serum creatinine greater than 1.5 x the upper limit of normal or creatinine clearance less than 60 mL/min at least 12 hours following methotrexate administration.

Protocol Amendments
November 2005

- Dose of glucarpidase capped at 2000 units regardless of weight
- Collection of further PK samples removed from the protocol

Demographics and Baseline Characteristics

Table 6: Trial 006 Demographics and Baseline Characteristics

Demographics and Baseline Characteristics n = 149	
Gender	
Male 94 (64%)	Female 54 (36%)
Age (years)	
Mean - 31.8	0 - 12 35 (23%)
Median - 18	13 - 18 41 (28%)
Range - 1 month to 85 years	19 - 65 54 (36%)
	66 - 85 19 (13%)
Weight in Kg	
Mean - 67.1 Median - 68.2	Range - 3.5 to 155.4
Diagnosis	
Osteosarcoma/sarcoma 47 (32%)	Other 7 (5%)
Leukemia Lymphoma 93 (63%)	Unknown n=2
MTX Dose (available for n= 146)	
Mean - 7.5 g/m^2 Median - 5.0 g/m^2 Range - 10 mg/m^2 to 40 g/m^2	

Exposure to Glucarpidase

Patients in the safety population of Trial 006 received 1 (n=106) or 2 (n= 30) doses of glucarpidase. The number of doses was not specified in 13 patients. Doses ranged from 18 to 98 Units/kg per dose and with a median dose 49 Units/kg.

Safety

Methodology for Collecting Safety Data Trial 006

- Treating physicians were asked to fill out a flow sheet with a daily log of adverse events (AEs) categorized as:
  - Methotrexate Toxicity - diarrhea, nausea/vomiting, neurological, renal, stomatitis, other (these were categorized in the application as "not related to glucarpidase")
  - Glucarpidase Toxicity – allergy, other (these were categorized in the application as "glucarpidase-related")
  - Other Toxicities - (these were categorized in the application as "not related to glucarpidase")
- Additional information was collected from clinical records treating physicians submitted.

- AE information was abstracted from these documents by BTG using Common Terminology Criteria for Adverse Events (CTCAE) v 3

Table 7: Trial 006 Per Patient Toxicities

Per Patient Possible Glucarpidase Toxicities Excluding Hematologic, Hepatic, or Renal (n=149)		
	Any Grade	**≥ Grade 3**
Paraesthesia	6	
Flushing	4	1 Grade 3
Nausea/ Vomiting	3	
Hypotension	2	
Hypersensitivity	1	
Throat Tightness	1	
Tremor	1	
Somnolence	1	1 Grade 3*
Ventricular Tachycardia	1	1 Grade 4*
Tremor	1	
Headache	1	
Diarrhea	1	

*Based on review of the CRFs these toxicities are unlikely to be related to glucarpidase. These were pre-existing conditions in the patients exacerbated after methotrexate intoxication.

Conclusions

The methodology for collecting safety data was suboptimal. Safety information was not prospectively collected or characterized. Based on the information submitted, it appears treatment with glucarpidase appears to be adequately tolerated. See Section 6.1.4 for discussion of the efficacy analysis.

5.3.2 Trial 016

Schema

Table 8: Trial 016 "An Open-Label Treatment Protocol for the Use of Voraxaze as Adjunctive Treatment for Patients Experiencing or at Risk of Methotrexate Toxicity"

Study Design	Open Label Treatment Protocol
Trial Opened to Subject Entry:	June 2004
Trial Closed to Entry:	Ongoing; Cut-off for data analysis October 2010
Dose and Route:	Glucarpidase 50 Units/kg IV push over 5 minutes;
Indication:	For adjunctive treatment of patients receiving high-dose methotrexate ≥ 1 g/m^2 who are experiencing or at risk of methotrexate toxicity. Patients are considered at risk of methotrexate toxicity if they have impaired renal function, which can lead to a delay in methotrexate elimination, or have evidence of delayed elimination based on methotrexate levels.
Planned enrollment:	Up to 100 patients per year; Up to 400 patients
Actual enrollment:	At the time of cut-off for data analysis October 2010: Enrolled: n = 244 Documentation glucarpidase administered n = 171 Patients with safety information n = 141
Terminated early (YES/NO):	No

Study Objectives

Primary objective:

To provide compassionate use access to glucarpidase for patients receiving high-dose methotrexate ≥ 1 g/m^2 who are experiencing or are at risk of methotrexate toxicity. Patients receiving high-dose methotrexate are considered at risk of methotrexate toxicity if they have impaired renal function, which can lead to a delay in methotrexate elimination, or have evidence of delayed elimination based on methotrexate levels.

Secondary objective:

To further assess the safety of glucarpidase administration

Inclusion Criteria:
Male or female patients of any age receiving high-dose methotrexate ≥ 1 g/m^2 who are experiencing or are at risk of methotrexate toxicity will be eligible to receive glucarpidase if they have impaired renal function and evidence of delayed methotrexate elimination based on renal dysfunction and methotrexate levels defined as follows.

Osteosarcoma Patients

- Plasma methotrexate level greater than 50 µmol/L at 24 hr, greater than 5 µmol/L at 48 hr, or greater than 2 standard deviations above the mean methotrexate excretion curve at greater than 12 hours following methotrexate administration
- Abnormal renal function greater than 2-fold increase in serum creatinine above pretreatment level.

Patients with Other Diagnoses

- Plasma methotrexate level greater than 10 µmol/L for more than 42 hours after start of methotrexate infusion or greater than 2 standard deviations above the mean methotrexate excretion curve at least 12 hours following methotrexate administration
- Abnormal renal function defined by serum creatinine greater than 1.5 x the upper limit of normal or creatinine clearance less than 60 mL/min at least 12 hours following methotrexate administration.

Protocol Amendments
September 2007

- Change of sample times for anti-glucarpidase antibody testing
- Modified to allow for case by case evaluation by BTG of inclusion of individual patients not meeting study inclusion criteria
- Warning regarding the risks of retreatment

September 2010

- Change in contract research organization (CRO) center information
- Updated expected number of patients to be enrolled to up to 400
- Clarification of hypersensitivity exclusion criteria
- Expanded adverse events AE collection criteria to be consistent with 21 CFR 312 [Note this data collection change was instituted for patients accrued to the study after the safety population evaluated in this application.]
- Expanded renal function monitoring

Results

Demographics

Table 9: Trial 016 Demographics and Baseline Characteristics

Demographics of Safety Population Trial 016 n = 141	
Gender	
Male 92 (65%)	Female 49 (35%)
Age (years)	
Mean - 28.7	0 - 12 49 (35%)
Median - 16	13 – 18 33 (23%)
Range - 6 months to 85 years	19 – 65 40 (28%)
	66 – 85 19 (13%)
Weight in Kg	
Mean - 64.6 Median - 64.4	Range - 5.3 to 138
Diagnosis	
Osteosarcoma/sarcoma 46 (33%)	Other 7 (5%)
Leukemia Lymphoma 88 (62%)	
MTX Dose (available for n=139)	
Mean – 7.6 g/m^2 Median – 6.0 g/m^2	Range - 0.7 g/m2 to 20 g/m^2

Efficacy

No efficacy evaluation was conducted on these patients

Exposure to Glucarpidase

Patients in the safety population of Trial 016 received 1 (n=119) or 2 (n= 19) doses of glucarpidase. The number of doses was not specified in 3 patients. Doses ranged from 6 to 189 Units/kg and with a median dose 50 Units/kg. [The datasets probably erroneously report doses of 0.06 (Pt ID 016- 038) and 0.49 (Pt ID 016 146) unit per kg.]

Safety

Methodology for Collecting Safety Data Trial 016

- Only glucarpidase-related AEs were collected
- Data captured on a form which requested dates, serious (yes/no), grade, relationship glucarpidase (possible, probable, definite), treatment, outcome

Table 10: Trial 016 Per Patient Toxicities

Per Patient Possible Glucarpidase Toxicities (n=149)	
	Grade 1 or 2
Nausea/ Vomiting	2
Paraesthesia	1
Rash	1
Flushing	1
Hypertension	1
Blurred Vision	1
Headache	1

Conclusions

The methodology used for adverse reaction reporting on this trial was somewhat superior to that employed in Trial 006, as the method of safety data collection was prospectively specified in the protocol. However, the data collected was suboptimal because only 80% of the investigators returned safety information and only adverse events that investigators considered to be related to glucarpidase were collected. Given these limitations the safety of glucarpidase appears to be acceptable for the treatment of patients with toxic methotrexate levels secondary to delayed renal clearance.

5.3.3 Trial 005

Schema

Table 11: Trial 005 "A Trial to Determine the Pharmacokinetics of Glucarpidase (Voraxaze™) in Subjects with Normal and Impaired Renal Function"

Study Design	Open-label, single-site, pharmacokinetic study of glucarpidase administered intravenously at a dose of 50 units/kg to healthy and renally impaired volunteers
Trial Opened to Subject Entry:	July 2004
Trial Closed to Entry:	October 2004
Dose and Route:	Glucarpidase administered as a single intravenous dose of 50 units/kg.
Indication:	PK study of glucarpidase in volunteer subjects with normal and abnormal renal function
Planned enrollment:	12; 8 with normal renal function and 4 with impaired renal function
Actual enrollment:	12
Terminated early (YES/NO):	NO

Study Objectives:

- To determine pharmacokinetic parameters of glucarpidase in subjects with a range of renal functions (normal and severely impaired renal function).
- To determine whether glucarpidase was eliminated unchanged renally.
- To determine whether glucarpidase pharmacokinetics were altered by renal impairment.
- To confirm the safety and tolerability of glucarpidase.
- Assess incidence of anti-glucarpidse antibodies

Eligibility Criteria

Inclusion Criteria For Healthy Subjects:

- Men or women over the age of 18 who give written informed consent to participate
- Calculated creatinine clearance >80 mL/min

Inclusion Criteria for Subjects with Impaired Renal Function

- Males or females 18 or older who gave written informed consent to participate.

- Calculated creatinine clearance <30 mL/min.

Exclusion Criteria for Healthy Subjects:

- Were unable to give informed consent to participate, as defined by the Investigator, using the criteria established by the designated IRB.
- Had received an investigational drug within 30 days prior to dosing.
- Had significantly impaired cardiac function (e.g., Class 3 or 4 heart failure, active arrhythmias, unstable coronary artery disease, recent myocardial infarction) or pulmonary function (e.g., chronic obstructive pulmonary disease [COPD], emphysema).
- Had liver function, renal function, or hematologic tests that were not within normal limits (WNL).
- Were experiencing a bacterial or viral infection.
- Were women who were pregnant or breastfeeding, or were WOCBP (i.e., women who had not either been postmenopausal for at least 1 year or had a hysterectomy) who were unable or unwilling to follow birth control guidelines. Acceptable methods of birth control included: hormonal methods (e.g., oral contraceptives, Depo-Provera®, Norplant®); an intrauterine device (IUD); double barrier methods; and bilateral tubal ligation.
- Were taking any medication other than allowable prophylactic or preventative health medications
- Were smoking more than 10 cigarettes per day or taking any illicit drugs.

Exclusion Criteria for Subjects with Impaired Renal Function

- Were unable to give informed consent to participate, as defined by the Investigator, using the criteria established by the designated IRB [institutional review board].
- Had received an investigational drug within 30 days prior to dosing.
- Had significantly impaired cardiac function (e.g., Class 3 or 4 heart failure, active arrhythmias, unstable coronary artery disease, recent myocardial infarction) or pulmonary function (e.g., COPD, emphysema).
- Had liver function >Grade 1 as defined by the NCI's Common Toxicity Criteria
- Had hemoglobin levels <9 g/dL (sustainable by transfusion), white blood count (WBC) >2,500/mm3, or platelet counts that were not within normal limits.
- Were experiencing a bacterial or viral infection.
- Were on any form of dialysis (peritoneal or hemodialysis).
- Were not producing sufficient urine to permit an adequate urine collection for determination of glucarpidase renal clearance.
- Were women who were pregnant or breastfeeding, or were WOCBP who were unable or unwilling to follow birth control guidelines. Acceptable methods of birth control included: hormonal methods (e.g., oral contraceptives, Depo-Provera®, Norplant®); an IUD; double barrier methods; and bilateral tubal ligation.
- Were taking any medication except chronic medication needed for severe renal impairment or other concomitant diseases commonly.

Results

Demographics

Table 12: Trial 005 Demographics

Demographics Trial 005		
	Impaired Renal Function n=4	Normal Renal Function n=8
Gender		
Male	3 (75%)	6 (75%)
Female	1 (25%)	2 (25%)
Age (years)		
Mean	41	39
Median	41	42
Range	32 to 51	22 to 50
Race		
Black	3 (75%)	6 (75%)
White	1 (25%)	2 (25%)
Weight (kg)		
Mean	89.2	88.3
Median	87.5	83.4
Range	75.3 to 106.4	67.4 to 114.7
Baseline Creatinine (mg/dL)		
Mean	1.1	7.2
Median	1.1	6.0
Range	0.0 to 1.4	4.2 to 15.4

Pharmacokinetics: (Table copied from Study Report)

Table 13: Trial 005 Summary of Pharmacokinetic Evaluation of Glucarpidase in Normal and Renally Impaired Subjects

Assay	PK Parameter	Impaired Renal Function Mean (SD) (N=4)	Normal Renal Function Mean (SD) (N=8)
Enzymatic Method (enzyme activity)	C_{max} (µg /mL)	2.76 (0.552)	3.29 (0.812)
	T_{max}[a] (hr)	0.550 (0.100 , 4.00)	0.175 (0.100 , 1.00)
	AUC_{0-t} (µg •hr/mL)	17.3 (4.32)	19.7 (7.12)
	$AUC_{0-\infty}$ (µg •hr/mL)	23.0 (5.78)	23.3 (7.24)
	$t_{1/2}$ (hr)	8.17 (2.591)	5.64 (0.662)
	CL (mL/min/kg)	0.0873 (0.02376)	0.0891 (0.02736)
	V_{ss} (mL/kg)	56.7 (14.02)	42.0 (11.98)
ELISA Method (unchanged glucarpidase)	C_{max} (µg /mL)	2.86 (0.828)	3.08 (0.843)
	T_{max}[a] (hr)	0.550 (0.100 , 1.00)	0.250 (0.100 , 2.00)
	AUC_{0-t} (µg •hr/mL)	21.5 (10.49)	20.2 (5.22)
	$AUC_{0-\infty}$ (µg •hr/mL)	24.5 (9.43)	23.4 (6.85)
	$t_{1/2}$ (hr)	9.97 (2.061)	9.00 (3.180)
	CL (mL/min/kg)	0.0860 (0.02855)	0.0892 (0.03018)
	V_{ss} (mL/kg)	67.9 (29.64)	58.0 (18.08)

Safety
No adverse events were reported for any subjects in this study.

Electrocardiogram (ECG) Evaluation
Subjects were evaluated with ECGs at study screening and Day 28. A summary of the ECG results are presented below.

Table 14: Trial 005 ECG Results for Subjects on Trial 005 at Baseline and 28 Days

Subject Number	Renal Status	Timepoint	Ventricular Heart Rate (beats/min)	PR Interval (msec)	QRS Duration (msec)	QT Interval (msec)	QTc Interval (msec)	ECG Interpretation
01	Impaired	Screening	52	150	94	412	383	Abnormal - NCS
		Day 28	52	156	88	412	383	Abnormal - NCS
02	Impaired	Screening	84	150	94	342	404	Abnormal - NCS
		Day 28	93	142	84	324	402	Abnormal - NCS
03	Impaired	Screening	74	162	110	470	521	Abnormal - NCS
		Day 28	76	160	102	464	522	Abnormal - NCS
04	Normal	Screening	78	156	90	366	417	Normal
		Day 28	71	170	92	374	406	Normal
05	Normal	Screening	58	192	92	412	404	Abnormal - NCS
		Day 28	57	156	88	414	402	Abnormal - NCS
06	Normal	Screening	78	142	92	380	433	Normal
		Day 28	86	132	96	366	437	Normal
07	Normal	Screening	47	160	84	484	428	Abnormal - NCS
		Day 28	53	164	84	432	405	Abnormal - NCS
08	Normal	Screening	58	120	116	412	404	Abnormal - NCS
		Day 28	64	124	120	396	408	Abnormal - NCS
09	Normal	Screening	51	154	88	396	398	Normal
		Day 28	58	162	92	408	400	Abnormal - NCS
10	Impaired	Screening	54	168	96	432	409	Abnormal - NCS
		Day 28	62	172	96	398	403	Normal
11	Normal	Screening	70	136	84	394	425	Abnormal - NCS
		Day 28	81	136	88	394	457	Abnormal - NCS
12	Normal	Screening	59	160	88	430	425	Abnormal - NCS
		Day 28	60	154	84	442	442	Normal

NCS – Not Clinically Significant

REVIEWER COMMENT:
No clinically important differences were noted in pre-treatment compared to Day 28 post treatment ECGs. Abnormal ECG findings were not clinically significant and represented minor variations in sinus rhythm or other aspects of the ECGs that were not necessarily indicative of underlying cardiac abnormalities or disease.

Immunogenicity (Copied from Study Report)
Blood samples were collected for assessment of glucarpidase antibody on Day 0 (prior to dose), at the follow-up visits on Days 7 and 14, and at Study Completion on Day 28. Overall, 58.3% of subjects (62.5% of subjects with normal renal function and 50.0% of subjects with impaired renal function) developed antibodies to glucarpidase during the study. All subjects had a negative glucarpidase antibody result at baseline and Day 7. Of the 8 subjects with normal renal function, 2 developed a positive glucarpidase antibody result by Day 14, 3 developed a positive result by Day 28, and 3 had negative

antibody results throughout the entire study. Of the subjects with impaired renal function, 1 developed a positive glucarpidase antibody result by Day 14, 1 developed a positive result by Day 28, and 2 had negative antibody results throughout the entire study.

Anti-glucarpidase antibodies were not detected in any of the subjects with normal renal function at the 3 month visit, but one subject with impaired renal function who had positive antibody results at Days 14 and 28 also had detectable antibodies at 3 and 6 months after glucarpidase administration. One of 12 antibody positive samples produced a moderate (44%) reduction in glucarpidase enzyme activity.

There did not appear to be important differences with respect to glucarpidase antibody development between subjects with normal renal function and subjects with severe renal impairment.

Conclusions
There was little effect of renal impairment on the pharmacokinetic parameters of glucarpidase administered as a single dose of 50 Units/ kg.

There were no safety signals detected.

Anti-glucarpidase antibodies can persist in a small number of subjects and that the antibodies can cause a moderate reduction in glucarpidase enzyme activity in a small proportion of such subjects.

5.3.4 Trial 010

Schema

Table 15: Trial 010 " Investigation of the Effect of Glucarpidase on Leucovorin Pharmacokinetics in Healthy Male Subjects"

Study Design	Randomized, crossover study, double-blind placebo controlled in volunteer subjects. There was a minimum of 14 days between each treatment period.
Trial Opened to Subject Entry:	March 2006
Trial Closed to Entry:	April 2006
Dose and Route:	Glucarpidase at a dose level of 50 Units/Kg IV Leucovorin at a dose level of 150 mg/m^2 q 6 hours for 5 doses starting 2 hours after glucarpidase/placebo.
Indication:	Drug interaction study of glucarpidase and leucovorin in volunteer subjects
Planned enrollment:	6
Actual enrollment:	6
Terminated early (YES/NO):	No

Study Objectives:

Primary Objective:

- To assess the effect of glucarpidase on the pharmacokinetics of the active L stereoisomer of leucovorin (LV) ((6) L/S-LV) following repeated doses of LV.

Secondary Objectives:

- To assess the effect of glucarpidase on the pharmacokinetics of the D stereoisomer of LV ((6) D/R-LV), and 5-methyl tetrahydrofolate ((6) L/S-5-MeTHF, the active metabolite of (6) L/S-LV).
- To further assess the safety and tolerability of a single IV dose of glucarpidase in healthy male subjects when given in combination with LV.
- The pharmacokinetics of (6) D/R-5-MeTHF (the metabolite of (6) D/R-LV) was also added as a secondary objective.

Eligibility Criteria:

Inclusion Criteria:

- Subjects will be males of any ethnic origin between 18 and 60 years of age and with a body mass index (BMI) between 19 and 29 kg/m^2 inclusive.

- Subjects must be in good health, as determined by a medical history, physical examination, 12-lead ECG and clinical laboratory evaluations (congenital non-haemolytic hyperbilinibinaemia is acceptable).
- Subjects will have given their written informed consent to participate in the study and to abide by the study restrictions.

Exclusion Criteria:

- Male subjects who are not willing to use appropriate contraception (e.g. condoms) from the time of the first dose until 1 month after the post-study visit.
- Subjects who have received any prescribed systemic or topical medication within 14 days of dose administration.
- Subjects who have used any non-prescribed systemic or topical medication within 7 days of dose administration (with the exception of vitamin/mineral supplements) unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise safety.
- Subjects who have received any medications known to chronically alter drug absorption or elimination processes within 30 days of dose administration.
- Subjects who have participated in a clinical study involving administration of an investigational drug (new chemical entity) in the past 4 months, or a marketed drug within the past 3 months.
- Subjects who have had previous exposure to glucarpidase.
- Subjects who have donated any blood, plasma or platelets in the past month, or who have made donations on more than two occasions within the 12 months preceding dose administration.
- Subjects with a significant history of drug allergy, especially known hypersensitivity to calcium folinates.
- Subjects who have any clinically significant allergic disease (excluding non-active
- hayfever).
- Subjects who have a sitting blood pressure and sitting pulse rate at screening higher than 150/90 mmHg and 90 heats per minute, respectively, or lower than 100/50 mmHg and 40 beats per minute, respectively.
- Subjects who consume more than 28 units of alcohol per week or who have a significant history of alcoholism or drug/chemical abuse (one unit of alcohol equals 1/2 pint [285 mL] of beer or lager, one glass [125 mL] of wine, or 1/6 gill [25 mL] of spirits).
- Subjects who smoke more than 15 cigarettes or the equivalent, in tobacco per day.
- Subjects with, or with a history of, any clinically significant neurological (e.g. epilepsy), gastrointestinal, renal, hepatic, cardiovascular, psychiatric, respiratory, metabolic, endocrine, haematological (e.g. pernicious anaemia or vitamin B_{12} deficiency) or other major disorders.
- Subjects who have had a clinically significant illness within 4 weeks of the start of the study.

- Subjects who are known to have serum hepatitis or who are carriers of the hepatitis B surface antigen (HBsAg), or hepatitis C antibody, have a positive result to the test for HIV antibodies, or who admit to belonging to a "high risk" group for contracting HIV.
- Subjects who, in the opinion of their general practitioner (GP) or the Investigator, should not participate in the study.

Protocol Amendments

April 2006

- In accordance with protocol amendment 2, the pharmacokinetics of (6) D/R-5-MeTHF (the metabolite of (6) D/R-LV) was also to be assessed as a secondary objective.
- Revisons regarding the analysis of samples

Results

Demographics

Table 16: Trial 010 Demographics

Demographics Trial 010	
Gender	
Male	6 (100%)
Age (years)	
Mean	38
Median	38.5
Range	20 to 57
Race	
White	6 (100%)
Weight (kg)	
Mean	76.2
Median	77.6
Range	63.2 to 85.1
Body Mass Index (kg/m^2)	
Mean	24.7
Median	24
Range	21 to 28

Safety

Table 17: Trial 010 Adverse Events

Adverse Events Reported in Trial 010		
Subject ID	Glucarpidase and Leucovorin	Placebo and Leucovorin
ID 010 - 001	Injection site pain	Injection site pain
		Injection site paraesthesia
		Fatigue
ID 010 - 004	Dysgeusia	Dysgeusia
ID 010 - 005	Dysgeusia	Dysgeusia

REVIEWER COMMENT:
There were no adverse events associated with the administration of glucarpidase.

Pharmacokinetics

Table 18: Trial 010 Pharmacokinetic Parameters of Leucovorin ((6) L/S-LV)

	50 U/kg glucarpidase + 150 mg/m^2 LV q6h		Placebo + 150 mg/m^2 LV q6h		Ratio of LS means Glucarpidase+LV:Placebo +LV (95% CI)	
Parameter	Dose 1 (N=6)	Dose 5 (N=6)	Dose 1 (N=6)	Dose 5 (N=6)	Dose 1	Dose 5
$AUC_{0-\tau}$ (µmol.h/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)
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)
t_{max} (h)	0.0667 (0.0500, 0.0833)	0.0833 (0.0500, 0.183)	0.0583 (0.0500, 0.167)	0.0667 (0.0500, 0.0833)		
$t_{½}$ (h)	0.448 (18.3)	0.634 (5.62)	0.806 (14.0)	0.774 (11.0)		
CL (mL/min)	859 (28.4)	577 (26.3)	451 (44.1)	451 (40.0)		
V_z (L)	33.3 (17.0)	31.7 (23.0)	31.5 (48.3)	30.2 (44.3)		
V_{ss} (L)	27.4 (24.3)	28.9 (37.9)	25.4 (57.4)	25.5 (50.8)		
RA_{AUC}		1.49 (19.4)		1.01 (15.1)		
RA_{Cmax}		0.831 (34.3)		1.11 (22.0)		

Table 19: Trial 010 Pharmacokinetic Parameters of Leucovorin ((6) D/R-LV)

	50 U/kg glucarpidase + 150 mg/m^2 LV q6h		Placebo + 150 mg/m^2 LV q6h		Ratio of LS means Glucarpidase+LV:Placebo +LV (95% CI)	
Parameter	Dose 1 (N=6)	Dose 5 (N=6)	Dose 1 (N=6)	Dose 5 (N=6)	Dose 1	Dose 5
$AUC_{0-\tau}$ (µmol.h/L)	128 (21.2)	265 (21.4)	129 (35.8)	269 (42.4)	0.988 (0.793, 1.23)	0.985 (0.791, 1.23)
C_{max} (µmol/L)	61.8 (23.7)	73.0 (29.2)	54.9 (41.6)	87.9 (42.7)	1.13 (0.929, 1.37)	0.831 (0.686, 1.01)
t_{max} (h)	0.0667 (0.0500, 0.0833)	0.125 (0.0833, 1.50)	0.0833 (0.0667, 0.500)	0.0667 (0.0500, 0.0833)		
CL (mL/min)	NC	35.6 (20.8)	NC	35.0 (46.9)		
RA_{AUC}		2.07 (7.42)		2.08 (23.3)		
RA_{Cmax}		1.18 (10.0)		1.60 (18.7)		

Conclusions

- IV administration of 50 Units/kg glucarpidase 2 hours before leucovorin reduced (6S)-Leucovorin AUC_{0-3h} by 33% and C_{max} by 54%, and also reduced leucovorin active metabolite, (6S)-5-methyl-tetrahydrofolate, AUC_{0-3h} by 92% and C_{max} by 93%.
- Therapy with leucovorin should be continued according to its prescribing information for delayed methotrexate elimination
- Leucovorin should not be administered within 2 hours before or after a dose of glucarpidase due to its pharmacokinetic interaction with glucarpidase.
- The five IV doses of leucovorin were safe and well tolerated in healthy male subjects in the presence or absence of glucarpidase. There were no specific adverse event identified in the glucarpidase/ leucovorin therapy compared to the placebo/leucovorin therapy.

5.3.5 Trial 012

Schema

Table 20: Trial 012 "Randomized, Blinded, Placebo-controlled Trial of High Dose Methotrexate with Leucovorin Rescue (HDMTX-LV) with or without Glucarpidase in Osteosarcoma"

Study Design	Randomized Blinded, Placebo-controlled, Crossover Study There was a separate arm for compassionate administration of glucarpidase
Trial Opened to Subject Entry:	October 2008
Trial Closed to Entry:	March 2009
Dose and Route:	Glucarpidase 50 Units/Kg administered 2 hours following the first IV dose of leucovorin, which is administered 24 hours following high dose methotrexate administration. (2 doses 24 hours apart)
Indication:	Glucarpidase post high dose methotrexate to facilitate timely administration of subsequent therapy
Planned enrollment:	36 in Randomized Arm 10-14 in Compassionate Use Arm
Actual enrollment:	4 enrolled in Randomized Arm, 2 received agent 5 enrolled in Compassionate Use Arm
Terminated early (YES/NO):	YES - Poor accrual; Inadequate personnel to supervise trial

Study Objectives:

Primary objective:

- Determine whether a greater proportion of glucarpidase-treated patients had a successful advancement to the next cycle of chemotherapy at the scheduled time compared to placebo treated patients.

Secondary objectives:

- Assess safety and tolerability of HDMTX when given with LV with and without glucarpidase.
- Assess safety and efficacy (reduction of serum MTX concentration) of glucarpidase after single and multiple chemotherapy cycles.
- Assess cost of therapy for inpatient versus outpatient treatment with and without glucarpidase.

- Assess proportion of patients with anti-glucarpidase antibody responses and impact on safety and efficacy (reduction of serum MTX concentration) of glucarpidase.
- Assess the pharmacokinetics (PK) of glucarpidase following HDMTX.

Eligibility Criteria:
Inclusion Criteria:

- A diagnosis of osteosarcoma (biopsy proven)
- Ages ≥8 years old and ≤50 years old
- Eligible to receive 2 sequential cycles of HDMTX-LV
- Acceptable hematologic, hepatic and renal function
- ECOG Performance Status 0 or 1
- Compassionate glucarpidase patients: Any diagnosis, any hematologic or hepatic function, any performance status, and after HDMTX have:
    - a rise in serum creatinine >1.5 mg/dL from baseline and/or
    - delayed clearance with serum MTX concentration >50 µmol/L at 24 hours or >5 µmol/L at 48 hours
- For females of childbearing potential, a negative serum pregnancy test must be documented prior to enrollment.
- Patients who enter this study and their sexual partners who are of childbearing potential must agree to use an effective form of contraception throughout participation in this study.

Exclusion Criteria:

- History of MTX anaphylaxis
- Prior administration of glucarpidase
- Receiving other cytotoxic chemotherapy concomitantly with HDMTX-LV (within 6 days prior to the first cycle of HDMTX through to recovery of at least 6 days following the second cycle of HDMTX).
- Documented progression of disease while on previous MTX treatment

Results

Demographics

Table 21: Trial 012 Demographics

Demographics Trial 012		
	Randomized n=4	Compassionate n=5
Gender		
Male	1 (25%)	3 (60%)
Female	3 (75%)	2 (40%)
Age (years)		
Mean	16.7	40.4
Median	16.5	45
Range	16 to 18	16 to 67
Weight (kg)		
Mean	61.3	83.3
Median	62.3	89.9
Range	54.4 to 66	57.9 to 109.3
Diagnosis		
Osteosarcoma	4 (100%)	3 (60%)
Leukemia		2 (40%)

Efficacy

The trial was prematurely terminated. Efficacy can not be evaluated. Only 2 patients received glucarpidase and placebo. One patient withdrew from study prior to study drug administration (Pt 012 – 002). One patients was determined to be ineligible prior to study drug administration (Pt 012 – 004).

Safety

Table 22: Compariason of Adverse Events in Subjects in Randomized Subjects events

Adverse Events Reported in Trial 012 in Randomized Patients Treated with Both Glucarpidase and Placebo (Non Hematologic)		
Subject ID	Glucarpidase and Leucovorin	Placebo and Leucovorin
ID 012 - 001	Asthenia	Back Pain
	Edema	
	Dysguesia	
ID 012 - 003	Epistaxis	Nausea
	Rash	Mucositis
	Nausea	
	Fatigue	

Table 23: Trial 012 Adverse Events Possibly Related to Glucarpidase

Per Patient Possible Glucarpidase Toxicities (n=7)		
	Grade 1 or 2	**Grade 3**
Nausea	3	
Arthralgia	2	
Fatigue	2	
Pleural Effusion	2	
Pain	2	
Epistaxis		1
Constipation	1	
Cough	1	
Decreased Appetite	1	
Dyguesia	1	
Edema	3	
Rash		
Respiratory Tract Congestion	1	
Stomatitis	1	

Conclusions

- It was not possible to isolate adverse events associated with glucarpidase administration in the cross over patients due to the early termination of this study.
- The adverse events reported as possibly related to glucarpidase were more likely related to methotrexate toxicity.
- The reported adverse events were tolerable in the study population.

5.3.6 Trial 017

Schema

Table 24: Trial 017 "An Open-label Study to Assess the Pharmacokinetics of Leucovorin in Patients Receiving High Dose Methotrexate, with or without Voraxaze Treatment"

Study Design	Open-label, Nonrandomized Multicenter PK Study of Leucovorin
Trial Opened to Subject Entry:	July 2008
Trial Closed to Entry:	July 2009
Dose and Route:	Glucarpidase at a dose level of 50 Units/Kg to subjects on Arm A
Indication:	Markedly delayed methotrexate clearance due to renal failure/dysfunction
Planned enrollment:	12
Actual enrollment:	Arm A - 11, Arm B - 9
Terminated early (YES/NO):	No

Study Objectives:

Primary Objective:

- Assessing the pharmacokinetics (PK) of the active L stereoisomer of LV (L-LV) following administration of high-dose methotrexate (HDMTX) (≥1 g/m2) and LV, with or without glucarpidase.

Secondary Objectives:

- Assessing the PK of MTX, the D stereoisomer of LV (D-LV) and the L and D stereoisomers of 5-methyl tetrahydrofolate (5-MeTHF, active metabolite of LV) following administration of HDMTX and LV with or without glucarpidase;
- Further assessing the safety of glucarpidase administration; and
- Assessing changes in plasma and red blood cell (RBC) folate concentrations.

Eligibility Criteria:

Inclusion Criteria:

Arm A Inclusion Criteria

- Male or female patients of any age weighing ≥23 kg.
- Subjects receiving high dose methotrexate (≥1 g/m^2) who were experiencing or at risk of methotrexate toxicity and had impaired renal function and evidence of delayed methotrexate elimination based on renal dysfunction and methotrexate levels defined as follows:

  - Patients with osteosarcoma:
    - Plasma methotrexate >50 µmol/L at 24 hours, >5 µmol/L at 48 hours or plasma levels >2 standard deviations (SD) above the mean methotrexate elimination curve at least 12 hours following methotrexate administration, and
    - Serum creatinine increased >2-fold above baseline (pretreatment with methotrexate) level.
  - All other subjects:
    - Plasma methotrexate >10 µmol/L for >42 hours after the start of methotrexate infusion or plasma levels >2 SD above the mean methotrexate elimination curve at least 12 hours following methotrexate administration, and
    - Serum creatinine >1.5 x upper limit of normal or creatinine clearance <60 mL/min at least 12 hours following methotrexate administration.\
- Eastern Cooperative Oncology Group (ECOG)35 performance status 0-2
- Patients who required IV LV rescue therapy, either ≥15 mg or ≥10 mg/m2 q6h.
- Institutional Review Board (IRB)-approved signed informed consent.

Arm B Inclusion Criteria
- Male or female patients of any age weighing ≥23 kg receiving high dose methotrexate (≥1 g/m^2).
- A serum creatinine, taken within 24 hours post methotrexate administration, with a value equal to or less than the maximum value, based on age/gender, defined by Schwartz formula:
- ECOG performance status 0-2.
- Patients who required IV LV rescue therapy, either ≥15 mg or ≥10 mg/m2 q6h.
- IRB-approved signed informed consent.

Exclusion Criteria:
Arm A Exclusion Criteria
- Patients with known hypersensitivity to glucarpidase (carboxypeptidase) or to any of the excipients (lactose, Tris-HCl with zinc buffer).
- Patients who have previously experienced allergic reactions to medicines containing lactose. Patients intolerant to lactose in food (eg, dairy products) could still receive glucarpidase.
- Patients with rare hereditary problems of fructose intolerance, galactose intolerance, galactosemia, or glucose-galactose malabsorption.

Arm B Exclusion Criteria
- Patients requiring high doses of LV rescue therapy (>25 mg/m^2).
- Evidence of delayed elimination of methotrexate defined as follows:
  - Patients with osteosarcoma:

- Plasma MTX >50 µmol/L at 24 hours, >5 µmol/L at 48 hours or plasma levels >2 SD above the mean MTX elimination curve at least 12 hours following MTX administration

- All other patients:
  - Plasma MTX >10 µmol/L for >42 hours after the start of MTX infusion or plasma levels >2 SD above the mean MTX elimination curve at least 12 hours following MTX administration.

Protocol Amendments

January 2008

- Minimum weight increased from 15 kg to 23 kg to ensure no more than 5% blood volume drawn
- All adverse events regardless of attribution collected

May 2008

- Revision to sampling to increase participation

Results

Demographics

Table 25: Trial 017 Demographics

Demographics Trial 017		
	Arm A (Glucarpidase) n = 11	Arm B n = 9
Gender		
Male	6 (55%)	7 (78%)
Female	5 (45%)	2 (22%)
Age (years)		
Mean	26.9	14.1
Median	19	10
Range	11 to 84	7 to 31
Weight (kg)		
Mean	81.3	44.8
Median	84	33.2
Range	34.8 to 122.8	24.3 to 80
Maximum Creatinine (mg/dL)		
Mean	2.1	0.5
Median	2.0	0.4
Range	1.3 to 2.9	0.3 to 0.9
Diagnosis		
Osteosarcoma	5 (45%)	2 (22%)
Leukemia/Lymphoma	6 (55%)	7 (78%)

Safety

Table 26: Trial 017 Adverse Events Possibly Related to Glucarpidase

Adverse Event	Arm A (Glucarpidase) n = 11
Paraesthesia	1
Flushing	1

These adverse event were reported in Pt 017 – 007. This patient received a second dose of glucarpidase without repeat of these reactions.

Pharmacokinetics

The pharmacokinetic population consisted of 8 patients in Arm A and 9 patients in Arm B. The administration of glucarpidase did not reduce exposure to leucovorin and its active metabolite to below the level achieved in patients who have not received glucarpidase, supporting the principle that adequate leucovorin rescue can be maintained in the presence of glucarpidase if leucovorin dosing is based upon pre-glucarpidase plasma methotrexate concentration.

Conclusions

- The glucarpidase related adverse event documented in this study, paraesthesia and flushing are adverse events identified in the safety population in Trial 006 and Trial 016. Of note this patient received a second dose of glucarpidase without experiencing these reactions.
- The administration of glucarpidase did not reduce exposure to leucovorin and its active metabolite to below the level achieved in patients who have not received glucarpidase.

5.3.7 Trial 001 CAMR Lot 004

Schema

Table 27: Trial 001 "Study of Recombinant Carboxypeptidase G2 (CPG2) for the Management of Patients with Delayed Methotrexate (MTX) Clearance or Intrathecal MTX Overdosage"

Study Design	Prospective, Open-label, Nonrandomized Multicenter Trial
Trial Opened to Subject Entry:	January 2000
Trial Closed to Entry:	August 2003
Dose and Route:	Glucarpidase 50 Units/kg IV push over 5 minutes; Second dose glucarpidase for subjects with methotrexate > 0.1 µmol/L 24 hours later allowed.
Indication:	Delayed elimination of methotrexate in association with renal dysfunction
Planned enrollment:	No predetermined sample size
Actual enrollment:	44
Terminated early (YES/NO):	No

Study Objectives:

- The protocol-defined objectives of this study were to evaluate the safety and efficacy of glucarpidase in patients with impaired methotrexate clearance due to methotrexate induced renal failure following intravenous administration of high-dose methotrexate therapy, or in patients with intrathecal MTX overdose.

Eligibility Criteria
Inclusion Criteria:

- Patients ≥18 years of age who were receiving high-dose methotrexate (>1 g/m^2 BSA given as an infusion over 24 hours) for the treatment of ALL [acute lymphoblastic leukemia], non-Hodgkin's lymphoma, or a solid tumor were eligible for participation in the study if their serum methotrexate concentration was:
  - >5 µmol/L 42 hours or later after the start of methotrexate infusion; or
  - >1 µmol/L 42 hours or later after the start of methotrexate infusion together with renal insufficiency; or
  - >0.4 µmol/L 48 hours or later after the start of methotrexate infusion together with renal insufficiency.

- Renal insufficiency was defined as serum creatinine >1.5 times the upper limit of normal (ULN) and/or oliguria (urine output <500 mL/24 hours despite adequate hydration, diuretics and alkalinization)].
- Patients with intrathecal methotrexate overdose (≥50 mg of methotrexate) could be treated with glucarpidase after consultation with the Principal Investigator.
- In patients with intrathecal methotrexate overdose, immediate cerebrospinal fluid (CSF) removal by lumbar puncture, ventriculolumbar perfusion or continuous CSF drainage was to be considered. Additional alkalinization and leucovorin rescue were to be instituted, and anticonvulsive and dexamethasone therapies were also to be considered.

Exclusion Criteria:
Patients were excluded from the study if they:
- Were pregnant or lactating females; or
- Were unwilling to provide informed patient consent.

Protocol Amendments
None documented

Results
Demographics and Baseline Characteristics
Table 28: Trial 001 Demographics and Baseline Characteristics

Demographics and Baseline Characteristics n = 44	
Gender (not recorded)	
Age (years)	
Mean – 50.0	0 – 18 2 (5%)
Median – 53	19 - 65 36 (82%)
Range - 10 to 78	66 - 85 6 (14%)
Weight in Kg (n=42)	
Mean – 81.0 Median – 82.5 Range - 31 to 109	
Diagnosis	
Leukemia Lymphoma 42 (95%)	Other 2 (5%)
MTX Dose (available for n= 43)	
Mean – 3.4 g/m^2 Median – 3.0 g/m^2 Range – 0.9 mg/m^2 to 12.1 g/m^2	

Exposure to Glucarpidase
The majority 40/44 (91%), of patients received a single dose of glucarpidase. The dose was documented for 41 patients. The median dose 50 Units/ kg and ranged between 10

to 58 Units/kg. Four patients received a 2nd dose. The mean was 50 Units/kg, the median of was 51 Units/kg and ranged between 41 to 57 Units/kg.

Safety

BTG states that the CRFs for this study did not always provide a date of onset for AEs. As a result, in most cases it was not possible to determine whether an AE was treatment-emergent. This limits the usefulness of this patients population to contribute to the analysis of the safety of glucarpidase.

There were 6 patients with adverse event classified as possibly related to glucarpidase. These included:

Pt 001 004 – Coma, Quadraplegia, Progressive Neurological Deterioration
[Based on review of CRF this appears to be related to methorexate toxicity.]

Pt 001 005 – Allergic Skin Reaction

Pt 001 013 – Bradycardia (Received 2 doses)
[Review of CRF –bradycardia 64 minutes after infusion; did not recur with 2nd dose of glucarpidase]

Pt 001 026 – Pyrexia

Pt 001 035 – Erythema, Urticaria
[Review of the CRF – not clear the skin, lesion was urticaria. The translation seems to be blisters rather than hives.]

Pt 001 040 – Aggression (Received 2 doses)
[Based o review of CRF this appears related to methotrexate toxicity. The patient was confused and somnolent. The patient had no reactions reported with the second dose.]

Conclusions

- The administration of glucarpidase was well tolerated in this study. The adverse reactions associated with administration of glucarpidase were well tolerated and in the 2 patients who received a second dose these reactions did not recur.

5.3.8 Trial 002 CAMR Lot 004

Schema

Table 29: Trial 002 "A Trial of Carboxypeptidase-G2 (CPG2) for the Management of Patients with Methotrexate Toxicity and Renal Dysfunction"

Study Design	Open Label, Nonrandomized, Compassionate Use Protocol
Trial Opened to Subject Entry:	November 1993
Trial Closed to Entry:	May 2004
Dose and Route:	Original (April 1992) Glucarpidase 50 Units/kg intravenously over 5 min x 3 doses at 4 hr intervals Patients with >1 log decrease in plasma methotrexate but persistent methotrexate concentration > 1µmol/L may receive additional doses Thymidine as a 24-hr continuous intravenous infusion at a dose of 8 g/m^2/day. Leucovorin should be withheld for 4 hours prior to the first dose of glucarpidase and not administered during the course of glucrpidase administration. See Protocol Amendments below for subsequent protocol modifications
Indication:	Markedly delayed methotrexate clearance due to renal failure/dysfunction
Planned enrollment:	No pre-determined sample size
Actual enrollment:	262
Terminated early (YES/NO):	No

Study Objectives:
The overall objective of the study was to determine the effectiveness of glucarpidase or a combination of glucarpidase and thymidine in rescuing patients with delayed methotrexate elimination secondary to renal dysfunction.

- To determine the utility of the combination of glucarpidase and leucovorin with or without the addition of thymidine in patients with delayed methotrexate excretion secondary to renal dysfunction;
- To study the pharmacokinetics (PK) of methotrexate and methotrexate metabolites following glucarpidase rescue; and
- To evaluate the immune response to glucarpidase in patients treated with 1 or more doses of glucarpidase.

Eligibility Criteria:
Inclusion Criteria:
Patients of any age were eligible if they had a plasma methotrexate concentration ≥10 µmol/L 42 hours or more after the start of high dose methotrexate infusion or serum creatinine ≥1.5 times the upper limit of normal or creatinine clearance (≤60 mL/m^2/minute and plasma methotrexate concentration ≥2 standard deviations above the mean at least 12 hours after methotrexate administration.

Protocol Amendments
November 1995
- Glucarpidase 50 Units/kg IV one dose only
- Patients with persistent levels of methotrexate concentration > 1µmol/L because the first 12 patients treated did not have further decrease in methotrexate concentration with additional doses.
- Sample handling revised

July 1997
- Sample handling revised
- Glucarpidase 50 Units/kg IV repeat in 24 hours
- Thymidine modified
- Leucovorin modified should not be administered 2 hours prior or 2 hours after glucarpidase

December 1997
- Glucarpidase 50 Units/kg IV one dose only
- Patients with persistent levels of methotrexate concentration > 1µmol/L because the first 12 patients treated did not have further decrease in methotrexate
- Thymidine modified
- Leucovorin – base dose on HPLC result form (b) (4)
- Sample handling revised

April 2000
- Dosing instructions for obese patients
- Glucarpidase 50 Units/kg IV one dose only if methotrexate immediately prior to glucarpidase < 100 µmol/L; > 100 µmol/L second dose 48 hours later
- No more central testing of samples at (b) (4)

February 2002
- Glucarpidase 50 Units/kg, maximum dose 2000 Units IV

November 2003

- Thymidine discontinued

January 2004

- Protherics acquired the product

Results

Demographics

Table 30: Trial 002 Demographics and Baseline Characteristics

Demographics of Safety Population Trial n = 214	
Gender	
Male 123 (57%)	Female 71 (33%)
Age in years n = 211	
Mean – 29.7	0 - 12 50 (24%)
Median - 17	13 – 18 70 (33%)
Range – 5 months to 82 years	19 – 65 64 (30%)
	66 – 85 27 (13%)
Weight in Kg n=202	
Mean - 66.9 Median - 65	Range - 6.6 to 157
Diagnosis n = 189	
Osteosarcoma/sarcoma 75 (40%)	Other 3 (2%)
Leukemia Lymphoma 111 (59%)	
MTX Dose (available for n = 208)	
Mean – 7 g/m^2 Median – 5.3 g/m^2	Range - 0.4 to 19.4 g/m^2

Efficacy

Efficacy review was not done. The laboratory methodology for these measurement were not validated as documented on the OSI inspection of the (b) (4) central laboratory. See section 3.1.

Exposure to Glucarpidase (copied from Trial 002 Study report page 87/766)
Glucarpidase administration was recorded for 204 patients in the safety population. Patients in the safety population received up to 3 doses of glucarpidase: 144 (70.6%) received 1 dose, 53 (26.0%) received 2 doses, and 7 (3.4%) received 3 doses. The median dose for the first glucarpidase administration in the safety population was 49.23 U/kg (range: 10.87 to 63.73 U/kg).

Safety
Of the 262 patients registered in this study, 214 (81.7%) received at least 1 dose of glucarpidase or had evidence of follow-up regardless of data availability of glucarpidase administration, and they comprise the safety population. (copied from Trial 002 Study report page 87/766)

In addition to glucarpidase patients enrolled on this trial were receiving thymidine. Evaluation of adverse events in compassionate use trials is obfuscated by the underlying toxicity associated with methotrexate intoxication. Specifically myelosuppression, liver abnormalities, renal abnormalities, mucosal toxicity and infections. In this study evaluation of the role of glucarpidase is further complicated by the coadministration of thymidine.

There were 17 subjects with adverse events identified as probably or possibly related to glucarpidase and excluding hematopoietic, renal, hepatic, infectious and mucosal events. These adverse events were not consistently graded for severity.

Table 31: Trial 002 CAMR Lot 004 Per Patient Glucarpidase Toxicities

Per Patient Possible Glucarpidase Toxicities Excluding Hematologic, Hepatic, or Renal (n = 214)		
Body System	Preferred Term	Per Patient Incidence
Cardiac Disorders	Tachycardia	1
Gastrointestinal Disorders	Abdominal pain	1
	Diarrhea	1
	Nausea	1
General Disorders and Administration Site Conditions	Feeling hot	3
Nervous System Disorders	Burning sensation	2
	Formication	1
	Headache	2
	Hypoesthesia	1
	Paraesthesia	3
	Somnulence	1
	Tremor	2
Respiratory, Thoracic and Mediastinal Disorders	Dyspnea	1
	Pneumonitis	1
	Throat tightness	1
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis	1
	Pruritus	1
	Rash	1
	Skin burning sensation	1
Vascular Disorders	Flushing	4
	Hot Flush	1
	Hypertension	1

The most common toxicity in 10 patients was sensory symptoms characterized as paraesthesia, hypoaesthesia, flushing feeling hot, hot flush, formication skin burning sensation. Two subjects were reported to have experienced tremors. The remaining adverse event were only reported for a single subject.

Patients in this study received up to 3 doses of glucarpidase. Patients received 3 doses within 24 hours and thus the repeat doses were administered prior to the time when sensitization would be expected to occur. No allergic reactions, hives, or episodes of bronchospasm were reported.

Conclusions

- The most common adverse events associated with the administration of glucarpidase were the sensory symptoms. These glucarpidase related adverse event were documented in the safety population of Trial 006 and Trial 016.
- No definitive hypersensitivity or allergic reactions were documented.

5.3.9 Trial 003 CAMR Lot 004

Schema

Table 32: Trial 003 "A trial of Carboxypeptidase-G2 (CPG2) for the Management of Patients with Methotrexate Toxicity and Renal Dysfunction"

Study Design	Open Label, Nonrandomized, Compassionate Use Protocol
Trial Opened to Subject Entry:	March 1997
Trial Closed to Entry:	March 2002
Dose and Route:	Glucarpidase 50 Units/kg IV push Patients with > one logarithm decrease in plasma methotrexate but with plasma methotrexate >1 µmol/L could receive additional doses
Indication:	Rescue agent for delayed methotrexate excretion in the presence of renal impairment
Planned enrollment:	No pre-determined sample size
Actual enrollment:	82
Terminated early (YES/NO):	No

Study Objectives:

- To determine the utility of single-dose glucarpidase in patients with delayed methotrexate excretion secondary to renal dysfunction;
- To study the PK of methotrexate following glucarpidase rescue; and
- To evaluate the immune response to glucarpidase in patients treated with one or more doses of glucarpidase.

Eligibility Criteria:

Inclusion Criteria:

Patients of any age, at risk of life-threatening toxicity following methotrexate administration, secondary to delayed methotrexate excretion as defined below, were eligible for participation in the study:

- Plasma methotrexate concentration
  - >10 µmol/L more than 36 hours, or
  - >5 µmol/L more than 42 hours, or
  - >3 µmol/L more than 48 hours after the start of the infusion; and

Delayed methotrexate excretion documented by serial plasma methotrexate levels (>2 SD above the mean) at least 12 hours after methotrexate administration; and

- Renal dysfunction as indicated by:
  - Decreased diuresis; or
  - Serum creatinine >1.5 x ULN and documented increase during the infusion period.

Results

Demographics

Table 33: Demographics of Safety Population Trial 003 CAMR Lot 004

Demographics of Safety Population Trial 003 CAMR Lot 004 n = 69	
Gender (not recorded)	
Age (years) n = 61	
Mean – 26.8	0 - 12 18 (30%)
Median - 15	13 – 18 18 (30%)
Range – 11 months to 71 years	19 – 65 21 (34%)
	66 – 71 4 (6%)
Weight in Kg n = 63	
Mean – 62.0 Median - 65.5	Range 7.6 to 110
Diagnosis n = 63	
Osteosarcoma/sarcoma 11 (17%)	Other 5 (8%)
Leukemia Lymphoma 47 (75%)	
MTX Dose (n = 65)	
Mean – 6.1 g/m^2 Median – 5.0 g/m^2	Range 0.01 g/m^2 to 12 g/m^2

Exposure to Glucarpidase (copied from Trial 003 Study report page 71/432)
Glucarpidase administration was recorded for 62 of 69 patients in the safety population. The median dose for the first glucarpidase administration was 50 units/kg (range: 16.6 to 100 U/kg). Fifty-three (85.5%) patients received a single glucarpidase dose, 8 (12.9%) patients received a total of 2 doses, and 1 (1.6%) patient received 3 doses.

Safety

Data collection (copied from Trial 003 Study Report page 28/435)
Raw data were collected by the coordinating investigator/site staff via telephone interviews with personnel at the study centers using data sheets prepared centrally.

REVIEWER COMMENT:
The data is very difficult to assess.

Table 34: Trial 003 CAMR Lot 004 Per Patient Glucarpidase Toxicities

Per Patient Possible Glucarpidase Toxicities Excluding Hematologic, Hepatic, or Renal (n = 69)						
Body System	Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade
Gastrointestinal Disorders	Nausea	10	9	7	4	30
	Vomiting	11	8	7	2	29
	Diarrhea	9	5	1	2	17
	Abdominal pain	1				3 (2 unknown)
Immune system Disorders	Hypersensitivity	2			1	4 (1 unknown)
Musculoskeletal and Connective Tissue Disorder	Pain in extremety	1				1
Nervous System Disorders	Headache					1 (unknown)
	Hypoaesthesia	1				1
	Neurotoxicity peripheral	6			1	8 (1 unknown)
	Neurotoxicity central	5			2	7
Respiratory, Thoracic and Mediastinal Disorders	Lung disorder		1	3	3	7
Skin and Subcutaneous Tissue Disorders	Skin reaction	9	4			11
	Rash					2 (unknown
	Flushing					

Conclusions

- There were 4 subjects with adverse reactions coded as hypersensitivity. Given the retrospective methodology of the data collection, there were no details regarding the events. The verbatim code was "hypersensitivity" for each of these events. One was coded as grade 4, but there are no details of the reaction provided.
- The lack of details and the retrospective collection of the information limits the usefulness of this data.

6 Review of Efficacy

Efficacy Summary

Glucarpidase is an enzyme that breaks down methotrexate to non toxic metabolites. High dose methotrexate is a standard component of therapy for a number of malignant conditions. Methotrexate is predominantly metabolized through the kidney. If a patient develops renal insufficiency or renal failure after administration of high dose methotrexate they are at risk for severe possibly life-threatening toxicity due to persistent elevated levels of methotrexate. Glucarpidase is intended to rescue patients from methotrexate toxicity in this situation. It is not feasible to study glucarpidase in a prospective randomized study for this indication because delayed methotrexate clearance as a consequence of renal insufficiency is an unpredictable emergency situation. It would not be ethical to withhold this antidote from a patient with potentially life-threatening methotrexate intoxication in order to study glucarpidase in a controlled trial.

Plasma levels of methotrexate lower than 1 µmol/L are considered below the level associated with severe toxicity. Below this level the methotrexate toxicity can be successfully ameliorated with leucovorin. Therefore a dose and schedule of glucarpidase that reliably results in rapid and sustained plasma levels of methotrexate below this threshold in patients with renal compromise and toxic levels of methotrexate due to delayed methotrexate clearance represents a pharmacodynamic endpoint that is an acceptable surrogate endpoint for clinical benefit.

Because of the possibility of *ex vivo* metabolism of methotrexate by glucarpidase in patient plasma samples, the applicant was required to validate the sample handling method used to collect samples in Trial 006. According to the protocol for Trial 006 investigators were instructed to place samples on ice immediately after they were drawn and to inactivate the enzyme by the addition of HCl immediately after separation of plasma. Acid could not be added to whole blood because it causes agglutination of the samples. The acidified plasma samples were to be stored frozen until required for analysis.

The applicant conducted spiking experiments in whole blood and plasma to evaluate *ex vivo* metabolism of methotrexate by glucarpidase. These confirmed the sample handling specifications were adequate to prevent the *ex vivo* metabolism of plasma methotrexate by glucarpidase.

As discussed in section 2, DAMPA interferes with the measurement of methotrexate concentration using immunoassays resulting in an erroneous measurement which overestimates the methotrexate concentration. The plasma methotrexate levels that support the efficacy of glucarpidase were done centrally (b) (4) using an HPLC

methodology. There were 27 patients treated between July 2004 to November 2005 with samples evaluated at (b) (4) Of these, 22 patients were eligible and evaluable.

6.1 Indication

BTG proposed indication:
Voraxaze® (glucarpidase) is indicated for the (b) (4) reduction of toxic methotrexate concentrations due to impaired renal function.

FDA indication:
VORAXAZE® (glucarpidase) is indicated for the treatment of toxic plasma methotrexate concentrations due to impaired renal function through the (b) (4) reduction of methotrexate concentrations

Voraxaze is not indicated for use in patients who have received methotrexate but do not have severely delayed methotrexate clearance related to renal dysfunction.

6.1.1 Methods

Statistical Analysis Plan (SAP)
The FDA agreed to an amended SAP submitted to IND 11557 as amendment 27 on 6/30/06. The data submitted was analyzed in this review according to this SAP.

Study Population
The primary efficacy analysis to include patients with plasma methotrexate concentrations measured by HPLC and who have plasma methotrexate ≥1 µmol/L in the last sample taken before glucarpidase was administered.

REVIEWER COMMENT
It was known at the time the SAP was submitted that there were 27 subjects with these samples submitted.

Efficacy Analysis
Primary analysis: Analysis of HPLC plasma methotrexate concentrations

The primary efficacy endpoint was defined as a clinically important reduction (CIR) in plasma methotrexate concentration. For purposes of clarity (b) (4), FDA revised this name to rapid and sustained clinically important reduction (RSCIR). This was to be evaluated as the proportion of patients with a reduction of plasma methotrexate concentration to 1 µmol/L or less in all post-glucarpidase samples. The value of 1 µmol/L was chosen because patients with this concentration of methotrexate can usually be managed with standard doses of leucovorin and patients with plasma methotrexate concentrations above 1 µmol/L have been found to have a higher incidence of severe toxicity. The observed proportion of evaluable patients who satisfy

the definition of RSCIR will be computed, and a 95% confidence interval on this proportion will be computed.

6.1.2 Patient Population

Patient Eligibility
There were 27 patients with plasma samples available for testing at the central laboratory at [redacted] (b) (4) Four of these subjects were not included in the efficacy analysis set because the plasma methotrexate concentration in the sample obtained prior to glucarpidase was less than 1 µmol/L. [Pt 249 – 0.27 µmol/L; Pt 260 - 0.05 µmol/L; Pt 268 - 0.99 µmol/L; Pt 274 – 0.66 µmol/L]

One additional patient [Pt 236] was excluded because this patient did not meet eligibility criteria to be treated on Trial 006. This patient was entered based on an initial methotrexate level that was mistakenly reported as 500 µmol/L but was actually 50 µmol/L. The level of 50 µmol/L and subsequent methotrexate levels prior to glucarpidase were within 2 standard deviations of the expected methotrexate clearance nomogram. This patient did not have evidence of renal insufficiency with a pre-methotrexate baseline creatinine of 1.2 mg/dL and a maximum creatinine of 1.3 mg/dL.

Table 35: Demographic and Patient Characteristics of the Efficacy Subset

Demographic and Patient Characteristics of the Efficacy Subset		
Eligible Subjects n = 22		
Male 13 (59 %)	Female 9 (41%)	
Age (years)		
Mean – 29	5 - 12 n = 3 (14%)	
Median – 15.5	13 - 18 n = 9 (41%)	
Range - 5 to 84	19 - 65 n = 7 (32%)	
	66- 84 n = 3 (14%)	
Weight (kg)		
Mean – 64.8	Median – 63.8	Range – 24.8 to 119.0
Diagnosis		
Osteosarcoma/sarcoma n = 11 (55%)	Other n = 1 (<1%)	
Leukemia Lymphoma n = 10 (45%)		
Methotrexate Dose (g/m^2)		
Mean – 8.9	Median – 9.1	Range – 1.4 to 20

6.1.3 Exposure

The majority (16/22) of eligible subjects received a single dose of glucarpidase. The median dose was 50 Units/ kg and ranged between 39 to 52 Units/kg. The second dose of glucarpidase was to be given at 48 hours for patients with base line methorexate level > 100 µmol/L. Six of the 7 patients with a baseline methotrexate level > 100 µmol/L received 2 doses of glucarpidase. The median of the second dose was 50 Units/kg and ranged between 49 to 56 Units/kg.

6.1.4 Analysis of Primary Endpoint(s)

There were 10 of 22 patients 45.5% (95% CI 26.9 to 65.3) who met the criteria for a RSCIR in plasma methotrexate concentration. There were 2 patients who missed being classified as a response due to the result of the 15 minute post- glucarpidase methotrexate concentration being greater than 1 µmol/L. [Pt 223 - 1.7 µmol/L see Table 46 and Figure 12; and Pt 252 – 1.3 µmol/L see Table 47 and Figure 13]

All 22 patients included in the analysis demonstrated a greater than 95% reduction in methotrexate concentration up to 8 days.

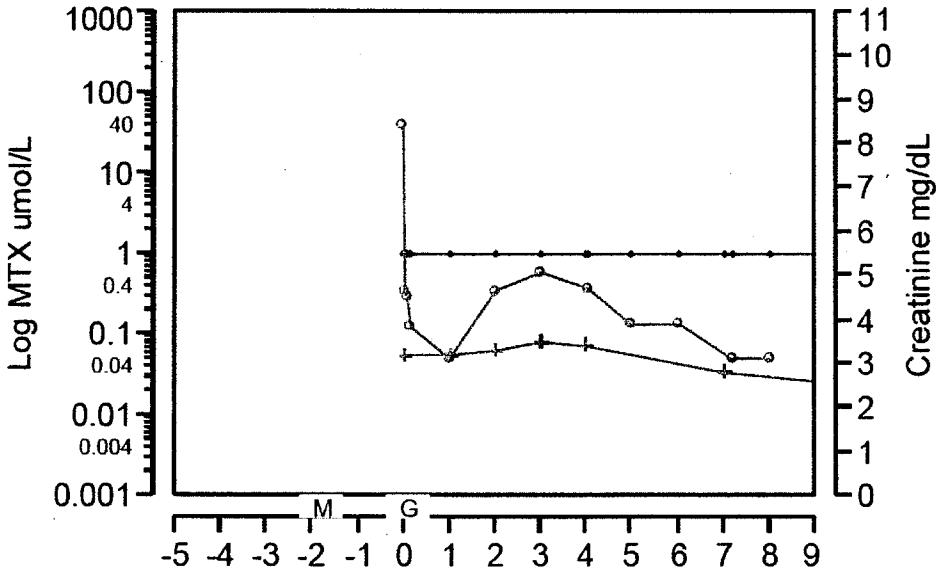
See Table 36 through Table 57 and Figure 2 through Figure 23 for the individual patient information.

RESPONDERS

Table 36: Pt 226 Responder

ID 006 226	DX - Lymphoma	Age – 52	Gender - M
Wt - 89.5 Kg	Hgt – 66 in	BSA 1.99 m^2	
MTX (grams)	MTX Dose 13.7 g	MTX/m^2 6.9 g/m^2	MTX Duration 24 hr
Creatinine ULN - 1.18 mg/dL	Pre MTX 1.0	Pre Glucarpidase 3.2	Max 3.5
MTX level (µmol/L)	Local Pre Gluc 39.2	Central Pre Gluc 40	
Glucarpidase 1	Dose 4500	Dose/kg 50 U/kg	Time from MTX 35 hr

Figure 2: Pt 226 Responder



Subject PR001-CLN-006-03-0226

Left Scale: ○ — MTX

Right Scale: + — Creatinine

Table 37: Pt 233 Responder

ID 006 233	DX – CNS Lymphoma	Age – 84 yr	Gender - M
Wt - 66 Kg	Hgt – 66 in	BSA 1.75	
MTX (grams)	MTX Dose 2.5 g	MTX/m^2 1.4 g/m^2	MTX Duration 2 hr
Creatinine ULN – 1.18 mg/dL	Pre MTX 1.2	Pre Glucarpidase 2.6	Max 3.2
MTX level (µmol/L)	Local Pre Gluc 11.8	Central Pre Gluc 6.1	
Glucarpidase 1	Dose 3300 U	Dose/kg 50 U/kg	Time from MTX 64 hr

Figure 3: Pt 233 Responder

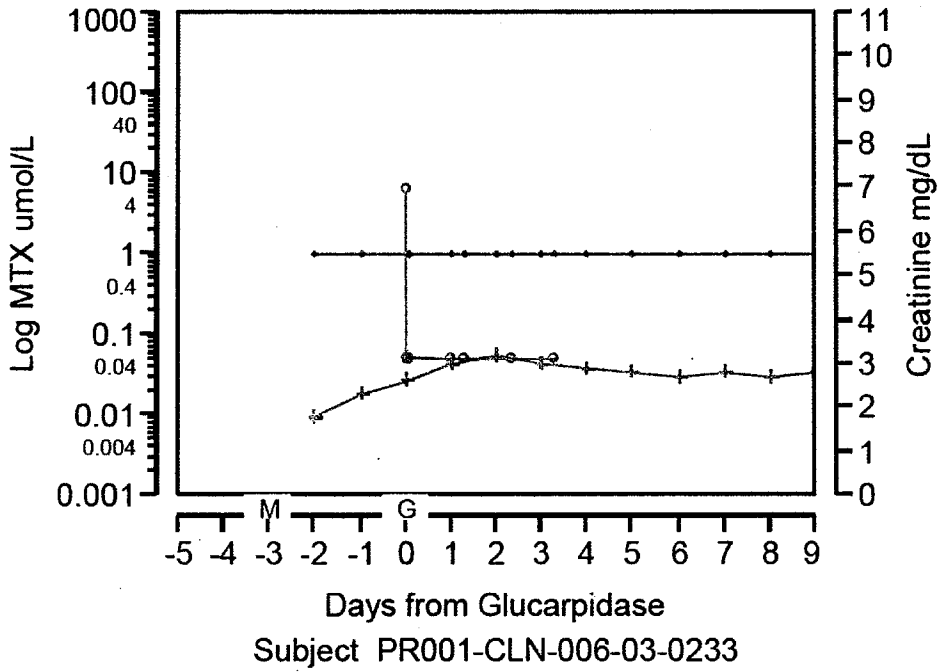
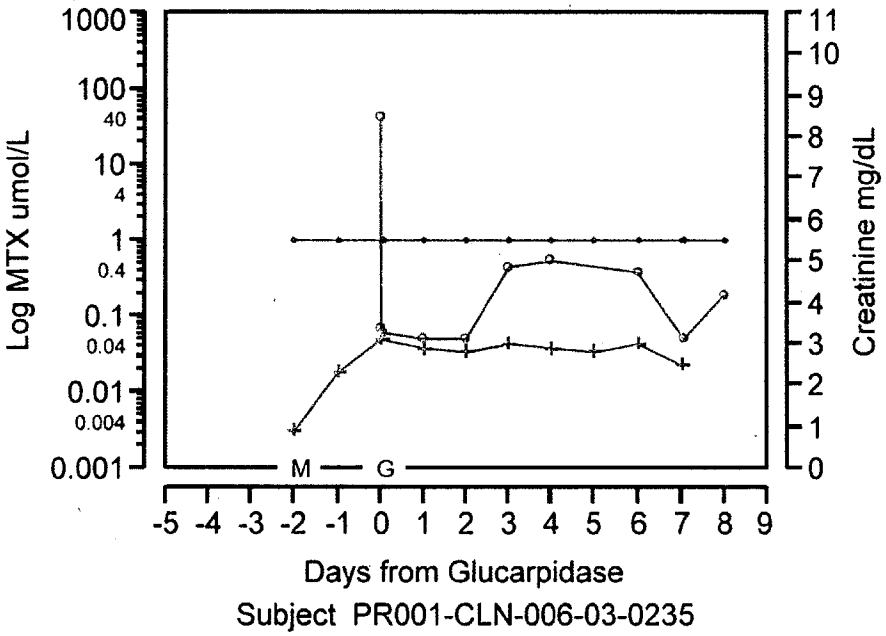


Table 38: Pt 235 Responder

ID 006 235	DX – CNS Lymphoma	Age – 74 yr	Gender - M
Wt - 88.6 Kg	Hgt – 70 in	BSA 2.06	
MTX (grams)	MTX Dose 7.2 g	MTX/m^2 3.5 g/m^2	MTX Duration 2 hr
Creatinine ULN – 1.18 mg/dL	Pre MTX 0.9	Pre Glucarpidase 3.1	Max 3.1
MTX level (µmol/L)	Local Pre Gluc 54	Central Pre Gluc 41.6	
Glucarpidase 1	Dose 4430 U	Dose/kg 50 U/kg	Time from MTX 41 hr

Figure 4: Pt 235 Responder



Left Scale: ○ — MTX

Right Scale: + — Creatinine

Table 39: Pt 240 Responder

ID 006 240	DX – Osteosarcoma	Age – 20 yr	Gender - M
Wt - 67.7 Kg	Hgt – NA	BSA 1.86	
MTX (grams)	MTX Dose 22.3 g	MTX/m^2 12 g/m^2	MTX Duration 4 hr
Creatinine ULN – 1.18 mg/dL	Pre MTX 0.9	Pre Glucarpidase 2.4	Max 2.4
MTX level (µmol/L)	Local Pre Gluc 65.6	Central Pre Gluc 37.8	
Glucarpidase 1	Dose 3500 U	Dose/kg 50 U/kg	Time from MTX 47 hr

Figure 5: Pt 240 Responder

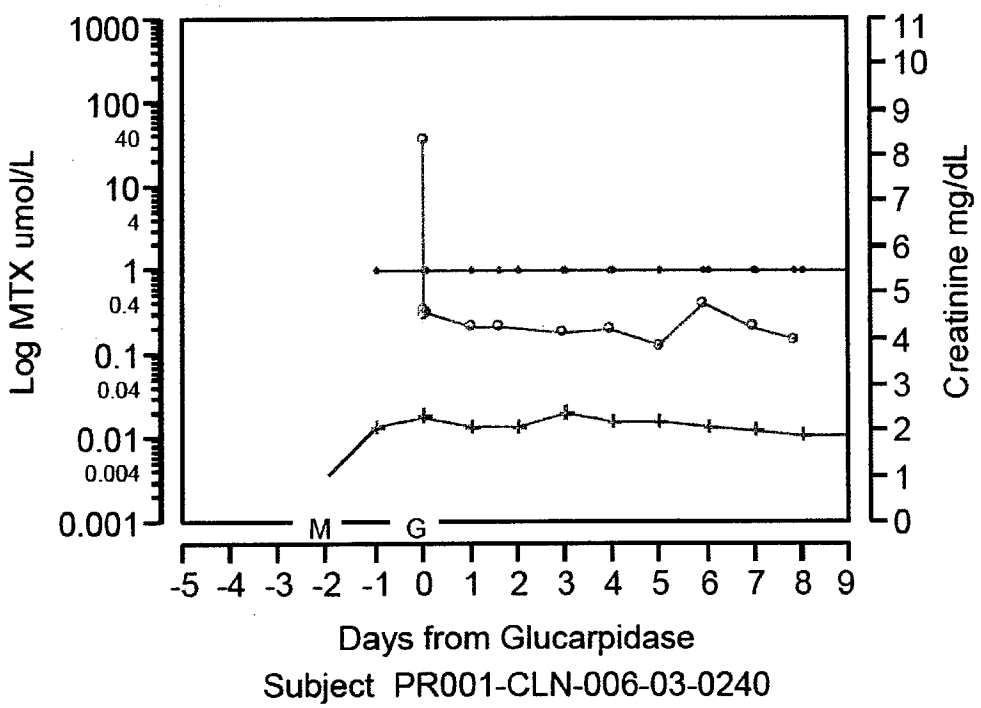


Table 40: Pt 259 Responder

ID 006 259	DX – Leukemia	Age – 49 yr	Gender - M
Wt - 101.5 Kg	Hgt – 68 in	BSA 1.8	
MTX (grams)	MTX Dose 5.4 g	MTX/m^2 3 g/m^2	MTX Duration 2 hr
Creatinine ULN – 1.18 mg/dL	Pre MTX 0.9	Pre Glucarpidase 2.7	Max 9.5
MTX level (µmol/L)	Local Pre Gluc 22.9	Central Pre Gluc 11.1	
Glucarpidase 1	Dose 4000 U	Dose/kg 39.4 U/kg	Time from MTX 43 hr

Figure 6: Pt 259 Responder

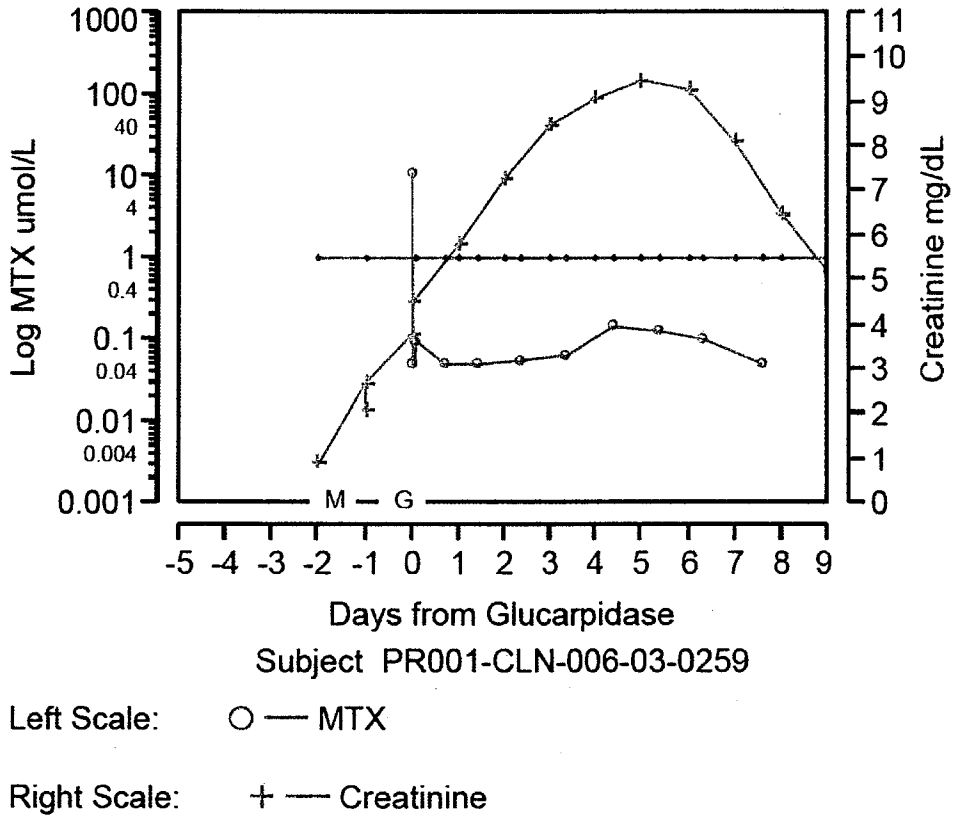


Table 41: Pt 263 Responder

ID 006 263	DX – Leukemia	Age – 16 yr	Gender - M
Wt - 70 Kg	Hgt – 165.2 cm	BSA 1.82	
MTX (grams)	MTX Dose 9.1 g	MTX/m^2 5 g/m^2	MTX Duration 24 hr
Creatinine ULN – 1.18 mg/dL	Pre MTX 0.4	Pre Glucarpidase 4.4	Max 4.4
MTX level (µmol/L)	Local Pre Gluc 63	Central Pre Gluc 36.3	
Glucarpidase 1	Dose 3500 U	Dose/kg 50 U/kg	Time from MTX 59 hr

Figure 7: Pt 263 Responder

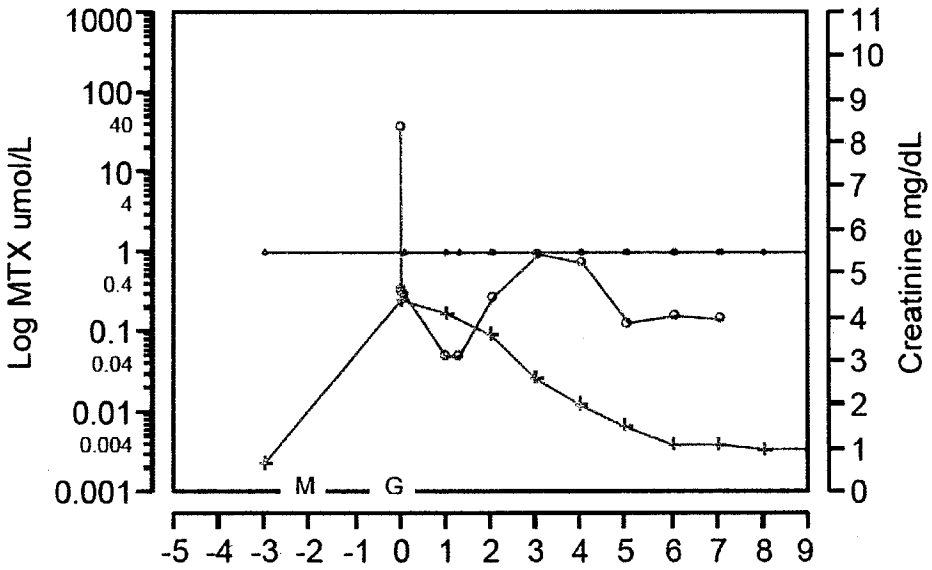


Table 42: Pt 265 Responder

ID 006 265	DX – Lymphoma	Age – 48 yr	Gender - M
Wt - 68 Kg	Hgt – 76 in	BSA 1.96	
MTX (grams)	MTX Dose 15.0 g	MTX/m^2 8.0 g/m^2	MTX Duration 4 hr
Creatinine ULN – 1.18 mg/dL	Pre MTX 0.7	Pre Glucarpidase 3.9	Max 3.9
MTX level (µmol/L)	Local Pre Gluc 25	Central Pre Gluc 21.4	
Glucarpidase 1	Dose 3500 U	Dose/kg 51 U/kg	Time from MTX 72 hr

Figure 8: Pt 265 Responder

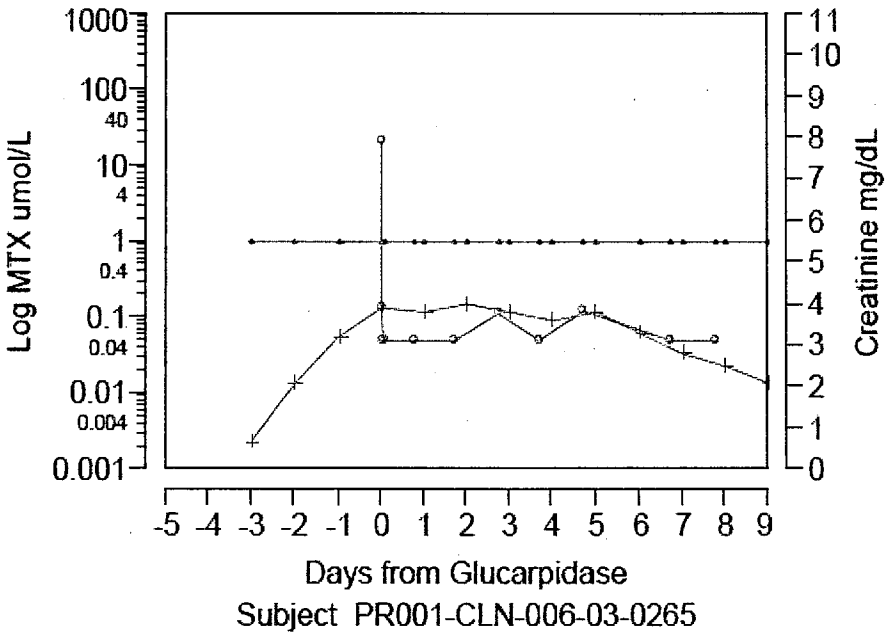


Table 43: Pt 270 Responder

ID 006 270	DX - Osteosarcoma	Age - 5 yr	Gender - F
Wt - 24.8 Kg	Hgt - NA	BSA 0.94	
MTX (grams)	MTX Dose 18.8 g	MTX/m^2 20 g/m^2	MTX Duration 4 hr
Creatinine ULN - 0.48 mg/dL	Pre MTX 0.4	Pre Glucarpidase 1.6	Max 1.7
MTX level (µmol/L)	Local Pre Gluc 25	Central Pre Gluc 8.1	
Glucarpidase 1	Dose 1240 U	Dose/kg 50 U/kg	Time from MTX 71 hr
Note: The data was incomplete, dates missing from daily MTX levels. All samples except pre-glucarpidase sample were < 1µmol/L. Therefore this patient is classified as a responder.			

Figure 9: Pt 270 Responder

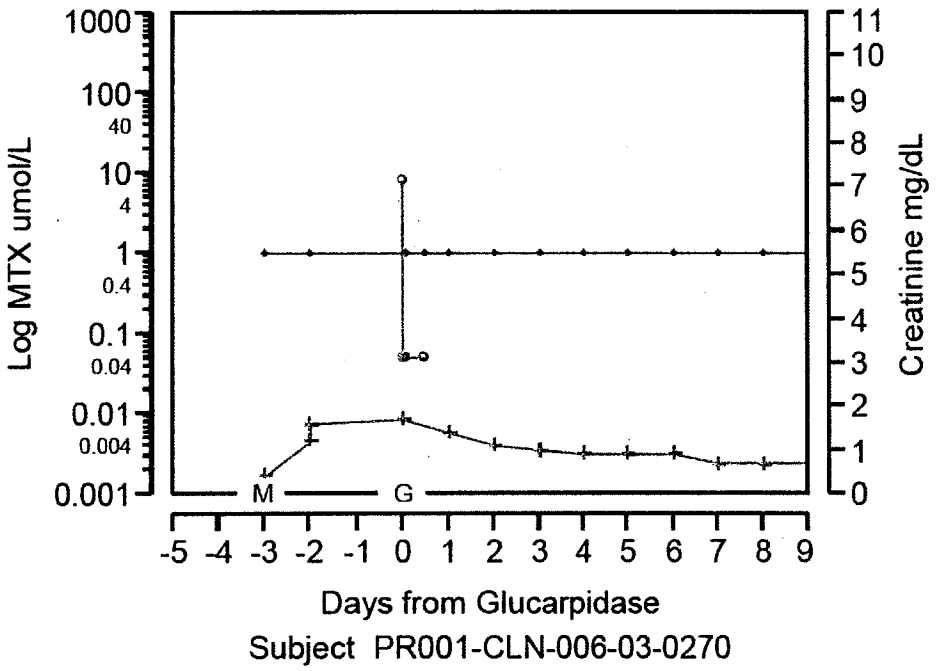


Table 44: Pt 279 Responder

ID 006 279	DX – Leukemia	Age – 15 yr	Gender - F
Wt - 45.1 Kg	Hgt – 161 cm	BSA 1.4	
MTX (grams)	MTX Dose 7.0 g	MTX/m^2 5.0 g/m^2	MTX Duration 24 hr
Creatinine ULN – 0.81 mg/dL	Pre MTX 0.8	Pre Glucarpidase 1.3	Max 1.3
MTX level (µmol/L)	Local Pre Gluc 10	Central Pre Gluc 3.9	
Glucarpidase 1	Dose 2255 U	Dose/kg 50 U/kg	Time from MTX 65 hr
Note: This patients just met the renal inclusion criteria of an increase in creatinine 1.5 times the upper limit of normal (that is > 1.2 mg/dL)			

Figure 10: Pt 279 Responder

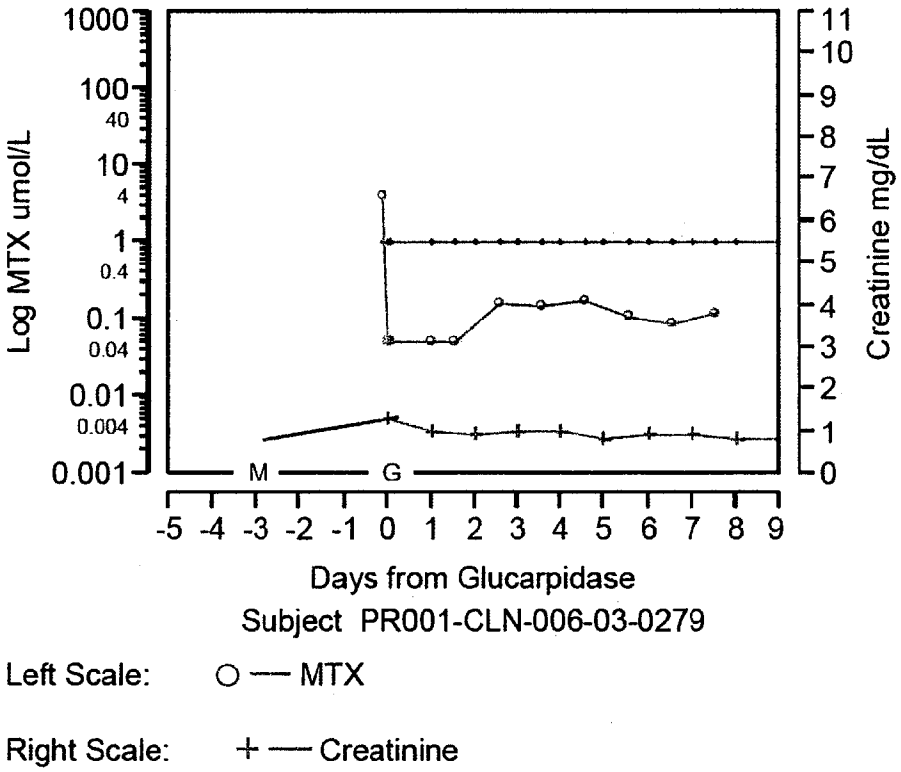
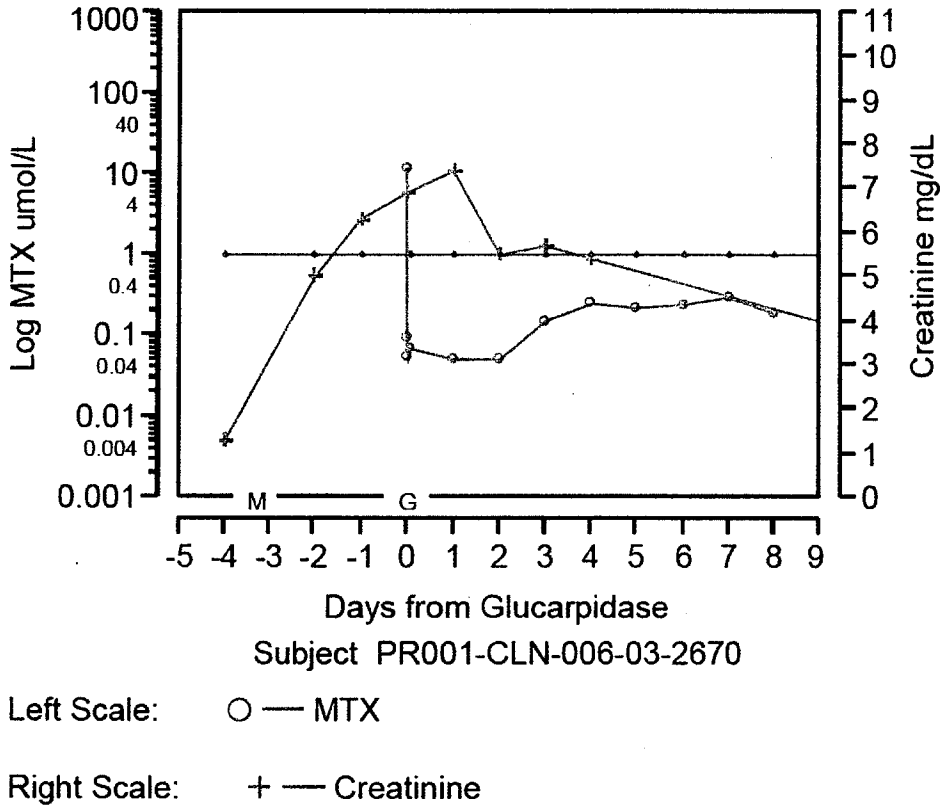


Table 45: Pt 2670 Responder

ID 006 2670	DX – CNS Lymphoma	Age – 73 yr	Gender - M
Wt - 85.5 Kg	Hgt – 168 cm	BSA 1.95	
MTX (grams)	MTX Dose 15.6 g	MTX/m^2 8 g/m^2	MTX Duration 5 hr
Creatinine ULN – 1.18 mg/dL	Pre MTX 1.0	Pre Glucarpidase 6.9	Max 7.4
MTX level (µmol/L)	Local Pre Gluc 21	Central Pre Gluc 12	
Glucarpidase 1	Dose 4250 U	Dose/kg 50 U/kg	Time from MTX 86 hr
Note: This patient was dialyzed days 1, 2, 3.			

Figure 11: Pt 2670 Responder



NON-RESPONDERS

Table 46: Pt 223 Non-Responder Missed Responder Criteria due to 15 minute Methotrexate Level

ID 006 223	DX - Lymphoma	Age - 23 yr	Gender - M
Wt - 69.5 Kg	Hgt – 78 in	BSA 2.0 m^2	
MTX (grams)	MTX Dose 13.5 g	MTX/m^2 6.7 g/m^2	MTX Duration 24 hr
Creatinine ULN - 1.18 mg/dL	Pre MTX 0.9	Pre Glucarpidase 2.9	Max 4.0
MTX level (µmol/L)	Local Pre Gluc 112	Central Pre Gluc 50.4	
Glucarpidase 1	Dose 3500 U	Dose/kg 50 U/kg	Time from MTX 48 hr

Figure 12: Pt 223 Non-Responder Missed Responder Criteria due to 15 minute Methotrexate Level

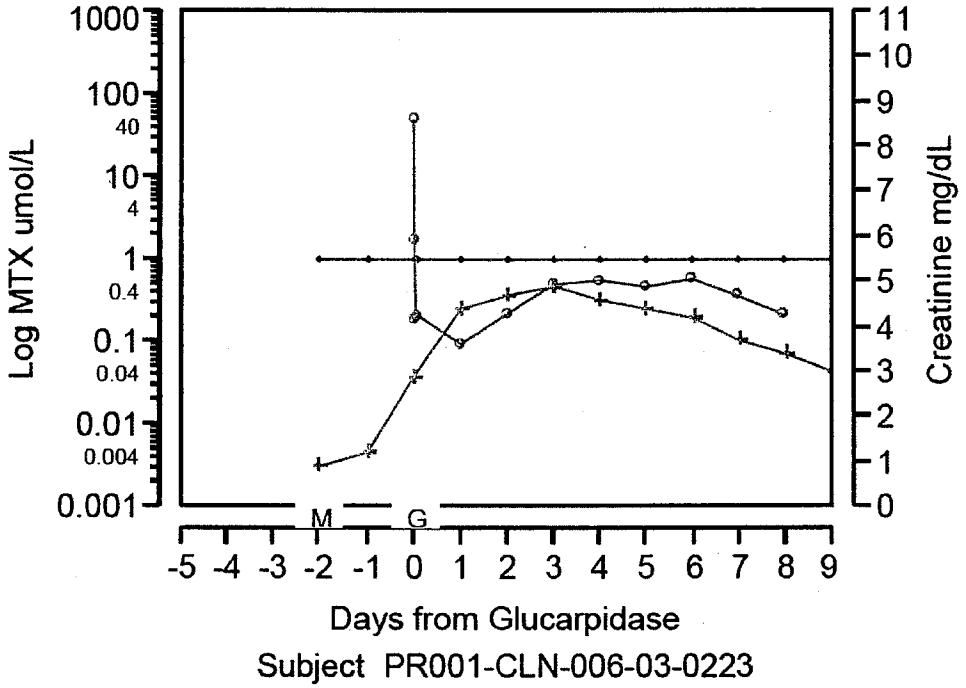


Table 47: Pt 252 Non-Responder 2 Doses of Glucarpidase Missed Responder Criteria due to 15 minute Methotrexate Level

ID 006 252	DX – Lymphoma	Age – 20 yr	Gender - M
Wt - 72 Kg	Hgt – NA	BSA 1.92	
MTX (grams)	MTX Dose 15.4 g	MTX/m^2 8 g/m^2	MTX Duration 4 hr
Creatinine ULN – 1.18 mg/dL	Pre MTX 1.0	Pre Glucarpidase 1.3	Max 4.3
MTX level (µmol/L)	Local Pre Gluc 239	Central Pre Gluc 286	
Glucarpidase 1	Dose 3500 U	Dose/kg 48.6 U/kg	Time from MTX 29 hr
Glucarpidase 2	Dose 4000 U	Dose/kg 55.5 U/kg	Time from Gluc 1 48 hr
Note: This patient was dialyzed on day 3 and day 4.			

Figure 13: Pt 252 Non-Responder 2 Doses of Glucarpidase Missed Responder Criteria due to 15 minute Methotrexate Level

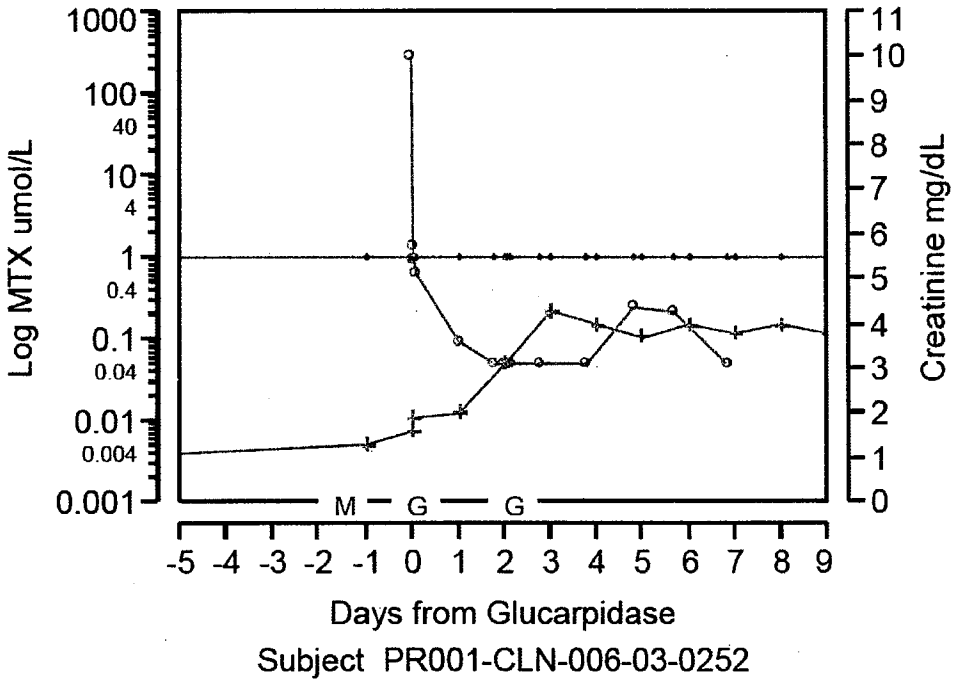


Table 48: Pt 224 Non-Responder 2 Doses of Glucarpidase

ID 006 224	DX - Osteosarcoma	Age - 14 yr	Gender - F
Wt - 55 Kg	Hgt - NA	BSA 1.57	
MTX (grams)	MTX Dose 18.84 g	MTX/m^2 12 g/m^2	MTX Duration 4 hr
Creatinine ULN - 0.81	Pre MTX 0.5	Pre Glucarpidase 1.9	Max 8.6
MTX level (µmol/L)	Local Pre Gluc 920	Central Pre Gluc 708	
Glucarpidase 1	Dose 2750 U	Dose/kg 50 U/kg	Time from MTX 34 hr
Glucarpidase 2	Dose 2750 U	Dose/kg 50 U/kg	Time from Gluc 1 48 hr

Figure 14: Pt 224 Non-Responder 2 Doses of Glucarpidase

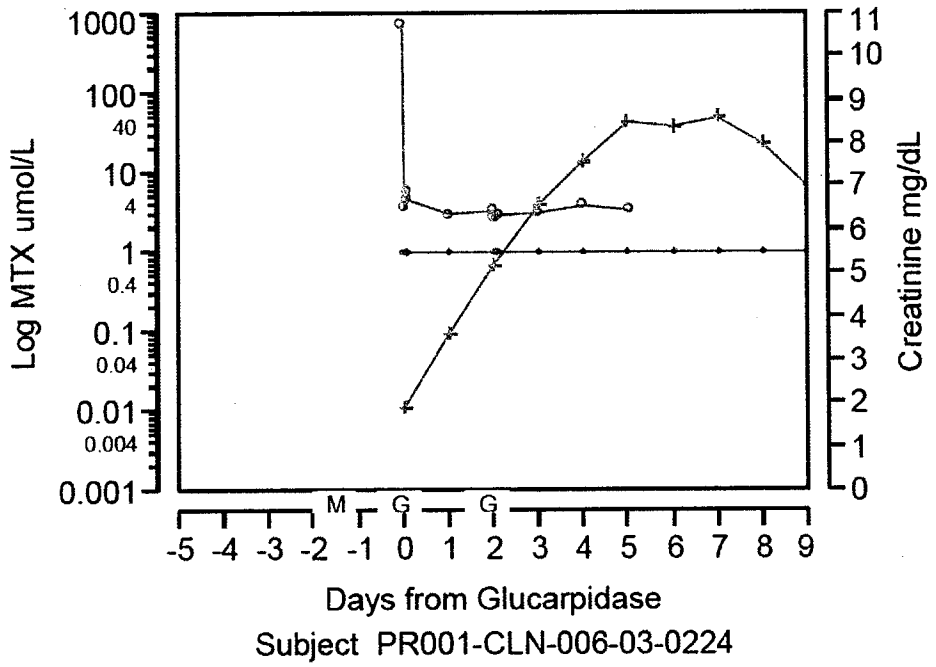


Table 49: Pt 228 Non-Responder 2 Doses of Glucarpidase

ID 006 228	DX - Osteosarcoma	Age - 47 yr	Gender - M
Wt - 119 Kg	Hgt – 180.2 cm	BSA 2.45	
MTX (grams)	MTX Dose 25.0 g	MTX/m^2 10.2 g/m^2	MTX Duration 24 hr
Creatinine ULN - 1.18	Pre MTX 0.9	Pre Glucarpidase 5.4	Max 7.6
MTX level (µmol/L)	Local Pre Gluc 500	Central Pre Gluc 361.6	
Glucarpidase 1	Dose 6000 U	Dose/kg 50 U/kg	Time from MTX 48 hr
Glucarpidase 2	Dose 6000 U	Dose/kg 50 U/kg	Time from Gluc 1 49 hr
Note: This patient developed anuric renal failure on Day -1 and underwent daily dialysis starting on Day -1 continuing after hospital discharge on Day 13 as an outpatient.			

Figure 15: Pt 228 Non-Responder 2 Doses of Glucarpidase

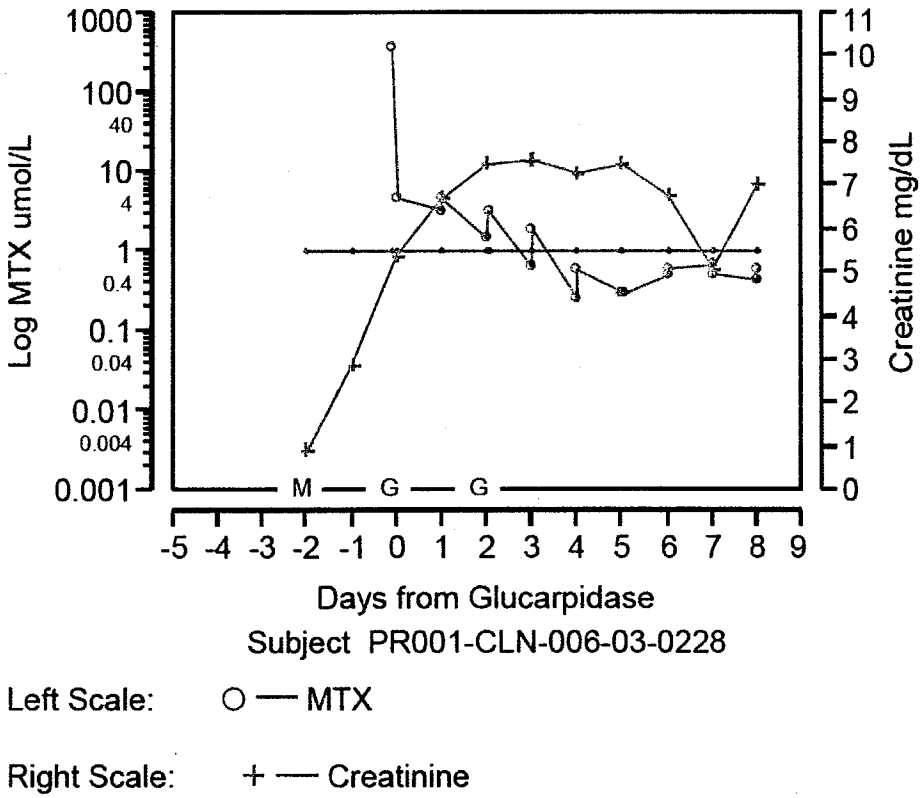


Table 50: Pt 243 Non-Responder 2 Doses of Glucarpidase

ID 006 243	DX - Osteosarcoma	Age - 13 yr	Gender - F
Wt - 40 Kg	Hgt – NA	BSA 1.34	
MTX (grams)	MTX Dose 16.0 g	MTX/m^2 11.9 g/m^2	MTX Duration 4 hr
Creatinine ULN - 0.81	Pre MTX 0.5	Pre Glucarpidase 2.7	Max 9.7
MTX level (µmol/L)	Local Pre Gluc 573	Central Pre Gluc 628.7	
Glucarpidase 1	Dose 2000 U	Dose/kg 50 U/kg	Time from MTX 34 hr
Glucarpidase 2	Dose 2000 U	Dose/kg 50 U/kg	Time from Gluc 1 48 hr
Note: Patient dialyzed on day 6			

Figure 16: Pt 243 Non-Responder 2 Doses of Glucarpidase

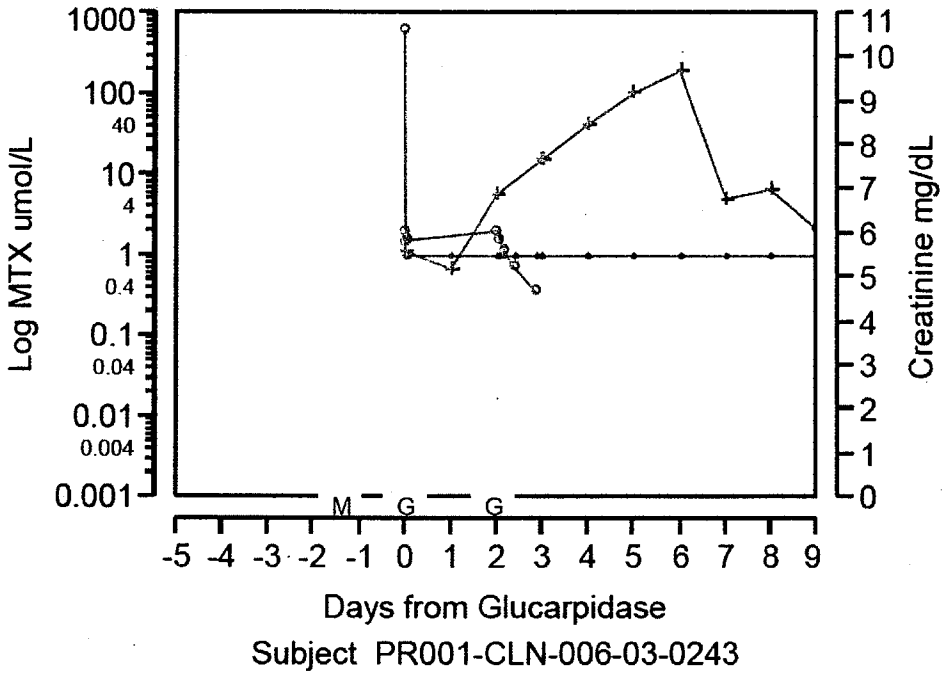


Table 51: Pt 245 Non-Responder 2 Doses of Glucarpidase

ID 006 245	DX - Osteosarcoma	Age - 11 yr	Gender - F
Wt - 61.5 Kg	Hgt – 154 cm	BSA 1.6	
MTX (grams)	MTX Dose 19.2 g	MTX/m^2 12 g/m^2	MTX Duration 4 hr
Creatinine ULN - 0.71	Pre MTX 0.6	Pre Glucarpidase 3.1	Max 6.2
MTX level (µmol/L)	Local Pre Gluc 303.8	Central Pre Gluc 521	
Glucarpidase 1	Dose 3000 U	Dose/kg 49 U/kg	Time from MTX 32 hr
Glucarpidase 2	Dose 3000 U	Dose/kg 49 U/kg	Time from Gluc 1 48 hr

Figure 17: Pt 245 Non-Responder 2 Doses of Glucarpidase

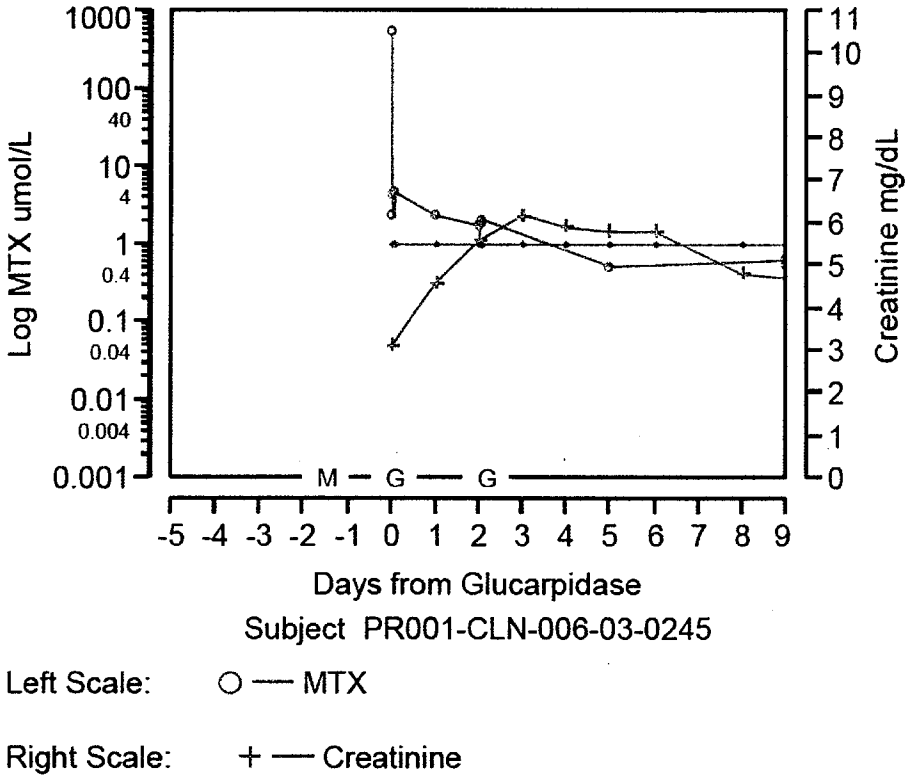
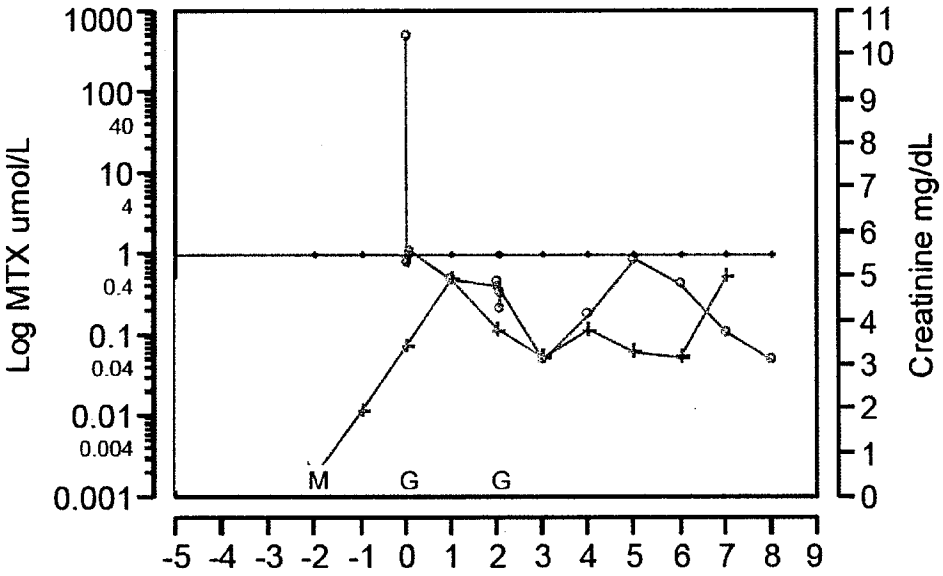


Table 52: Pt 244 Non-Responder 2 Doses of Glucarpidase Rebound

ID 006 244	DX - Osteosarcoma	Age - 10 yr	Gender - M
Wt - 47.4 Kg	Hgt – 164 cm	BSA 1.44	
MTX (grams)	MTX Dose 17.3 g	MTX/m^2 12 g/m^2	MTX Duration 4 hr
Creatinine ULN - 0.64	Pre MTX 0.5	Pre Glucarpidase 3.4	Max 4.9
MTX level (µmol/L)	Local Pre Gluc 417	Central Pre Gluc 507	
Glucarpidase 1	Dose 2500 U	Dose/kg 52 U/kg	Time from MTX 54 hr
Glucarpidase 2	Dose 2500 U	Dose/kg 52 U/kg	Time from Gluc 1 48 hr
Note: This patient underwent hemodialysis Day 0, 1, 2, 4, and 8.			

Figure 18: Pt Pt 244 Non-Responder 2 Doses of Glucarpidase Rebound



Subject PR001-CLN-006-03-0244

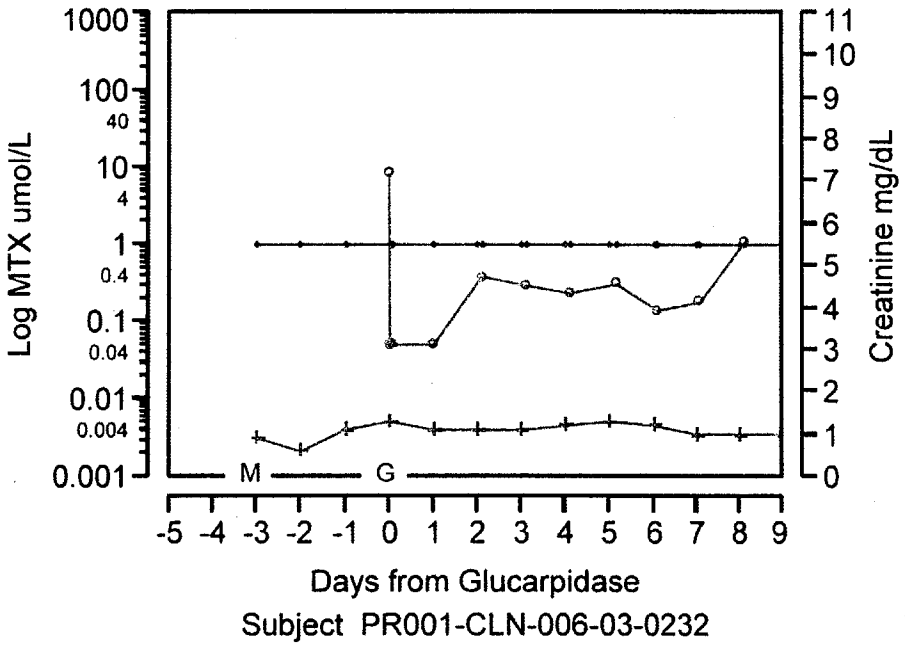
Left Scale: ○ — MTX

Right Scale: + — Creatinine

Table 53: Pt 232 Non-Responder Rebound

ID 006 232	DX – Malignant Myofibroblastic Tumor	Age - 14 yr	Gender - F
Wt - 48.9 Kg	Hgt – 159 cm	BSA 1.46 m^2	
MTX (grams)	MTX Dose 17.5 g	MTX/m^2 12 g/m^2	MTX Duration 4 hr
Creatinine ULN - 0.81 mg/dL	Pre MTX 0.6	Pre Glucarpidase 1.3	Max 1.3
MTX level (µmol/L)	Local Pre Gluc 11.4	Central Pre Gluc 8.6	
Glucarpidase 1	Dose 2235 U	Dose/kg 45.7 U/kg	Time from MTX 69 hr
Note: This patient developed pleural effusion after methotrexate infusion during 2 previous courses of methotrexate. A pleural effusion was not documented in the patient's CFRs with this course of methotrexate. A pleural effusion would explain the late rebound in methotrexate level.			

Figure 19: Pt 232 Non-Responder Rebound



Left Scale: ○ — MTX

Right Scale: + — Creatinine

Table 54: Pt 239 Non-Responder Rebound

ID 006 239	DX - Osteosarcoma	Age - 13 yr	Gender - F
Wt - 52.4 Kg	Hgt – 153.6 cm	BSA 1.5	
MTX (grams)	MTX Dose 18.5 g	MTX/m^2 12 g/m^2	MTX Duration 4 hr
Creatinine ULN - 0.81	Pre MTX 0.6	Pre Glucarpidase 2.3	Max 2.3
MTX level (µmol/L)	Local Pre Gluc 41.7	Central Pre Gluc 44.0	
Glucarpidase 1	Dose 2710 U	Dose/kg 50 U/kg	Time from MTX 48 hr

Figure 20: Pt 239 Non-Responder Rebound

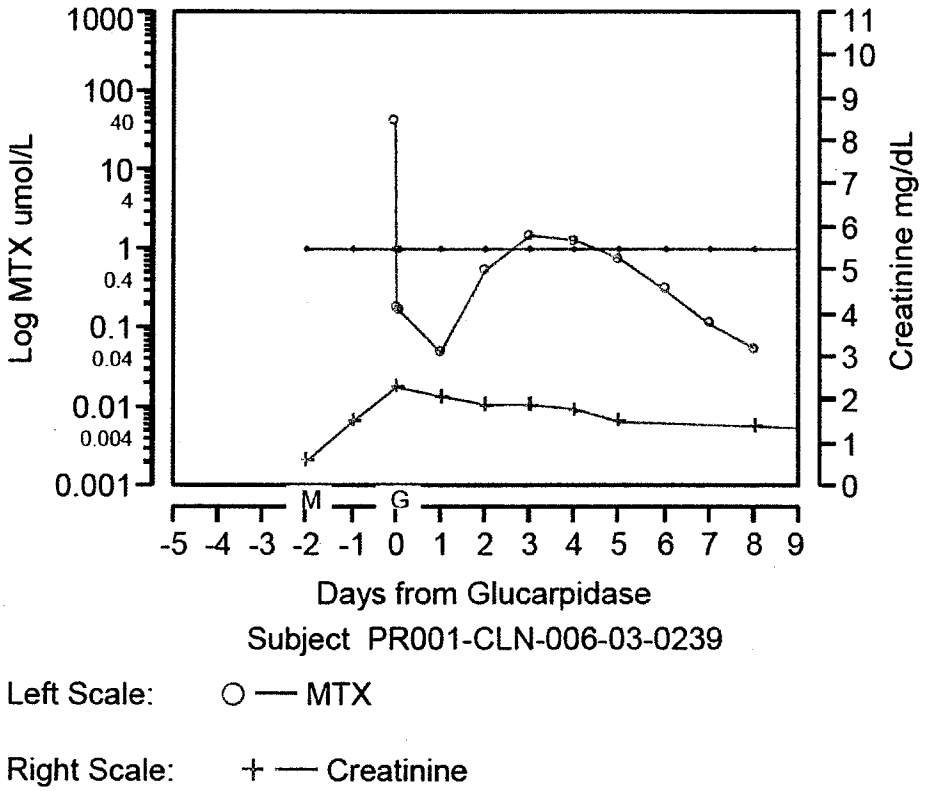


Table 55: Pt 255 Non-Responder Rebound

ID 006 255	DX – Osteosarcoma	Age – 13 yr	Gender - M
Wt - 55.3 Kg	Hgt – NA	BSA 1.64	
MTX (grams)	MTX Dose 20 g	MTX/m^2 12 g/m^2	MTX Duration 4 hr
Creatinine ULN – 0.81 mg/dL	Pre MTX 0.4	Pre Glucarpidase 1.5	Max 1.5
MTX level (µmol/L)	Local Pre Gluc 35	Central Pre Gluc 18.7	
Glucarpidase 1	Dose 2800 U	Dose/kg 50 U/kg	Time from MTX 54 hr

Figure 21: Pt 255 Non-Responder Rebound

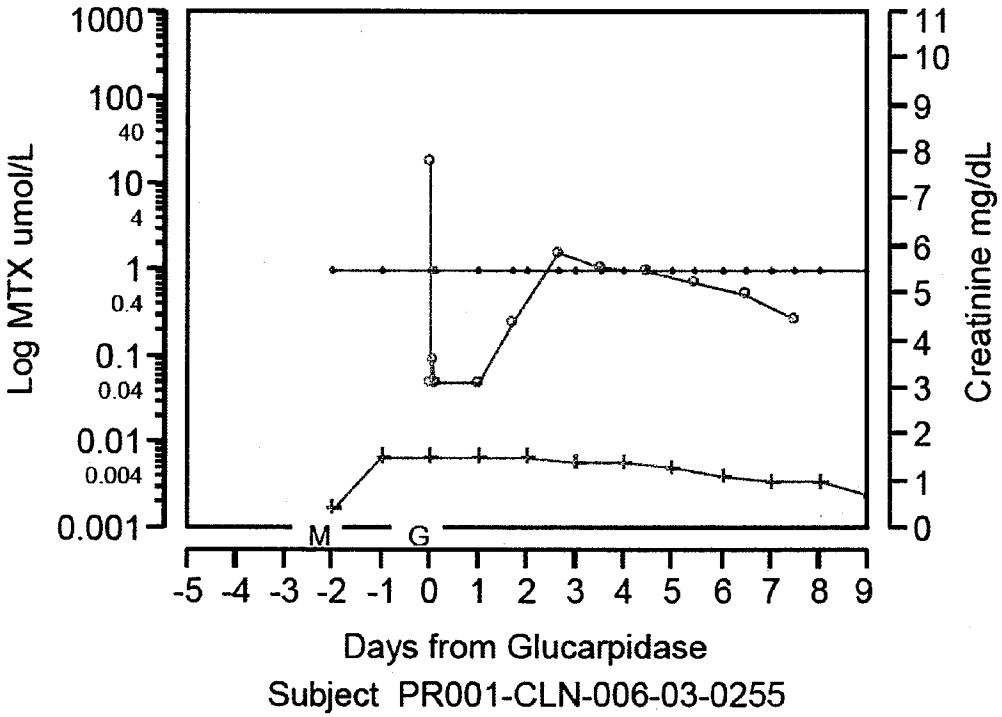
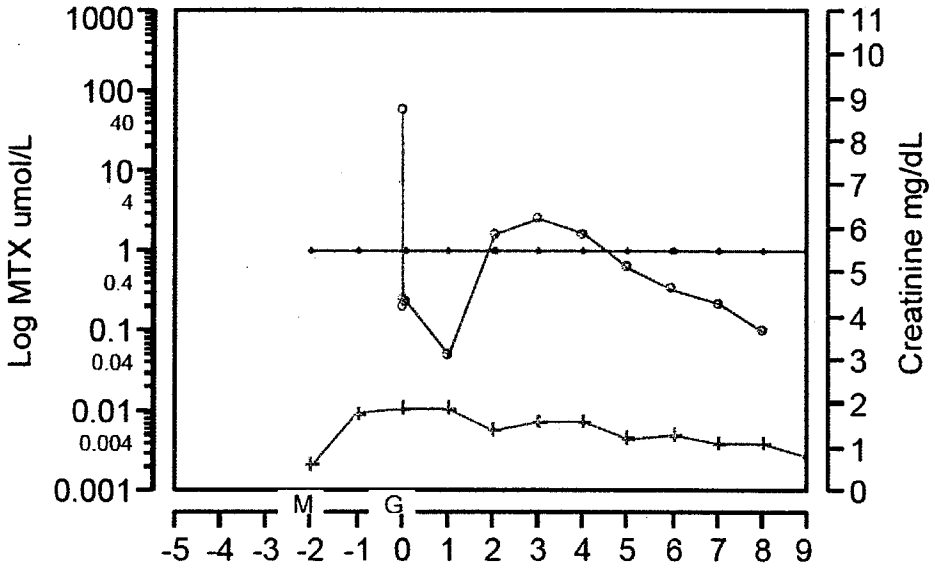


Table 56: Pt 280 Non-Responder Rebound

ID 006 280	DX – Osteosarcoma	Age – 13 yr	Gender - F
Wt - 46.7 Kg	Hgt – 156 cm	BSA 1.43	
MTX (grams)	MTX Dose 17 g	MTX/m^2 12 g/m^2	MTX Duration 4 hr
Creatinine ULN – 0.81 mg/dL	Pre MTX 0.8	Pre Glucarpidase 1.3	Max 1.3
MTX level (µmol/L)	Local Pre Gluc 56	Central Pre Gluc 57	
Glucarpidase 1	Dose 2350 U	Dose/kg 50 U/kg	Time from MTX 56 hr

Figure 22: Pt 280 Non-Responder Rebound



Subject PR001-CLN-006-03-0280

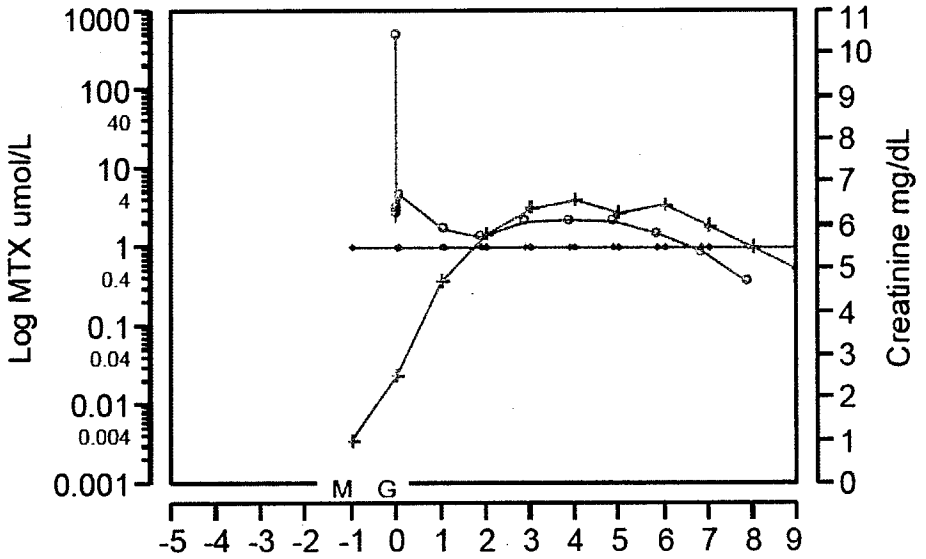
Left Scale: ○ — MTX

Right Scale: + — Creatinine

Table 57: Pt 284 Non-Responder

ID 006 284	DX – Osteosarcoma	Age – 13 yr	Gender - F
Wt - 51.2 Kg	Hgt – 165.3 cm	BSA 1.54	
MTX (grams)	MTX Dose 3.1 g	MTX/m^2 2 g/m^2	MTX Duration 4 hr
Creatinine ULN – 0.81 mg/dL	Pre MTX 0.8	Pre Glucarpidase 2.5	Max 6.6
MTX level (µmol/L)	Local Pre Gluc 651	Central Pre Gluc 500	
Glucarpidase 1	Dose 2560 U	Dose/kg 50 U/kg	Time from MTX 27 hr

Figure 23: Pt 284 Non-Responder



Subject PR001-CLN-006-03-0284

Left Scale: ○ — MTX

Right Scale: + — Creatinine

6.1.5 Analysis of Secondary Endpoints(s)

Subgroup Analysis of Response Based on Pre-Glucarpidase Methotrexate Level

Table 58: Response by Baseline Methotrexate

Pre-Glucarpidase Methotrexate	Number of Patients	Patients with a RSCIR
> 1 µmol/L	22	10 (46%)
> 1 to ≤ 50 µmol/L	13	10 (77%)
> 50 to ≤ 100 µmol/L	2	0
> 100 µmol/L	7	0

REVIEWER COMMENT:
The likelihood of a response was related to the pre-glucarpidase methotrexate level. No patients with plasma methotrexate concentrations greater than 50 µmol/L were classified as responders. Although patients with pre-glucarpidase methotrexate levels greater than > 50 µmol/L did not achieve response criteria, at 24 hours all patients demonstrated a 2 log or greater decrease in the methotrexate level.

6.1.6 Other Endpoints

Response to Second Dose of Glucarpidase

The protocol specified that patients were to receive a second dose glucarpidase at 48 hours if the pre-glucarpidase methorexate level was greater than 100 µmol/L. There were 7 patients with the pre-glucarpidase level greater than 100 µmol/L. Six of these received the second dose. The methotrexate level prior to the second dose of glucarpidase of 2 of these patients was less than 1 µmol/L. Three patients demonstrated further reduction in their methotrexate levels after the second dose. However, the further reduction in methotrexate level was modest as can be seen in Table 59.

Table 59: Methotrexate Level with Second Dose of Glucarpidase

Patient ID	Pre 2nd Glucarpidase Methotrexate Level	Day 1 Post 2nd Glucarpidase Methotrexate Level
Pt 244 (Figure 17)	0.4 µmol/L	0.05 µmol/L
Pt 252 (Figure 13)	0.05 µmol/L	0.05 µmol/L
Pt 228 (Figure 15)	3.2 µmol/L	1.8 µmol/L
Pt 245 (Figure 18)	2.3 µmol/L	0.5 µmol/L
Pt 243 (Figure 16)	2.0 µmol/L	0.4 µmol/L
Pt 224 (Figure 14)	3.3 µmol/L	3.1 µmol/L

Rebound

A patients was classified as having experienced rebound if they attained a methotrexate level less than 1 µmol/L and had a subsequent level greater than 1 µmol/L. By this definition there were 5 of 22 patients 22.7% (95% CI 10.1 to 43.4) with rebound. (Pt 244 Figure 18, Pt 232 Figure 19, Pt 239 Figure 20, Pt 255 Figure 21, Pt 280 Figure 22). Although only 5 patients met the definition of rebound the majority of patients demonstrated increased levels of methotrexate after reaching the original post-glucarpidase nadir. It is therefore important that the level of methorexate be monitored for a minimum of 3 days after the threshold for discontinuing the administration of leucovorin in order to ensure patients receive adequate leucovorin rescue.

6.1.7 Subpopulations

Subgroup Analysis by Diagnosis

Table 60: Response by Diagnosis

Diagnosis	Number of Patients	Patients with a RSCIR
Osteosarcoma Sarcoma	11	2 (18%)
Leukemia Lymphoma	10	8 (80%)

REVIEWER COMMENT:

The underlying diagnosis appears to be associated with response. Patients with osteosarcoma were less likely to respond. Patients with osteosarcoma were treated with higher doses of methotrexate with a median 12 range 2 to 20 g/m^2 compared to leukemia lymphoma patients with a median 5.8 range 1.4 to 8 g/m^2. The pre-glucarpidase methotrexate level was greater in the osteosarcoma patients median 361.7 range 8.1 to 708 µmol/L compared to the leukemia lymphoma patients with a median of 28.9 range 3.9 to 286.2 µmol/L. Another factor that may have contributed to the poor response in osteosarcoma patients is their previous exposure to cisplatin, an agent known to cause chronic renal toxicity.

Subgroup Analysis by Methotrexate Dose

Table 61: Response by Methotrexate Dose

Dose Methotrexate	Number of Patients	Patients with a RSCIR
1.4 to 3.5 g/m^2	4	3 (75%)
5.0 to 8.0 g/m^2	7	5 (71%)
10.2 to 12 g/m^2	10	1 (10%)
20 g/m^2	1	1 (100%)

REVIEWER COMMENT:
Patients treated with lower doses of methotrexate were more likely to be responders. In general patients treated with higher doses of methotrexate were more likely to have higher pre-glucarpidase methotrexate levels.

Subgroup Analysis by Age

Table 62: Response by Age

Age	Number of Patients	Patients with a RSCIR
5 to 16 years	12	3 (25%)
20 to 52 years	7	4 (57%)
73 to 84 years	3	3 (100%)

REVIEWER COMMENT:
The lower response in the younger patients reflects the diagnosis 9 of 12 were osteosarcoma patients, whereas only 2 of 10 adult patients had osteosarcoma.

Subgroup analysis by Gender

Gender	Number of Patients	Patients with a RSCIR
Female	9	2 (22%)
Male	13	8 (61%)

REVIEWER COMMENT:
The lower response in the female patients reflects the diagnosis 7 of 9 were osteosarcoma patients, whereas only 4 of 13 male patients had osteosarcoma.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant did not systematically evaluate dosing. The dose studied resulted in a 45% response that achieved the RSCIR to a plasma methotrexate concentration <1 µmol/L. It is unlikely that a change in dose would result in a better response rate. (b) (4)

(b) (4)

(b) (4) Therefore the recommended dose will be 50 Units per kg, the dose that was studied.

The recommendation that a second dose be administered in subjects with methotrexate levels greater than 100 µmol/L is not well justified. See section 6.1.6.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Glucarpidase is being evaluated as an antidote for methotrexate toxicity in patients treated with high dose methotrexate who develop toxic methotrexate levels due to renal impairment. This is an emergency situation. It is not anticipated that patients treated for this indication will frequently receive repeat doses.

If the applicant pursues establishing a broader indication, that is to use glucarpidase a routine component of a high dose methotrexate regimen, this will become an important consideration.

6.1.10 Additional Efficacy Issues/Analyses (Intrathecal Administration)

Glucarpidase has been administered intrathecally to patients who have received accidental intrathecal overdoses of methotrexate. High cerebrospinal methotrexate concentration has been associated with severe neurotoxicity. BTG has documented 9 cases of intrathecal glucarpidase therapy for intrathecal overdoses of methotrexate. A randomized study in humans to evaluate the effectiveness of intrathecal glucarpidase is not feasible. FDA will request that BTG conduct a study under the animal rule to evaluate the effectiveness of this therapy.

7 Review of Safety

Safety Summary

The major safety population that provided safety information to support the application indication: "the (b) (4) reduction of toxic methotrexate concentrations due to impaired renal function" were derived from 2 trials. See Table 63. These were treatment protocols. Patients on these trials were enrolled after they developed a significant delay in methotrexate clearance due to renal toxicity. Safety information was collected on a fraction of these patients, 81% in Trial 006 and 58% in Trial 016.

Additional safety information was collected from trials of glucarpidase in subjects or patients who were treated on protocols that did not include methotrexate or did not require delayed methotrexate clearance as a condition for inclusion. See Table 64. These were pharmacokinetic and drug interaction trials. These trials provide useful information. In Trial 005 and Trial 010 subjects were not receiving methotrexate allowing the toxicities of glucarpidase to be more readily isolated. In Trial 012 and Trial 017 patients were prospectively enrolled and were not manifesting methotrexate toxicity as an enrollment requirement .

Finally there is safety information from 3 trials conducted using glucarpidase manufactured as CAMR lot 004, Trial 001, Trial 002, and Trail 003. See Table 65. Because CAMR lot 004 was not demonstrated to be biochemically equivalent to Voraxaze this data can not be considered as substantial evidence supporting the safety or efficacy of Voraxaze. However, the clinical safety information reported in 283 patients treated with CAMR lot 004 glucarpidase provides an additional level of comfort regarding the safety profile of glucarpidase for this indication.

In the safety population, the most common related AEs were paraesthesia, flushing, nausea and/or vomiting, hypotension and headache. All AEs were grade 1 or 2 except one episode flushing categorized as grade 3.

The toxicity profile of glucarpidase supports approval of glucarpidase for the indication of treatment of toxic plasma methotrexate concentrations due to impaired renal function. (b) (4)

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 63: Major Studies Providing Safety Information for the Application Indication

Major Studies Supporting Safety of Glucarpidase in this Application			
Sponsor / Conducted	**Population**	**Dose Glucarpidase**	**Safety**
Title: Trial 006 "Special Exception Protocol for the Use of Carboxypeptidase-G2 for MTX Toxicity"			
NCI IND 11630 Jun 2004 to Apr 2007	Severely delayed MTX 2° to renal dysfunction	50 U/kg IV; 2nd dose 48 hr if baseline MTX > 100 µmol/L. Nov 2005 max 2000 U	Total enrolled n = 184 Safety Population n = 149
Title: Trial 016 "An Open-label Treatment Protocol for the Use of Voraxaze as Adjunctive Treatment for Patients Experiencing or at Risk of Methotrexate Toxicity"			
BTG IND 11557 May 2007 to Oct 2010 (ongoing)	Severely delayed MTX 2° to renal dysfunction	50 U/kg IV	Total enrolled n = 244 Total dosed n = 171 Safety Population n = 141

Table 64: Trials with Supportive Safety Information Not in Population with the Application Indication

PK and Drug Interaction Trials				
Sponsor / Conducted	**Trial Design**	**Population**	**Dose Glucarpidase**	**Safety**
Title: Trial 005 "A Trial to Determine the Pharmacokinetics of Glucarpidase (Voraxaze) in Subjects with Normal and Impaired Renal Function"				
BTG IND 11557 / Jul to Oct 2004	Phase 1 PK trial to evaluate renal effect	Subjects with normal (n = 8) or impaired (n = 4) renal function	50 U/kg IV	Safety for 12 subjects not complicated by MTX toxicity
Title: Trial 010 "Investigation of the Effect of Glucarpidase on Leucovorin Pharmacokinetics in Healthy Male Subjects"				
BTG in UK / Mar to Apr 2006	Randomized crossover double blind glucarpidase/ placebo with leucovorin	Healthy males (n= 6) co-administerd with leucovorin 150 mg/m2 q 6 hrs x 5	50 U/kg IV (glucarpidase or placebo)	Safety for 6 subjects not complicated by MTX toxicity
Title: Trial 012 Randomized, Blinded, Placebo-controlled Trial of High Dose Methotrexate with Leucovorin Rescue (HDMTX-LV) with or without Glucarpidase in Osteosarcoma.				
BTG at MD Anderson Oct 2008 to Mar 2009 Closed early due to poor accrual	Randomized crossover ± glucarpidase after MTX with leucovorin	Osteosarcoma patients Compare toxicity and ability to start nest course of therapy on schedule	2 doses of glucarpidase 50 U/kg, 24 hours apart versus placebo	Safety for 7 patients exposed to glucarpidase; 2 of 4 in the randomized arm and 5 in compassionate arm
Title: Trial 017 "An Open-label Study to Assess the Pharmacokinetics of Leucovorin in Patients Receiving High Dose Methotrexate, with or without Voraxaze Treatment"				
BTG IND 11557 / Jul 2008 to Jul 2009	Comparison PK leucovorin in normal versus delayed MTX clearance	Patient receiving HDMTX (n=11) Arm A delayed MTX Arm B normal MTX	Arm A 50 U/kg IV plus leucovorin Arm B leucovorin	

Table 65: Trials Conducted with Glucarpidase CAMR Lot 004 Providing Supportive Safety Information

(b) (4) Trials Utilizing CAMR Lot 004 Glucarpidase			
Sponsor / Conducted	**Population**	**Dose Glucarpidase**	**Safety**
Title: Trial 001 "Study of Recombinant Carboxypeptidase G2 (CPG2) for the Management of Patients with Delayed Methotrexate (MTX) Clearance or Intrathecal MTX Overdosage" [Berlin]			
Conducted in 29 German Centers / Jan 2000 to Aug 2003	Severely delayed MTX 2° to renal dysfunction	50 U/kg IV; 2nd dose if baseline MTX > 0.1 µmol/L at 24 hrs	Total enrolled n = 45 Safety Population n = 44
Title: Trial 002 "A Trial of Carboxypeptidase-G2 (CPG2) for the Management of Patients with Methotrexate Toxicity and Renal Dysfunction"			
NCI IND 4663 / Nov 1993 to May 2004	Severely delayed MTX 2° to renal dysfunction	50 U/kg IV (1 to 3 doses) Feb 2002 max 2000 U (Thymidine for some)	Total enrolled n = 263 Safety Population n = 214
Title: Trial 003 "A trial of Carboxypeptidase-G2 (CPG2) for the Management of Patients with Methotrexate Toxicity and Renal Dysfunction" [Bonn]			
Conducted in 13 non US Countries / Mar 1997 to Mar 2002	Severely delayed MTX 2° to renal dysfunction	50 U/kg IV 2nd dose if > 1 log decrease but remained MTX > 1 µmol/L	Total enrolled n = 82 Safety Population n = 69

7.1.2 Categorization of Adverse Events

Methodology for Collecting Safety Data Trial 006

Treating physicians were asked to fill out a flow sheet with a daily log of AEs categorized as:

- Methotrexate Toxicity - diarrhea, nausea/vomiting, neurological, renal, stomatitis, other (these were categorized in the application as "not related to glucarpidase")
- Glucarpidase Toxicity – allergy, other (these were categorized in the application as "glucarpidase-related")
- Other Toxicities - (these were categorized in the application as "not related to glucarpidase")

Additional information was collected from clinical records treating physicians submitted.

Methodology for Collecting Safety Data Trial 016

- Only glucarpidase-related AEs were collected
- Data captured on a form which requested dates, serious (yes/no), grade, relationship glucarpidase (possible, probable, definite), treatment, outcome
- Glucarpidase-related AEs were collected from the time of the first glucarpidase administration until 7 days after the last glucarpidase administration
- Serious adverse events considered related to glucarpidase were collected from the time of the first glucarpidase administration until 30 days after the last glucarpidase administration

Adverse events for both trials were categorized using the NCI CTCAE version 3.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety population that will be used to estimate the incidence of adverse reactions includes 290 patients treated with glucarpidase on Trial 006 and Trial 016 with safety data available. In Trial 006 184 patients were enrolled. Safety information is available for 149 patients. Trial 016 is an ongoing expanded access program. At the time of data cut-off 244 patients were enrolled and there was safety information available for 141 patients.

7.2 Adequacy of Safety Assessments

The data from Trial 006 and Trial 016 is limited by several factors.

- Patients treated with glucarpidase are experiencing methotrexate-associated toxicites including hepatic, renal and hematologic.
- There is no data from a control arm for comparison
- The safety data was not rigorously collected especially in Trial 006.

Given the indication, emergency treatment of patients with severe methotrexate toxicity, the safety information available is adequate to analyze the risk benefit of glucarpidase administered for this indication.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure

Trial 006

Glucarpidase exposure in the safety population of Trial 006 was available for 136 of the 149 patients. There were 106 patients who received 1 administration of glucarpidase

and 30 patients who received 2 administrations of glucarpidase. The doses ranged from 18 to 98 Units/kg per dose with a median dose of 49 Units /kg.

Trial 016
Glucarpidase exposure in the safety population of Trial 016 was available for 138 of the 141 patients. There were 119 patients who received 1 administration of glucarpidase and 19 patients who received 2 administrations of glucarpidase. Doses ranged from 6 to 189 Units/kg and with a median dose 50 Units/kg. [The datasets probably erroneously report doses of 0.06 (Pt ID 016- 038) and 0.49 (Pt ID 016 146) unit per kg.]

Demographics

Table 66: Demographics and Characteristics of the Safety Population

Demographics of Safety Population n = 290	
Gender	
Male 186 (64%)	Female 103 (36%)
Age (years)	
Mean - 30	0 - 12 84 (29%)
Median - 17	13 – 18 74 (26%)
Range - 1 months to 85 years	19 – 65 94 (32%)
	66 – 85 38 (13%)
Weight in Kg	
Mean – 65.9 Median - 66.4	Range – 3.5 to 155.4
Diagnosis	
Osteosarcoma/sarcoma 93 (32%)	Other 14 (5%)
Leukemia Lymphoma 181 (63%)	Unknown n = 2
MTX Dose (available for n=285)	
Mean – 7.6 g/m^2 Median – 5.0 g/m^2	Range - 10 mg/m^2 to 40 g/m^2

7.2.2 Explorations for Dose Response

No evaluation of dose response was submitted in the application.

7.2.3 Special Animal and/or In Vitro Testing

No special animal testing was submitted. FDA has informed the applicant that animal data regarding prevention of central nervous system toxicity in experimental animals who have received overdoses of intrathecal methotrexate will be required as a post marketing requirement.

7.2.4 Routine Clinical Testing

Trial 006
Investigators were asked to report the results of clinical laboratory testing on a flow sheet. The flow sheet indicated that hematologic parameters including hemoglobin, WBC, % granulocytes, and platelets be tested twice weekly for 3 weeks post glucarpidase. The flow sheet indicted that chemistry parameters including BUN creatinine, Na, K, Cl, and CO2 be tested daily for 1 week then as needed; AST, ALT and bilirubin be tested twice weekly for 3 weeks post glucarpidase; creatinine clearance or GFR be measured at baseline and 6 weeks post glucarpidase. Methotrexate levels be tested daily for 1 week then as needed.

Vital signs including temperature, pulse, blood pressure, and respirations were to be documented 2 hours after glucarpidase and twice a week until discharge.

Trial 016
Results of routine clinical laboratory testing and vital signs were not collected.

7.2.5 Metabolic, Clearance, and Interaction Workup

The PK, and drug interaction trials that were conducted are listed in Table 64.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no similar drugs.

7.3 Major Safety Results

7.3.1 Deaths

Safety Population
Trial 006
There were 8 deaths documented within 30 days of glucarpidase administration. No deaths were attributed to glucarpidase treatment. The cause of death and the timing related to glucarpidase is presented in Table 67.

Table 67: Trial 006 Deaths within 30 Days of Glucarpidase Exposure

Deaths within 30 Day of Exposure to Glucarpidase Trial 006 n = 149			
Patient ID	Days from Glucarpidase	Cause of Death	Glucarpidase Failure
006 248	22	Probably related to underlying disease; possibly related to methotrexate toxicity	Malignancy
006 250	3	Multiorgan failure - related to underlying malignancy	Yes
006 275	4	Neutropenic sepsis - probably related to methotrexate toxicity	Yes
006 293	7	Disease progression	Malignancy
006 303	6	No information	Unknown
006 308	12	No information	Unknown
006 328	18	Acute myocardial infarction with congestive heart failure; Sepsis - probably related to methotrexate toxicity	Yes
006 343	7 (estimated)	Urinary tract infection with neutropenic sepsis - probably related to methotrexate toxicity	Yes

The time of death related to glucarpidase exposure was not documented for Pt ID 006 348. The cause of death of this patient included bone marrow, pulmonary skin and mucosal toxicity. These were probably related to methotrexate toxicity.

Trial 016

Table 68: Trial 016 Deaths within 30 Days of Glucarpidase Exposure

Deaths within 30 Day of Exposure to Glucarpidase Trial 016 n = 141			
Patient ID	Days from Glucarpidase	Cause of Death	Glucarpidase Failure
016 001	19	Recovered from methotrexate toxicity; died at home of progressive disease	Malignancy
016 061	4	Died due to methotrexate toxicity - progressive pneumonia with neutropenia; ongoing progressive disease	Yes
016 150	3	Multi-organ failure secondary to septic shock	Yes

Pharmacokinetic and Drug Interaction Trials.
There were no deaths reported in these trials.

CAMR Lot 004 Trials
Trial 001 CAMR Lot 004
Table 69: Trial 001 Deaths within 30 Days of Glucarpidase Exposure

Deaths within 30 Day of Exposure to Glucarpidase Trial 001 n = 44			
Patient ID	Days from Glucarpidase	Cause of Death	Glucarpidase Failure
001 007	16	Multi-organ failure consistent with sequelae of methotrexate toxicity	Yes
001 009	19	Multi-organ failure assessed to be a sequelae of methotrexate toxicity	Yes
001 011	29	Neutropenic sepsis related to methotrexate toxicity	Yes
001 012	25	Peripheral circulatory collapse; No details of the event provided.	Yes
001 015	16	Necrotizing colitis and neutropenic sepsis; acute myocardial infarction and cardiac failure	Yes
001 029	5	Acute renal failure and respiratory failure	Yes
001 030	13	Central nervous system hemorrhage; probable *aspergillus* pneumonia; respiratory failure; assessed to be a sequelae of methotrexate toxicity	Yes
001 036	10	Hypernatremia and diabetes mellitus with subsequent neutropenic sepsis; the neutropenic sepsis consistent with sequellae of methotrexate toxicity	Yes
001 041	3	Progressive malignant disease	Malignancy
001 042	3	Progressive malignant disease	Malignancy
001 043	7	Pulmonary embolism; assessed not to be related to glucarpidase	Yes

Trial 002 CAMR Lot 004

Table 70: Trial 002 Deaths within 30 Days of Glucarpidase Exposure

Deaths within 30 Day of Exposure to Glucarpidase Trial 002 n = 214			
Patient ID	Days from Glucarpidase	Cause of Death	Glucarpidase Failure
002 005	6	Liver toxicity hyperbilirubinemia assessed not related to glucarpidase. *Pseudomonas aeruginosa* sepsis; consistent with sequellae of methotrexate toxicity.	Yes
002 012	29	Bone marrow failure and toxic shock syndrome; assessed to be related to methotrexate toxicity	Yes
002 031	18	Enterococcal sepsis	Yes
002 032	3	(Rhematoid Arthritis – oral methotrexate) Agranulocytosis, skin disorder, stomatitis; consistent with sequellae of methotrexate toxicity Patient also had elevated amylase	Yes
002 033	2	Hypotension sepsis; assessed not to be related to glucarpidase	Yes
002 034	6	Severe myelosupression; consistent with sequellae of methotrexate toxicity.	Yes
002 050	7	Progressive malignant disease	Malignancy
002 055	1	Arrhythmia; renal failure; investigator assessed not related to glucarpidase	Yes
002 058	19	Septic shock; Progressive malignant disease	Malignancy
002 063	13	Multiorgan failure with end stage lung disease; consistent with sequellae of methotrexate toxicity	Yes
002 068	15	Progressive malignant disease	Malignancy
002 072	22	Progressive malignant disease	Malignancy
002 106	1	Neutropenic sepsis; investigator assessed not related to glucarpidase	Yes
002 131	4	No information	Unknown
002 166	18	Progressive malignant disease	Malignancy
002 890	3	Neutropenic sepsis; consistent with sequellae of methotrexate toxicity	Yes

Trial 003 CAMR Lot 004

Table 71: Trial 003 Deaths within 30 Days of Glucarpidase Exposure

Deaths within 30 Day of Exposure to Glucarpidase Trial 003 n = 69			
Patient ID	Days from Glucarpidase	Cause of Death	Glucarpidase Failure
003 007	23	Sepsis and multiorgan failure; consistent with sequellae of methotrexate toxicity	Yes
003 027	5	Sepsis and multiorgan failure; consistent with sequellae of methotrexate toxicity	Yes
003 050	6	Sepsis and multiorgan failure; consistent with sequellae of methotrexate toxicity	Yes
003 077	26	Sepsis respiratory failure; consistent with sequellae of methotrexate toxicity	Yes
003 082	9	Sepsis and pulmonary aspergillosis; investigator assessed to be related to methotrexate toxicity	Yes

REVIEWER COMMENT:
There were no deaths that appeared to be directly related to treatment with glucarpidase. Deaths within 1 month of therapy with glucarpidase not related to progression of malignant disease represent treatment failures of glucarpidase. In the safety population on Trial 006 and Trial 016 there were 8 deaths within 30 days or glucarpidase exposure not related to progression of the underlying malignancy. This represents a 3% rate of failure of glucarpidase therapy to prevent death in the product indication population. This failure rate was greater (25/327, 8%) in the trials using the CAMR lot 004 product.

7.3.2 Nonfatal Serious Adverse Events - Excluding Hematologic, Hepatic, or Renal

Glucarpidase is intended to be administered as an antidote to toxic levels of methotrexate. Given this setting, patients are expected to have hematopoietic, hepatic, and renal toxicities. Hematopoietic, hepatic, and renal adverse events will be excluded from this analysis.

Safety Population

Trial 006

There were 2 patients with adverse events categorized as serious possibly related to glucarpidase. Pt ID 006 274 a 62 year old male with a central nervous system lymphoma reported to have depressed level of consciousness and somnolence. The CRF documents this patient was somnolent prior to the administration of glucarpidase and the somnolence was attributed to his seizure medication.

Pt ID 006 275 was a 42 year old male with Burkitt's lymphoma was reported to develop ventricular tachycardia. After treatment with cytosine arabinoside and methotrexate the patient developed tumor lysis syndrome. He subsequently received glucarpidase to treat delayed clearance of methotrexate. He developed ventricular tachycardia 4 days after glucarpidase and then developed neutropenic sepsis and died of multi-organ failure.

Trial 016

There were no nonfatal serious adverse events associated with glucarpidase administration reported in Trial 016.

Pharmacokinetic and Drug Interaction Trials.

There were no nonfatal serious adverse events reported in these trials.

CAMR Lot 004 Trials

The methodology of data collection in these trials precludes meaningful analysis nonfatal serious adverse events

7.3.3 Dropouts and/or Discontinuations

Glucarpidase is intended to be administered as an antidote to toxic levels of methotrexate. Glucarpidase was administered as a single 5 minute bolus. Investigators were allowed to give a second dose but this was not mandatory. Given this treatment setting there was not opportunity for early discontinuation of therapy.

7.3.4 Significant Adverse Events

Allergic Reactions

Glucarpidase is a recombinant enzyme cloned from *Pseudomonas* stain RS-16. Serious hypersensitivity reactions, including anaphylaxis are a concern because glucarpidase is a foreign protein derived from bacteria.

Trial 006
One subject was reported to have a grade 1 allergic reaction with the glucarpidase administration. This patient received a second dose of glucarpidase 2 days later without recurrence of the reaction.

There were 2 patients with episodes of hypotension. One patient, Pt 006 224, developed hypotension 1 hour after the administration of glucarpidase. The hypotension resolved within 30 minutes after a normal saline bolus. This patient received a second dose of glucarpidase 2 days later without recurrence of the hypotension. The second patients, Pt 006 244, tolerated the first administration of glucarpidase with no reported adverse events but developed nausea and hypotension after administration of the second dose of glucarpidase.

Additional symptoms reported that may have been related to an allergic reaction were "throat tightness," flushing, paraesthesias. However there were no reports of hives, itching, bronchospasm, swelling or anaphylaxis, adverse events more pathognomonic of allergic reactions.

Trial 016
There were no patients with allergic reactions reported. There were no reports of hives, itching, bronchospasm, swelling or anaphylaxis. Additional events reported that may have been related to an allergic reaction were rash, erythema, nausea and vomiting.

Pharmacokinetic and Drug Interaction Trials.
There were no episodes of hives, itching, bronchospasm, or anaphylactic allergic reactions reported in these trials. In Trial 012 there were 3 patients with grade 0 to 1 adverse events of edema, Pt ID 012 001 – edema; Pt ID 012 402 - peripheral edema; Pt ID 012 403 – facial edema. These adverse events were coded as not related to glucarpidase.

CAMR Lot 004 Trials
BTG did not demonstrate that the product used in these trials was equivalent to Voraxaze, and therefore it may have a different immunogenic potential.

Trial 001 CAMR Lot 004
The adverse event reporting for this trial is particularly problematic as it was retrospective and the CRFs were translated from German. Pt ID 001 005 was reported to have "allergic skin reaction" with no additional information regarding the event. Pt ID 001 035 was reported to have "wheals" converted to preferred term "hives." On review of the CRF it is not clear the skin lesion was urticaria. The reported event seems to be blisters rather than hives.

Trial 002 CAMR Lot 004
No definitive hypersensitivity or allergic reactions were documented.

Trial 003 CAMR Lot 004
There were 4 subjects with adverse reactions coded as hypersensitivity. Given the retrospective methodology of the data collection, there were no details regarding the events. The verbatim code was "hypersensitivity" for each of these events. One was coded as grade 4, but there are no details of the reaction provided.

Investigator Sponsored Studies
There are 3 trials being conducted outside of the US that are not under IND. Trial 009 "Randomized, cross-over, phase II study, to investigate the efficacy and safety of glucarpidase for routine use after high-dose methotrexate in patients with bone sarcoma"; Trial 015 "Phase 1 trial of escalating high dose methotrexate supported by glucarpidase to treat patients with primary central nervous system lymphoma (PCNSL)"; and Trial 019 "Treatment Protocol for Children and Young Adults (1.0 to 17.9 years of age) with Acute Lymphoblastic Leukemia (ALL) diagnosed in the Nordic countries."

Trial 009 and Trial 015 are evaluating use of glucarpidase as a standard component of a high dose methotrexate regimen. Patients receive repeated doses of glucarpidase, increasing the risk of allergic reactions. Trial 015 was closed because 2 of 4 patients enrolled developed dose limiting toxicities following administration of 3 g/m^2 of methotrexate meeting the pre-established stopping criteria. Two of the 4 patients enrolled experienced allergic reactions. Pt ID 015 002 experienced grade 3 allergic reactions, including bropnchospasm, related to glucarpidase with the 3^{rd} and 4^{th} course of therapy. Pt ID 015 004 experienced a grade 2 allergic reaction with the 3^{rd} cycle of glucarpidase.

REVIEWER COMMENT:
Allergic reactions do not appear to be a major problem when Voraxaze is administered for the proposed indication. There were no pathognomonic symptoms diagnostic of allergic or hypersensitivity reactions reported. The adverse events that may have been related to an allergic reaction, rash, erythema, edema, nausea and vomiting, were categorized as grade 1 or 2 in severity. For those patients who experienced these reactions and received subsequent dose of glucarpidase the reaction did not usually recur.

Because glucarpidase is a foreign protein allergic reactions remain a concern. Expansion of the use of glucarpidase beyond the current indication to use as a routine component of a high dose methortrexate regimen is likely to be associated with an increased incidence of allergic reactions As was seen in Trial 015.

7.3.5 Submission Specific Primary Safety Concerns

See section 7.3.4 above.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Glucarpidase is intended to be administered as an antidote to toxic levels of methotrexate. Given this setting, patients are expected to have hematopoietic, hepatic, renal toxicities and mucositis and infections. Hematopoietic, hepatic, and renal adverse events and mucositis and infections will be excluded from this analysis.

Trial 006

Table 72: Adverse Events Possibly, Probably, of Definitely Reported in Trial 006

Common Adverse Events Trial 006 n = 149						
Body System	Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade
Cardiac Disorders	Ventricular Tachycardia				1	1
Gastrointestinal Disorders	Nausea	2				2
	Vomiting	2				2
	Paraesthesia Oral					1[1]
	Diarrhea	1				1
General Disorders and Administration Site Conditions	Feeling hot					1[1]
Immune System Disorders	Hypersensitivity	1				
Nervous System Disorders	Tremor		1			1
	Somnolence			1		1
	Headache		1			
	Burning Sensation	1				1
	Paraesthesia	4	2			6

[1] No grade of toxicity documented

Trial 016

Table 73: Adverse Events Possibly, Probably, of Definitely Reported in Trial 016

Common Adverse Events Trial 016 n = 141						
Body System	Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade
Eye Disorders	Vision Blurred	1				1
Gastrointestinal Disorders	Nausea		1			1
	Vomiting	1	1			2
Nervous System Disorders	Headache	1				1
	Paraesthesia	1				1
Skin and Subcutaneous Tissue Disorders	Rash	1				1
Vascular Disorders	Hypertension	1				1
	Flushing	1				1

REVIEWER COMMENT:
Documented adverse events associated with the administration were infrequent and tolerable.

7.4.2 Laboratory Findings

Clinical laboratory values did not contribute meaningful data to inform the safety or efficacy evaluation of glucarpidase. Delayed methotrexate clearance is the result of renal dysfunction. The results of daily creatinine levels are graphically displayed in the efficacy population in Figure 2 through Figure 23. Delayed methotrexate clearance results in hematologic and hepatic toxicity. Because there are no controlled studies of glucarpidase in this indication, it is not possible to determine how glucarpidase treatment affects the laboratory abnormalities associated with these toxicities.

7.4.3 Vital Signs

No analysis of vital signs are included in this review.

7.4.4 Electrocardiograms (ECGs)

Electrocardiogram (ECG) data were collected in two clinical trials: Trial 005 in healthy subjects and subjects with impaired renal function and Trial 010 in healthy subjects.

Trial 005

No clinically important differences were noted in pre-treatment ECGs compared to Day 28 post treatment ECGs. Abnormal ECG findings identified were not clinically significant

and represented minor variations in sinus rhythm or other aspects of the ECGs that were not necessarily indicative of underlying cardiac abnormalities or disease.

Trial 010
ECGs were obtained at screening, 6 hours after the final leucovorin injection and at the end of the study, that is 5 to 7 days after the second treatment period. The ECG consisted of a 12-lead resting ECG with a 10 second rhythm strip. The ECG recorder computed the ECG PR and QT intervals, QRS duration, and heart rate, and corrected the QT interval for heart rate using Bazett's formula (QTcB). There were no clinically important findings in the 12-lead ECG parameters or morphology, for individual subjects during the study.

7.4.5 Special Safety Studies/Clinical Trials

No analysis of special safety studies are included in this review.

7.4.6 Immunogenicity

The immunogenicity evaluation population included all patients with at least one sample available for antibody testing after glucarpidase administration. At the original application evalution there were 96 patients included. At the time of the 120 day safety a total of 120 patients were available for this analysis.

Antibody evaluation included patients from 3 trials, Trial 012, Trial 016 and Trial 017. Antibody titers were determined using a validated bridging enzyme-linked immunosorbent assay (ELISA) for anti-glucarpidase antibodies.

There were 16 of 96 evaluable patients (17%) developed anti-glucarpidase antibodies following glucarpidase administration. Twelve of the 16 patients who developed anti-glucarpidase antibodies had received a single dose of glucarpidase, and four of the patients had received two doses of glucarpidase.

After the 120 day safety update this was revised to 23 of 120 patients (19%) developed anti-glucarpidase antibodies following glucarpidase administration. The number of doses of glucarpidase was not included with the 120 day safety data.

REVIEWER COMMENT:
The immunogenicity of this agent is tolerable for the proposed indication. The immunogenicity of the product is likely to be more problematic if the agent is expanded to be used as a component of a high dose methotrexate regimen given on multiple occasions.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No analysis of dose dependency for adverse events are included in this review.

7.5.2 Time Dependency for Adverse Events

No analysis of time dependency for adverse events are included in this review.

7.5.3 Drug-Demographic Interactions

Age

Table 74: Per Patient Incidence of Adverse Events Possibly, Probably, of Definitely Reported by Age

Per Patient Incidence of Adverse Event by Age in Safety Population n=290		
Age	**Number of Patients**	**Patients with Adverse Event**
1 month to 16 years	140	12 (9%)
17 to 65 years	112	10 (9%)
65 to 85 years	38	0

Gender

Table 75: Per Patient Incidence of Adverse Events Possibly, Probably, of Definitely Reported by Gender

Per Patient Incidence of Adverse Event by Gender in Safety Population n=289		
Gender	**Number of Patients**	**Patients with Adverse Event**
Female	103	12 (12%)
Male	186	10 (5%)

7.5.4 Drug-Disease Interactions

No evaluation of the drug-disease interaction of the safety of glucarpidase is included in this review.

7.5.5 Drug-Drug Interactions

No evaluation of the drug-drug interaction of the safety of glucarpidase is included in this review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity testing is not relevant.

7.6.2 Human Reproduction and Pregnancy Data

Evaluation of glucarpidase on human reproduction and pregnancy is not relevant.

7.6.3 Pediatrics and Assessment of Effects on Growth

Evaluation of effect of glucarpidase on pediatric growth and development is not relevant.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no data on overdose. There is no drug abuse potential.

7.7 Additional Submissions / Safety Issues

120-day Safety Update Report Submitted 11/15/11
The 120 day update included updated information on the treatment protocol Trial 016. The cut-off for information at the time of the original filing was 10/28/10. Additional clinical information submitted through 7/18/11 was included. The synopses for investigator sponsored studies Trial 008, trial 015, and Trial 019 were updated.

Trial 016
There were 39 patients with exposure and safety data accrued on Trial 016. Of these 62% were male, 23% with osteogenic sarcoma, 72% leukemia or lymphoma.

Trial 016 Deaths
There were 2 deaths within 30 days of exposure to glucarpidase assessed not related to glucarpidase. Pt ID 016 311 died 15 after glucarpidase exposure due to multi-organ failure. Pt ID 016 died 11 days from glucarpidase exposure due to an intracranial bleed. There were 2 additional deaths reported for patients in the original submission within 30 days of glucarpidase exposure both due to progressive malignant disease.

Trial 016 Related Events
Two events assessed as potentially related were reported flushing, and tingling.

Investigator Sponsored Studies
There are 3 trials being conducted outside of the US that are not under IND. Trial 009 "Randomized, cross-over, phase II study, to investigate the efficacy and safety of glucarpidase for routine use after high-dose methotrexate in patients with bone sarcoma"; Trial 015 "Phase 1 trial of escalating high dose methotrexate supported by glucarpidase to treat patients with primary central nervous system lymphoma (PCNSL)"; and Trial 019 "Treatment Protocol for Children and Young Adults (1.0 to 17.9 years of age) with Acute Lymphoblastic Leukemia (ALL) diagnosed in the Nordic countries."

Trial 009 and Trial 015 are evaluating use of glucarpidase as a routine component of high dose methotrexate therapy. Patients receive repeated doses of glucarpidase, increasing the risk of allergic reactions. Trial 015 was closed because 2 of 4 patients enrolled developed dose limiting toxicities following administration of 3 g/m^2 of methotrexate meeting the pre-established stopping criteria. Two of the 4 patients enrolled experienced allergic reactions. One patients was documented with grade 3 allergic reactions on 2 occasions. A second patients was documented with a grade 2 allergic reaction with the 3rd cycle of glucarpidase.

REVIEWER COMMENT:
The information included in the 120 day safety update does not change the safety profile of glucarpidase for the proposed indication.

8 Postmarket Experience

Glucarpidase has not been approved in any market to date. There is no postmarket experience.

9 Appendices

9.1 Abbreviations

Abbreviations	
AE	Adverse event
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BLA	Biologic License Application
BMI	Body mass index
BTG	BTG International Inc.
BUN	Blood urea nitrogen
CAMR	Centre for Applied Microbiology Research
CIR	Clinically important reduction
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
COPD	Chronic obstructive pulmonary disease
CRO	Contract research organization
CSF	Cerebrospinal fluid
DAMPA	2,4-diamino-N10-methylpteroic acid
DBGC	Division of Bioequivalence and GLP Compliance
DSI	Division of Scientific Investigations
ECG	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
FSR	Final study report
GFR	Glomerular filtration rate
GLP	Good laboratory practice
HPLC	High performance liquid chromatography
IND	Investigational new drug
IRB	Investigational Review Board
IV	Intravenous
LV	Leucovorin
MTX	Methotrexate
NCI	National Cancer Institute
NIH	National Institute of Health
OSI	Office of Scientific Investigation
PD	Pharmacodynamic

PETS	Pharmacology and Experimental Therapeutics Section
PK	Pharmacokinetic
RSCIR	Rapid and sustained clinically important reduction
SAP	Statistical analysis plan
WBC	White blood cell
ULN	Upper limit of normal
WNL	Within normal limits
WOCBP	Women of child bearing potential

9.2 Labeling Recommendations

FDA did not agree with BTG's approach to the label. (b) (4)

(b) (4)

See FDA's proposed label submitted to BTG 12/6/11 below.

(b) (4)

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

9.3 Advisory Committee Meeting

An advisory committee meeting was not required for this application.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125327 **Applicant: BTG International Inc.** **Stamp Date: 7/18/11**

Drug Name: Glucarpidase (Voraxaze®) **NDA/BLA Type: Priority** **PDUFA Date: 1/17/12**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	Dose chosen based on Rhesus Monkey study. In pre submission meetings FDA was aware of this and agreed a submission based on this dose could be submitted.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 PR001-CLN-006 Indication: Delayed methotrexate clearance	X			FDA agreed that a subset of patients on the PR001-CLN-006 study with central laboratory assessment

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					of methotrexate level by HPLC could serve as the basis of the demonstration of efficacy.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Previously agreed to trial design. Not possible to do placebo controlled studies for this indication.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?		X		I do not think this is a necessary evaluation for this agent of the nature of the agent, a large protein, and the nature of the patients, hospitalized in monitored setting.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			677 subject in the ISS population
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	adverse dropouts (and serious adverse events if requested by the Division)?				
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		X		Orphan status so PREA not applicable. Trial conducted in population which approximately 50 % pediatric
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	This submission is based on an adequate experience in the US population.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No potential filing issues were identified at this time.

8/11/11

Reviewing Medical Officer — Date

Reviewed with concurrence by Suzanne Demko, Team Leader — 8/11/11

Clinical Team Leader — Date