CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125327Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review
BLA 125327/0

Date	January 3, 2012
From	Suzanne G. Demko
Subject	Cross-Discipline Team Leader Review
BLA #	125327/0
Applicant	BTG International, Inc. (formerly Protherics)
Date of Submission	Rolling BLA: original submission, November 17, 2008, final submission July 18, 2011
PDUFA Goal Date	January 17, 2012
Proprietary Name / Established (USAN) names	Voraxase/ glucarpidase
Dosage forms / Strength	Lyophilized powder, 1000 units per vial
Proposed Indication(s)	For the (b) (4) reduction of toxic methotrexate concentrations due to impaired renal function
Recommended:	Approval

Acronyms used throughout this review:
OND=Office of New Drugs
OBP=Office of Biotechnology Products
CMC=Chemistry, Manufacturing, and Controls
OSI=Office of Scientific Investigations
DBGC=Division of Bioequivalence and GLP Compliance
DIDQ= Division of International Drug Quality
OPDP=Office of Prescription Drug Promotion (formerly DDMAC)
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Introduction

An original Biologic License Application (BLA) for glucarpidase (Voraxase®) was submitted under STN 125327/0 as a rolling BLA with the initial unit received by FDA on November 20, 2008 and the final unit received on July 18, 2011. The proposed indication is, "for the (b) (4) reduction of toxic methotrexate concentrations due to impaired renal function". The application was given a priority review status with a PDUFA goal date of January 17, 2012.

The initial investigational new drug application (IND) for glucarpidase was submitted to FDA on February 17, 2004 (IND 11557). The clinical development of glucarpidase began in 1993 under an expanded access program administered by the National Cancer Institute (NCI). The original manufacturer was the Centre for Applied Microbiology and Research (CAMR; Salisbury, UK).

Glucarpidase was acquired by Enact Pharma (Salisbury, UK) in 2002, and was subsequently acquired by Protherics (London, UK & Brentwood, Tennessee) in 2003. Protherics took over the development of glucarpidase, and then transferred manufacture to two contract manufacturing organizations, Eurogentec SA (Belgium) for the formulated bulk product and Cangene Corporation (Canada) for the finished product. In June 2004, the National Cancer Institute (NCI) began supplying glucarpidase manufactured by Protherics' contractors under a new expanded

access program under IND 11630. Protherics was acquired by BTG International (BTG; London, UK and Philadelphia, Pennsylvania) in 2008, and BTG has continued the development of glucarpidase since that time. Manufacture of the finished product was moved to Cangene bioPharma Inc. (CBI; Baltimore) in 2009. BTG continues to supply glucarpidase under the original expanded access program and on a 'named patient' basis in Europe and elsewhere under IND 11557.

The applicant submitted the data from four open-label, multicenter trials (summarized) in support of the efficacy of glucarpidase:

PR001-CLN-001 (001): Evaluation of the safety, efficacy and pharmacokinetics (PK) of glucarpidase in patients from 29 centers in the German Multicenter Study for the Treatment of Adult Acute Lymphoblastic Leukaemia (GMALL) Study Group who had impaired MTX clearance due to MTX-induced renal failure following HDMTX therapy, or who had intrathecal MTX overdose

PR001-CLN-002 (002): Evaluation of the safety, efficacy and PK of glucarpidase in patients from 149 centers in 9 countries who participated in a National Cancer Institute (NCI) study of glucarpidase, or a combination of glucarpidase and thymidine, in the treatment of patients with delayed MTX elimination secondary to renal dysfunction

PR001-CLN-003 (003): Evaluation of the safety, efficacy and PK of glucarpidase in patients from 13 countries who had delayed MTX excretion secondary to renal dysfunction

PR001-CLN-006 (006): Evaluation of the safety, efficacy and PK of glucarpidase in patients from 3 countries who participated in a NCI study of glucarpidase who had HDMTX-induced nephrotoxicity and delayed MTX elimination, with no other treatment options.

It should also be noted that one of the formulations of glucarpidase, CAMR lot 004, was extensively studied under IND 4663 and in Europe in two clinical trials, Berlin [Trial 001] and Bonn [Trial 003]. Data from these trials were submitted in support of this application. However, there were no data included in the current application demonstrating that CAMR lot 004 and the glucarpidase product under review in this BLA are comparable. In fact, a Final Study Report for a PK study in rabbits entitled "Pharmacokinetics of Voraxaze (glucarpidase) Following a Single Intravenous Administration in the Male Rabbit", which compared CAMR lot 004 with the intended commercial product, failed to confirm the bioequivalence of CAMR lot 004 glucarpidase and the Voraxase commercial product.

Of the trials submitted in support of this application, only the data from trial 006 was reviewed by FDA in support of the efficacy claim because trials 001, 002, and 003 were conducted using glucarpidase manufactured as CAMR lot 004. As noted, the applicant has not demonstrated that CAMR lot 004 is equivalent to Voraxaze, therefore the CAMR lot 004 data was not considered by the efficacy and safety review teams in their analyses. I concur with the approach taken by the FDA safety and effectiveness review teams.

The clinical efficacy of glucarpidase is supported by data from a subset of 22 patients enrolled in Trial 006, which was a prospective, open label, non-randomized, multicenter, single arm compassionate use trial conducted by NCI in 184 patients of any age who exhibited high dose methotrexate (HDMTX) -induced nephrotoxicity and delayed MTX excretion. The dosing regimen was a single dose of 50 Units/kg by intravenous injection over 5 minutes, up to a maximum of 2,000 Units per dose. If patients did not achieve or maintain a methotrexate concentration of ≤ μmol/L two or more days after the first dose, a second dose was permitted. The primary efficacy outcome of the trial was a pharmacodynamic (PD) endpoint defined as the proportion of patients who achieved a rapid and sustained clinically important reduction (RSCIR) in plasma MTX concentration to ≤ μmol/L at 15 minutes and sustained for up to 8 days following glucarpidase administration. This endpoint was deemed by FDA as an acceptable surrogate for clinical benefit. Following administration of glucarpidase, plasma MTX concentrations were measured at 15 minutes, 1 hour, 2 hours, and daily for a total of 8 days. Measurements of MTX plasma concentrations were performed utilizing a chromatographic method because results from other methods are deemed unreliable resulting from assay interference from one of the metabolites of the interaction between glucarpidase and MTX. Six patients met the pre-specified criteria for a second dose. None of the patients who received glucarpidase in Trial 006 had their doses capped at 2,000 Units per dose.

The data submitted in support of the efficacy claims for glucarpidase are adequate, and the pre-specified endpoint of the trial is clinically meaningful.

The FDA analyses of clinical safety for this application is supported by 290 patients treated with glucarpidase who were enrolled in Trial 006 (n=149) and Trial 016 (n=141) who had safety data available. Trial 016 is an ongoing, open-label treatment trial that uses glucarpidase as adjunctive treatment for patients who are experiencing or at risk of MTX toxicity. At the date of the data cut-off for the data analysis submitted in support of this BLA, October, 2010, 244 patients were enrolled on the treatment trial, 171 patients had documented evidence of glucarpidase administration, and 141 patients had adequate safety information collected.

In addition to the primary safety data base, supplemental safety information was reviewed from the pharmacokinetic and drug interaction trials in which MTX was not administered. Trial 005 was an open-label, single-site, pharmacokinetic trial of glucarpidase administered intravenously at a dose of 50 units/kg to 12 healthy and renally impaired volunteers. Trial 010 was a randomized, crossover, double-blind placebo controlled trial conducted in 6 volunteer subjects. Glucarpidase was administered at a dose level of 50 Units/Kg IV followed by Leucovorin at a dose level of 150 mg/m^2 q 6 hours for 5 doses starting 2 hours after glucarpidase/placebo. There was a minimum of 14 days between each treatment period. The safety results from Trial 005 and Trial 010 are deemed noteworthy because they isolate the adverse drug reactions of glucarpidase from those of methotrexate.

Data on an additional 327 patients enrolled in Trial 001, Trial 002, and Trial 003 were also reviewed. However, because these trials were conducted using glucarpidase manufactured as CAMR lot 004, these were not the primary data relied upon to confirm the safety of this product.

The safety information available for this application is adequate to characterize the risks and benefits of glucarpidase administered for this indication.

Notable issues that have arisen during the review cycle for glucarpidase which will be discussed at greater length in this review are the following:

- Limitation of use: there is a risk that using glucarpidase in any other setting than for patients with severely delayed methotrexate clearance could result in sub therapeutic exposure to methotrexate and decreased antitumor activity.

- Intrathecal route of administration: an approval for Voraxase will very likely lead to an increase in the use of the enzyme for patients who experience toxicity after accidental administration of inappropriately high doses of MTX by the intrathecal route. There were no data submitted in the application to support the safety and efficacy for this route of administration.

- (b) (4): late in the review cycle, on December 22, 2011, the Division of Therapeutic Proteins, Office of Biotechnology Products review team identified an issue regarding the use of the (b) (4) in the manufacturing fermentation process for glucarpidase and the assay used to measure the amount of this compound in the drug substance. The data submitted to date is insufficient to characterize (b) (4), and an assessment regarding potential toxicities of intravenously administered (b) (4) (based on structure-activity relationship) was not possible.

- Pre-license drug substance manufacturing inspection: the preliminary recommendation for the inspection was VAI. A final classification for the inspection is pending at the time of this review. A full compliance evaluation for the site is ongoing. Inadequacies in the firm's responses to some of the inspection findings have been noted and additional information has been requested by the Division of International Drug Quality (DIDQ). When the final results are known, an addendum to the appropriate reviews will update the DIDQ recommendation.

There were no major disagreements among the review disciplines involved with this application with regard to their recommendations for its disposition.

2. Background

Glucarpidase is an enzyme that hydrolyzes the carboxyl terminal glutamate residue from folic acid and its analogues, most importantly methotrexate (MTX), and cleaves the MTX molecule into inactive metabolites, 2,4-diamino-N_{10}-methylpteroic acid (DAMPA) and glutamate. The metabolites then undergo liver metabolism. The normal route of elimination of MTX is via the kidney.

Methotrexate is a cytotoxic agent that has been in use since 1948 either alone or as part of a combined chemotherapy regimen. It is administered in standard or high dose regimens for the treatment of different types of cancer. The use of high-dose MTX (HDMTX), defined as doses in excess of ≥ 1 g/m^2, is common as part of the treatment regimens for hematological malignancies

such as non-Hodgkin's lymphoma, acute lymphoblastic leukemia (ALL), and lymphomas including primary central nervous system lymphoma, as well as in osteosarcoma, and head and neck cancer. Some of the clinical regimens include the use of intrathecal MTX. At lower doses, MTX is used to treat other diseases. Because MTX inhibits reduction of folate to its active form, it is commonly administered with leucovorin (LV) calcium, which replenishes the intracellular source of reduced active folate. HDMTX is administered intravenously (IV) and is cleared from the plasma primarily by the renal route. It may cause acute nephrotoxicity, either directly or from its precipitation, or precipitation of its relatively less soluble metabolites, in acidic urine (pH 7.0). If it develops, the nephrotoxicity can lead to delayed MTX elimination, and a marked increase in hematological and nonhematological toxicities associated with MTX, such as myelosuppression, oro-gastrointestinal mucositis, and dermatitis. In addition, at elevated MTX concentrations, reduced efficacy of LV rescue can occur. In one review of patients supplied by the applicant, osteosarcoma patients treated with HDMTX who developed Grade 2 or worse nephrotoxicity were reported to have a mortality rate of 4.4%.

HDMTX has be administered safely to patients with normal renal function using methods such as hydration, alkalinisation of the urine, routine monitoring of serum MTX levels, and administration of leucovorin (LV) calcium. In spite of these measures, MTX-induced nephrotoxicity still occurs and this condition and its possible sequelae are considered a medical emergency.

There are no FDA-approved treatment options available for patients with toxic levels of MTX and renal dysfunction. Extra-corporeal methods such as hemodialysis, hemofiltration, peritoneal dialysis, and transfusion exchange are used with mixed outcomes. Peritoneal dialysis is ineffective due to a combination of factors including protein binding, the high degree of ionization and the low lipid solubility of MTX. Hemodialysis and hemoperfusion have variable efficacy and usually produce only transient decreases in plasma MTX concentrations. High-flux hemodialysis, charcoal hemofiltration and hemodiafiltration have shown some benefit in literature reports, but clinical use is limited by the time to implement the procedure, the need for continuous dialysis and the risks associated with vascular access and heparinization.

In patients who exhibit delayed elimination of MTX and nephrotoxicity after HDMTX, glucarpidase allows for an alternate route of MTX elimination by catabolism of MTX to its inactive metabolites. Because of its high molecular weight, the glucarpidase protein does not access the intracellular space and it will not counteract the anti-tumor effect of intracellular MTX. In addition, glucarpidase will not replace leucovorin (LV) in the setting of HDMTX rescue since it does not gain entry into the cell; thus, intracellular MTX will continue to inhibit reduction of folate to its active form, and treatment with LV will continue to be needed to replenish the intracellular source of reduced active folate. It should be noted that LV competes with MTX for entry into the cell because it is actively transported by the same cell transport system as MTX. The concentration of LV needed to rescue normal hematopoietic cells from MTX has been shown to be dependent upon the concentration of MTX present.

A tabular regulatory history of this enzyme follows.

Regulatory History (from the clinical review of Patricia Dinndorf, M.D.)

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) ▪ ▪ 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 in September 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 ▪ Filing action letter 9/16/11
3/31/11	Name Change Protherics Inc. acquired by BTG International Inc.

3. CMC

The information in this section was derived from the reviews of Emanuela Lacana, Ph.D., Akhilesh K. Nagaich, Ph.D., Howard Anderson, Ph.D., and Nikolay Spiridonov, Ph.D., Division of Therapeutic Proteins, Office of Biotechnology Products, Mary Farbman and Lakshmi Narasimhan, Office of Manufacturing Product Quality. Revisions were made for the purposes of this review.

The CMC review team recommends approval for this application. This recommendation is based on a determination that the data submitted in the application are adequate to support the conclusion that the manufacture of glucarpidase is well controlled, and leads to a product that is pure and potent. Deficiencies identified during the review process have largely been resolved. Any deficiency unresolved at the date of approval will be a postmarketing commitment. Notable at the time this review is being written are deficiencies with the reference standard qualification

process, drug product quality, qualification of complex raw materials for the fermentation process of the drug substance, and shipping validation of the drug substance. I concur with the evaluations and recommendations of the CMC reviewers.

Both drug substance and drug product manufacturing for Voraxaze were initially developed at the Centre for Applied Microbiology and Research (CAMR), UK, in 1991. In 2003, drug product manufacturing was transferred to Cangene Corporation in Manitoba, Canada and subsequently, in 2009, it was transferred to Cangene bioPharma Inc. (CBI), Baltimore, Maryland, USA.

Drug Substance (DS)
Glucarpidase is a 390 amino acid enzyme, originally isolated from *Pseudomonas sp.* RS-16, cloned and produced in *Escherichia coli* K12 strain RV308, using recombinant DNA methods. It is a zinc-dependent exopeptidase with two co-catalytic zinc ion centers and a conserved aminopeptidase fold. The final formulation contains Zinc acetate, (b) (4) (b) (4) The enzyme exists predominantly in dimeric form. Each subunit has a molecular mass of 41,440 daltons, with a dimeric molecular weight of 83 kDa. The enzyme has (b) (4)

Glucarpidase is a carboxypeptidase that hydrolyzes the carboxy terminal glutamate residue from folic acid and its analogues including methotrexate (MTX). It cleaves the MTX molecule into two inactive metabolites, 4-deoxy-4-amino-N10-methylpteroic acid (DAMPA) and glutamate. The affinity Constant (Km) for glucarpidase with MTX is approximately (b) (4) the catalytic Rate (kcat) is approximately (b) (4)

All manufacturing activities and in-process testing for Glucarpidase drug substance are performed at the Eurogentec site at Liege Science Park, Belgium. Limited release testing (protein concentration, specific activity, endotoxin and bioburden) and limited stability testing (endotoxin and bioburden) are also performed there. The remaining release tests are performed by (b) (4) (b) (4) and (b) (4)

Late in the review cycle, on December 22, 2011, the review team identified an issue regarding the use of the (b) (4) in the manufacturing fermentation process for glucarpidase and the assay used to measure it. The assay and lot release specifications were deemed to be inadequate to assess the amount of this compound in the drug substance. In addition, it was noted that there are no data to demonstrate the safe use of (b) (4) administered *via* the intravenous route. However, the applicant provided extensive drug substance characterization data to evaluate the primary and secondary structure, charge profile, purity and impurities profiles and potency of glucarpidase.
The issues that remain with the glucarpidase drug substance, including the issue with (b) (4) (b) (4) and the final inspection classification do not adversely impact the recommendation for approval. The areas affected are related to structure, purity, characterization of aggregates, potency, release and stability specifications, cake appearance, and assay reference standards. For each unresolved issue, a PMC has been generated to facilitate resolution (See section 13 of this review).

Drug Product (DP)
Voraxaze is supplied as a lyophilized powder in single use 3 ml USP Type I (b) (4) glass vials, stoppered with a 13 mm bromobutyl stopper and a standard 13 mm blue cap with a flip off seal. Each vial contains 1000 U of the active pharmaceutical ingredient glucarpidase and excipients (lactose, Tris and Zinc), and is preservative-free. There are no overages, and the product is filled at a (b) (4) (b) (4) The drug product is stored at 2-8°C for a period of 30 months. The product is reconstituted with 1 mL of sterile saline for injection, USP by gently rolling and tilting the vial; shaking is not appropriate. Reconstituted Voraxaze should be used immediately or stored under refrigeration at 36° to 46°F (2° to 8°C) for up to 4 hours. Voraxaze is (b) (4) (b) (4) as measured by SDS-PAGE and SEC-HPLC. (b) (4) (b) (4)

DP Stability
The DTP review team has concluded that the assays used to monitor the stability of Voraxase are suitable to detect production degradation induced by a variety of stress conditions. However, it was noted that there is a small reduction in the SEC-HPLC main peak which could be due to the fact that large aggregates could not be adequately recovered from the column. In fact, the applicant has not performed studies aimed at demonstrating that there is a high recovery of the protein loaded onto the analytical SEC-HPLC column. Furthermore, analytical ultracentrifugation has not been conducted on aggregated samples, to cross-validate SEC-HPLC. These issues will be addressed by a PMC.

DP Manufacturing Process
The manufacturing process of glucarpidase is deemed by the DPT review team to be robust enough to consistently manufacture a product that meets expected quality criteria and be safe and effective for human use. A number of issues identified with the manufacturing process during the review cycle were resolved. However, unresolved issues remain with regard to batch qualification, shipping validation studies, and the mixing step in the process. For each unresolved issue, a PMC has been generated to facilitate resolution (See section 13 of this review).

Facilities review/inspection
Drug product (fill and finish) facility inspection was waived on October 26, 2011. The waiver states that this decision was based on the compliance history of the firm (Cangene BioPharma, Inc.), their GMP status at the time of proposed inspection, as well as the fact that the firm is approved to manufacture multiple licensed products using the same manufacturing process as that of glucarpidase.

A pre-license drug substance manufacturing inspection of Eurogentec S.A. was conducted from October 19 – 27, 2011. The preliminary recommendation for the inspection was VAI. A final classification for the inspection is pending. As of the date of this review, full compliance evaluation for Eurogentec S.A. is ongoing. Inadequacies in the firm's responses to some of the inspection findings have been noted and additional information has been requested of the applicant by the Division of International Drug Quality (DIDQ). When the final results are

known, an addendum to the appropriate reviews will update the DIDQ recommendation. The final classification for this inspection is not expected to affect the approval of the application.

Other notable issues
The applicant has requested a categorical exclusion from the environmental assessment requirement under 21 CFR 25.31(c). The active component of the drug, the glucarpidase enzyme, is produced by naturally occurring bacteria of the *Pseudomonas, Flavobacterium and Acinetobacter* genera. (b) (4) (b) (4) (b) (4) Most of the protein will be administered to patients and will be metabolized. Thus, manufacturing will not significantly alter the distribution of the substance. The Division of Therapeutic proteins recommends that categorical exclusion from environmental assessment be granted. I concur with this recommendation.

4. Nonclinical Pharmacology/Toxicology

The information in this section was derived from the reviews of M. Stacey Ricci, Sc. D. and Anne Pilaro, Ph.D. Revisions were made for the purposes of this review.

The Nonclinical review team has recommended approval for this BLA. The team further recommends a post-marketing requirement (PMR) for the applicant to study the safety and efficacy of glucarpidase administered by the intrathecal route under The Animal Rule. This recommendation is based on an expectation that glucarpidase will be used to treat accidental intrathecal methotrexate (IT MTX) overdoses. In addition, there are no nonclinical data in the application that support the safety of (b) (4) used in the manufacturing fermentation process for the glucarpidase drug substance, for intravenous use. The applicant has agreed to perform a nonclinical study as a PMC to address this issue. I concur with the recommendations of the nonclinical review team.

The Nonclinical review team was consulted by the CMC team on December 23, 2011. Requested was a toxicologic evaluation of (b) (4) (b) (4) that is used in the manufacturing process for glucarpidase. Additional information was requested of the applicant to complete the nonclinical review. The results of the review are pending at this time, but could represent a safety issue. An addendum to this review will be written when the issue(s) pertaining to this matter are resolved.

Glucarpidase pharmacology and toxicology were evaluated predominantly using *in vivo* analyses in mice, rats, rabbits, dogs and Rhesus monkeys. Because glucarpidase catabolism of MTX results in elevated DAMPA levels, the safety and pharmacokinetics of DAMPA were also evaluated by the applicant. Included in the applicant's submission were pharmacology and toxicology data in the form of original research reports from studies conducted by contract research labs or by the National Cancer Institute, and published, peer-reviewed journal articles from research conducted at academic institutions.

The use of carboxypeptidase G1 (CPG1) to treat MTX toxicity was first examined in the 1970s. Because clinical data were available for CPG1 that suggested that enzymatic degradation of

MTX offered a potential treatment option for HDMTX-related renal toxicity, initial *in vitro* pharmacology studies using glucarpidase (CPG2) were not conducted prior to submission of the original IND. Subsequent *in vitro* analysis of glucarpidase activity in human plasma characterized the ability of glucarpidase to hydrolyze MTX, leucovorin (LV) and the active metabolite of LV, 5-methyltetrahydrofolic acid (5-MeTHF).

Nonclinical proof-of-concept studies involved administration of MTX to animals followed by glucarpidase. Two rescue pharmacology studies in mice evaluated LV rescue of MTX-induced toxicity with or without glucarpidase. The addition of glucarpidase to LV alone improved some MTX-induced tissue damage, but there was not a clear, overall benefit from adding glucarpidase to LV rescue over LV alone. Glucarpidase rescue of intrathecal HDMTX overdose was also evaluated in both rabbits and monkeys. Rabbits did not respond well to intrathecal treatments, but results from studies in monkeys demonstrated glucarpidase alone reduced cerebrospinal fluid MTX concentrations and support the possible use of glucarpidase treatment of intrathecal MTX overdose.

Safety pharmacology studies were conducted to evaluate DAMPA toxicity using dogs and isolated rabbit hearts. In dogs being monitored by telemetry, treatment with DAMPA elicited minimal effects on blood pressure and heart rate, and on ECG intervals and waveform rhythms. Clinical signs in the dog included changes to the sclera of the eye after the high dose administration, and reddening and/or swelling of the muzzle. In isolated rabbit hearts, DAMPA treatment *in vitro* did not cause any cardiovascular effects that appeared to be treatment-related.

The toxicology program included a 3-day repeat-dose toxicology study in the rat, and a 14-day repeat dose toxicology study in the dog. A dose-escalation study was conducted in the dog preceding conduct of the repeat dose dog study. Glucarpidase was well-tolerated in the rat when administered daily by the IV route for 3 days at doses of 50 or 5000 Units/kg. Single glucarpidase doses of 50, 500, 1000, 2500, 3750 or 5000 Units/kg were evaluated in the dog dose-escalation study. Glucarpidase doses less than or equal to 2500 Units/kg were well-tolerated. Changes in clinical signs, clinical chemistry and hematology parameters that suggested damage to the hepatic and/or renal systems were observed at doses greater than 2500 Units/kg, but tissues were not collected, so correlation of the clinical pathology findings with histomorphologic changes was not possible.

In the 14-day repeat-dose study, dogs received 50, 500 or 2500 Units glucarpidase/kg every other day for up to 14 days. Seven early deaths occurred in dogs receiving 500 or 2500 Units/kg. The cause of death in these animals was not determined after microscopic evaluation of the tissues by the study pathologist. Clinical signs in the early decedent animals included central nervous system effects (ataxia, prostration), gastrointestinal system effects (red discharge from anogenital region, soft stool, vomitus, red material in pan/bedding), red discoloration of ears or entire body, labored breathing, and excessive salivation. Liver transaminases were markedly elevated in these animals, although no corresponding lesions in liver were observed microscopically. Some of these effects could be the result of prolonged folic acid depletion and might represent an exaggerated pharmacological effect of glucarpidase. Effects could also be consistent with an immunogenic response to glucarpidase in the dog. Anti-glucarpidase antibodies were detected in all glucarpidase-treated animals by Study Day 15. Platelets decreased significantly in a dose-

dependent manner on Day 12 in all treated males, but not in females. Toxicokinetic evaluation showed that detectable concentrations of glucarpidase were present in plasma at all doses following the first dose, and that the AUC increased in a supra-proportional manner from the 50 to 500 Units/kg doses and in a dose-proportional manner from 500 to 2500 Units/kg. Lack of data due to early deaths prevented a statistical analysis of the PK data at the 13-day time point, but the few available data points suggested that there was no accumulation of glucarpidase with repeat dosing.

No genetic toxicology, carcinogenicity or reproductive and developmental toxicology studies were conducted using glucarpidase.

5. Clinical Pharmacology/Biopharmaceutics

The information in this section substitutes for a statistical review and was derived from the reviews of Patricia Dinndorf, M.D., Division of Oncology Products 2 and Lillian H. Zhang, Ph.D., Division of Clinical Pharmacology 5 (DCP5). Revisions were made for the purposes of this review.

It is the opinion of the Clinical Pharmacology and Clinical reviewers that this BLA includes acceptable data to support the effectiveness of glucarpidase for the intended indication and the application should be approved. I concur with these recommendations.

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

***Clinical Study Design*:** The efficacy of glucarpidase in this application is supported by the data from Trial 006, a prospective, open label, non-randomized, multicenter, single arm compassionate use trial conducted by NCI in which 184 patients of any age who exhibited HDMTX-induced nephrotoxicity and delayed MTX excretion. The dosing regimen was a single dose of 50 Units/kg by intravenous injection over 5 minutes, up to a maximum of 2,000 Units per dose. If patients did not achieve or maintain a methotrexate concentration of $\leq$ μmol/L two or more days after the first dose, a second dose was permitted. The primary efficacy outcome was a pharmacodynamic (PD) endpoint defined as the proportion of patients who achieved a rapid and sustained clinically important reduction (RSCIR) in plasma MTX concentration to $\leq$ μmol/L at 15 minutes and sustained for up to 8 days following glucarpidase administration. The protocol also specified that patients continue receiving intravenous hydration, urinary alkalinization and leucovorin (LV), and that LV administration be adjusted to assure it is not administered within 2 hours before or after glucarpidase due to an observed PK drug-drug interaction between glucarpidase and LV. Following administration of glucarpidase, plasma MTX concentrations were measured at 15 minutes, 1 hour, 2 hours, and daily for a total of 8 days. Measurements of MTX plasma concentrations were performed utilizing a chromatographic

method because DAMPA (mean $t_{1/2}$ ~ 9 hours) interferes with the immunoassays used to measure MTX concentrations. Plasma MTX concentrations within 48 hours following administration of glucarpidase can only be reliably measured by a high performance liquid chromatography (HPLC) method, which was utilized to collect the efficacy data in this trial.

Efficacy Results: Among the 149 patients treated with glucarpidase in the trial, the clinical endpoint, RSCIR, was achieved in 10 of the 22 patients [45.5% (95% CI: 26.9, 65.3%] who met the trial inclusion criteria, i.e., having a pre-glucarpidase MTX concentration >1 μmol/L and plasma MTX samples measured by the chromatographic method. An exploratory analysis performed by Dr. Zhang revealed that none of the patients with pre-glucarpidase MTX level >50 μmol/L achieved RSCIR. Of the 12 patients who failed to achieve RSCIR, five patients (22.7%) attained a transient plasma MTX concentration of ≤ μmol/L; but their MTX levels rebounded with the median time to reach a plasma MTX concentration >1 μmol/L after attainting a level of ≤ μmol/L occurring between 2 and 3 days, and the median increase of plasma MTX concentration from nadir of 1.4 μmol/L (0.34 to 2.5 μmol/L). There were six patients who met the protocol specified second dose criteria, pre-1st dose glucarpidase MTX concentrations >100 μmol/L, who received a second 50 Units/kg dose of glucarpidase administered 48 hours after the first dose. (b) (4)

(b) (4)

Below is a table of efficacy results from trial 006 that compares the FDA analysis of the results of Trial 006 with those of the Applicant. The Applicant's efficacy analysis is based on data from a total of 27 patients who had at least 1 post-glucarpidase MTX concentration measured by an HPLC method following glucarpidase administration. FDA's analysis excludes five patients who either did not meet the inclusion criteria for the trial or had a pre-glucarpidase MTX concentration ≤ μmol/L. The primary efficacy results analyzed by the FDA and the Applicant are presented in the table below. Based on the FDA analysis, 45.5% of patients achieved a RSCIR after treatment with a single dose of glucarpidase.

Summary of Primary Efficacy Results (from the review of Dr. Zhang)

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

Subgroup Analyses

- *Age and Tumor Type*

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

Analyses of Subgroups (from the review of Dr. Zhang)

Tumor Type	**Age Group n (%)**	**Median MTX Dose (g/m^2) (Min, Max)**	**Median Pre-Glucarpidase MTX Conc. (μmol/L) (Min, Max)**

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

Since majority of the pediatric patients had the diagnosis osteogenic sarcoma with a higher pre-glucarpidase MTX concentration, patients with osteosarcoma were less likely to respond. Patients with osteosarcoma were treated with higher doses of methotrexate with a median of 12 (range 2 to 20 $g/m^{2)}$ compared to leukemia lymphoma patients with a median of 5.8 (range 1.4 to 8 $g/m^{2)}$. The pre-glucarpidase methotrexate level was greater in the osteosarcoma patients with a median of 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.

- *Methotrexate Dose*

As noted in the table below, taken from Dr. Dinndorf's review, 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.

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%)

- *Gender*

The lower response in the female patients, 22% RSCIR vs. 61% for males, reflects the diagnosis. Seven of 9 female patients had an osteosarcoma diagnosis, whereas only 4 of 13 male patients had the same diagnosis.

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

hours by the enzymatic method, ~3.0 hours by ELISA) than that observed in the healthy subjects (~5.6 hours by the enzymatic method, ~9.0 hours by ELISA).

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

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

Immunogenicity: In the clinical studies, 16 of 96 evaluable patients (16.7%) had treatment-emergent anti-glucarpidase antibodies (AGAs) detected at one or more time points ranging from day 7 to month 7 following exposure to glucarpidase. Twelve of the 16 patients who developed AGAs had received a single dose of glucarpidase and the remaining four patients had received two doses of glucarpidase. The impact of immunogenicity on glucarpidase PD was not observed in the registration trial (006) because a ≥97% reduction in plasma MTX concentration at 15 minutes occurred in all of the 22 patients included in the efficacy dataset. In addition, the impact of immunogenicity on glucarpidase PK is not anticipated due to a short $t_{1/2}$ of glucarpidase relative to the time needed for anti-glucarpidase antibody formation.

Rebound: A patient 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) who exhibited evidence of rebound. 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. Both the clinical and clinical pharmacology reviewers have concluded that this finding supports the importance of monitoring MTX levels 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. Clinical Microbiology

Not relevant to this application

7. Clinical/Statistical- Efficacy

No statistical review was performed because the primary trial results did not require one. Instead, the primary efficacy review was performed by the clinical pharmacology review team, was based on a PD endpoint, and is discussed under section 4 above.

8. Safety

The information in this section was derived from the primary clinical review of Patricia Dinndorf, M.D. Revisions were made for the purposes of this review.

The primary clinical safety reviewer for this application, Dr. Patricia Dinndorf, has concluded that glucarpidase is safe for the indication proposed and the application should be approved.

Because there is a risk that using glucarpidase in any other setting than for patients with severely delayed methotrexate clearance could result in sub-therapeutic exposure to methotrexate and decreased antitumor activity, Dr. Dinndorf has also recommended that the indication statement limit the use of glucarpidase for the treatment of toxic (>0.1 micromol per liter) plasma methotrexate concentrations in patients with delayed methotrexate clearance due to impaired renal function. (b) (4)

(b) (4)

It is also noted that an approval for Voraxase will very likely lead to an increase in the use of the enzyme for patients who experience toxicity after accidental administration of inappropriately high doses of MTX by the intrathecal route.

A study to be performed as a postmarketing requirement (PMR) under the conditions of the so-called "Animal Rule" (21 CFR 601.90) to evaluate the safety and efficacy of glucarpidase administered by the intrathecal route, recommended by the Nonclinical review team, is supported by Dr. Dinndorf.

I concur with Dr. Dinndorf's analyses and recommendations regarding the safety of glucarpidase.

The analyses of clinical safety for this application is supported by 290 patients treated with glucarpidase who were enrolled in Trial 006 (n=149) and Trial 016 (n=141) and who had safety data available. Trial 006 was discussed in detail in Section 4 of this review. Trial 016 is an ongoing, open-label treatment trial in which glucarpidase is administered as adjunctive treatment for patients who are experiencing or at risk of MTX toxicity. At the date of the data cut-off for the data analyses submitted to support this BLA, October, 2010, 244 patients were enrolled to the treatment trial, 171 patients had documented evidence of having received at least one dose of glucarpidase, and 141 patients had adequate safety information collected.

In addition to the primary safety data base utilized by the FDA safety reviewer in her analyses, supplemental safety information was assessed from the application's pharmacokinetic and drug interaction trials (Trial 005 and Trial 010) in which MTX was not administered. Trial 005 was an

open-label, single-site, pharmacokinetic trial of glucarpidase administered intravenously at a dose of 50 units/kg to 12 healthy and renally impaired volunteers. Trial 010 was a randomized, crossover, double-blind placebo controlled trial conducted in 6 volunteer subjects. Glucarpidase was administered at a dose level of 50 Units/Kg IV followed by Leucovorin at a dose level of 150 mg/m^2 q 6 hours for 5 doses starting 2 hours after glucarpidase/placebo. There was a minimum of 14 days between each treatment period. The safety results from Trial 005 and Trial 010 are deemed noteworthy by the primary clinical reviewer because they isolate the adverse drug reactions of glucarpidase from those of methotrexate.

Trial 001, Trial 002, and Trial 003 discussed previously in this review were conducted using glucarpidase manufactured as CAMR lot 004. The applicant failed to verify that this material was comparable to the commercial product, Voraxase. These trials include safety information on 327 patients who received glucarpidase. They were assessed by Dr. Dinndorf to determine if there was any new safety signals reported that were not otherwise identified.

Major Studies Supporting Safety of Glucarpidase (from the review of Dr. Dinndorf)			
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

The data from Trial 006 and Trial 016 are limited by several factors:

- Patients treated with glucarpidase also experience methotrexate-associated toxicities 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.

However, given the indication, emergency treatment of patients with severe methotrexate toxicity, the safety information available is adequate to assess the risks and benefits of glucarpidase administered for this indication.

Because glucarpidase is intended to be administered as an antidote to toxic levels of methotrexate, patients would expected to have hematopoietic, hepatic, and renal toxicities in such a setting. As a result, Dr. Dinndorf's safety review excluded hematopoietic, hepatic, and renal adverse events from her primary safety review and analyses.

For the safety populations in all trials reviewed, the most common adverse events (AEs) related to glucarpidase were paraesthesia, flushing, nausea and/or vomiting, hypotension and headache. The majority of AEs were National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2. There was one event coded as "flushing" and categorized as CTCAE grade 3.

Deaths
In her review of the deaths reported during clinical trials of glucarpidase, Dr. Dinndorf determined that there were no deaths that appeared to be directly related to treatment with glucarpidase. Deaths within one month of therapy with glucarpidase that were not related to the progression of malignant disease were related to treatment failures of glucarpidase. Within the 006 and 016 safety populations, there were 8 deaths within 30 days of glucarpidase exposure not related to progression of the underlying malignancy. This represents a 3% failure rate for 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.

Serious Adverse Events
There were 2 patients with adverse events categorized as serious possibly related to glucarpidase. The first was a 62 year old male with a central nervous system lymphoma reported to have depressed level of consciousness and somnolence. The case report forms document that this patient was somnolent prior to the administration of glucarpidase and the somnolence was attributed to his seizure medication.

The second patient was a 42 year old male with Burkitt's lymphoma who developed 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.

There were no nonfatal serious adverse events reported in the PK and drug interaction trials (005 and 010).

Allergic Reactions
Because glucarpidase is a foreign protein that has the potential of stimulating allergic reactions, the primary safety review focused on allergic reactions and anaphylaxis for one of their analyses.

In Trial 006, one patient was reported to have a grade 1 allergic reaction with the initial glucarpidase administration. This patient received a second dose of glucarpidase 2 days later without recurrence of the reaction. In addition, there were 2 patients who experienced episodes of hypotension. One patient developed hypotension 1 hour after the administration of glucarpidase which resolved within 30 minutes after a normal saline bolus was administered. The patient received a second dose of glucarpidase 2 days later without recurrence of the hypotension. The second patient 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 AEs reported during Trial 006 that may have been related to allergic reactions were "throat tightness," flushing, and paraesthesias. However, there were no reports of adverse events more pathognomonic of allergic reactions such as hives, itching, bronchospasm, swelling or anaphylaxis.

In Trial 016, there were no patients reported who developed allergic reactions. There were also 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.

In Trial 005 and Trial 010, there were no reports of hives, itching, bronchospasm, or anaphylactic allergic reactions.

In the trials where CAMR lot 004 was administered, there were either no adverse events suggestive of an allergic reaction, or the adverse events that were reported were confounded by other factors.

Allergic reactions do not appear to be a major problem when Voraxaze is administered for the proposed indication. When an allergic reaction did occur, the symptoms were mild and the reaction did not recur with an additional dose of glucarpidase.

Common Adverse Events
The most common AEs are represented in the following two tables which were excerpted from the primary safety review of Dr. Dinndorf.

Common Adverse Events Trial 006 n = 149
(From the primary clinical review of Dr Patricia Dinndorf)

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

Common Adverse Events Trial 016 n = 141 (From the primary clinical review of Dr Patricia Dinndorf)						
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

Laboratory Values

Clinical laboratory values did not contribute meaningful data to inform the safety evaluation of glucarpidase. Delayed methotrexate clearance is the result of renal dysfunction. Delayed methotrexate clearance results in hematologic and hepatic toxicity. Because there are no controlled studies of glucarpidase to support this indication, it is not possible to determine how glucarpidase treatment affects the laboratory abnormalities associated with these toxicities.

Immunogenicity

In the clinical trials, 16 of 96 evaluable patients (16.7%) had treatment-emergent anti-glucarpidase antibodies (AGAs) detected at one or more time points ranging from day 7 to month 7 following exposure to glucarpidase. Antibody testing was performed at baseline, at weeks 1-2 and 4-6, and follow up testing was done between months 2-4 and 5-7. Mass equivalent antibody concentrations relative to a positive control antibody show that most patients had amounts below the limit of detection (<62.5 ng/ml); 3 out of 16 patients belonging to the group of patients that received 2 doses of glucarpidase remained positive 5-7 months post-treatment. Twelve of the 16 patients who developed AGAs had received a single dose of glucarpidase and the remaining four patients had received two doses of glucarpidase. However, an impact of immunogenicity on glucarpidase PD was not observed in the registration trial as a ≥97% reduction in plasma MTX concentration at 15 minutes occurred in all of the 22 patients included in the efficacy dataset. In addition, an impact of immunogenicity on glucarpidase PK is not anticipated due to a short $t_{1/2}$ of glucarpidase relative to the time needed for AGA formation.

Glucarpidase shows a high degree of immunogenicity in humans: almost 17% of patients develop antibodies after only one i.v. administration. No data are available as to how many of the AGA positive patients develop AGAs with neutralizing activity. Given the immunosuppressed status of the target population, the limited course of treatment, and the low degree of homology between carboxipeptidases from bacterial and human origin, development of AGAs with neutralizing activity should be rare, and if present, the short treatment time should not allow for a

major impact on the efficacy of glucarpidase. The catalytic domain is highly conserved between human and bacterial carboxypeptidases so there may be some immune tolerance to this domain. Moreover, this domain is embedded in the core of the homodimer making it less likely to be a primary target of an antibody response. Since the treatment will be carried out under clinical monitoring, the risk for an unattended infusion or hypersensitivity reaction should be minimal.

Neutralizing Antibodies
No data are available in the current submission on the number of patients who may have developed anti-glucarpidase Abs with neutralizing activity. The presence of neutralizing antibodies could alter the efficacy of glucarpidase in the event that treatment is required beyond a single administration. Therefore, the applicant will be asked to present a validated neutralizing assay as well as data on the detection of neutralizing antibodies in clinical samples obtained from patients included in the key trials submitted in support of this application as part of a post-marketing commitment.

120 Day Safety Update
The information included in the 120 day safety update did not change the safety profile of glucarpidase for the proposed indication.

9. Advisory Committee Meeting

No Advisory Committee meeting was planned or held for this application.

10. Pediatrics Orphan Drug

Orphan designation for glucarpidase was granted in August, 2003. There was no PERC review of glucarpidase.

11. Other Relevant Regulatory Issues

Exclusivity/Patents
Per 21 CFR 316.31(a), the applicant has been granted 7 years of marketing exclusivity as the result of their Orphan Drug Designation (#02-1637). (b) (4)

(b) (4)

Financial Disclosures
Financial Certification and Disclosures were provided to the applicant from the NCI for the two studies sponsored and conducted by the NCI (PR001-CLN-002 and PR001-CLN-006). The applicant notes that the Berlin and Bonn studies (PR001-CLN-001 and PR001-CLN-003) were both completed prior to BTG acquiring the rights to glucarpidase and the study data being transferred to BTG for analysis.

Section 1.3.4 of the application includes form 3454 which attests that the applicant submitted 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 was 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.

Other GCP issues,
The cover page of all study reports submitted in support of this application included the following declaration:

"This study was performed in compliance/accordance with Good Clinical Practices."

DSI 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 from the data to support the efficacy of this agent were taken, 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 would 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) (b) (4)

DBGC concluded that 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 were not be used to support the efficacy of glucarpidase in this application. BTG did not confirm that the CAMR lot 004 product was comparable to glucarpidase being evaluated in this application.
DBGC also concluded that methotrexate concentrations above 0.5 µmol/L from Trial 006 were adequate to support the application. A subset of patients from Trial 006 was used to support the efficacy of this product.

Consults
The following FDA Offices and Divisions supplied subject matter expertise by consulting on this application, OPDP (formerly DDMAC), OSI (bioequivalence), and for labeling, MHT, OSE (DRISK, DMEPA), OBP. No issues were identified that precluded recommendations for approval for this application.

11. Labeling

Proprietary name
A proprietary name review was originally requested under IND 011557 on May 16, 2006 . The proposed proprietary name, Voraxase was deemed acceptable at that time by the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology (OSE). A second proprietary name review for Voraxase was submitted by the applicant under the current BLA on June 30, 2011. The DMEPA review under the BLA again concluded that the proprietary name is acceptable from both a promotional and safety perspective.

- Address important issues raised by brief discussion of DDMAC and OSE Division comments.
- Physician labeling
- Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review.
- Carton and immediate container labels (if problems are noted)
- Patient labeling/Medication guide (if considered or required)

Physician Labeling
FDA did not agree with the applicant's approach to the label. The applicant's proposed label included (b) (4) (b) (4) Also included in the applicant's proposed label were (b) (4) (b) (4) In addition, FDA did not agree with the (b) (4) proposed by the applicant, which included (b) (4) (b) (4)

FDA's proposed label submitted to the applicant on December 6, 2011 is below.

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

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
Approval is recommended for this BLA contingent upon an acceptable final label.

Risk Benefit Assessment
Based on the data submitted with the application there is a favorable risk: benefit assessment for glucarpidase. Glucarpidase is intended as a rescue measure to treat the toxicities of MTX that result from impaired renal clearance of that drug. Patients with delayed methotrexate clearance develop life threatening complications including hematopoietic suppression, renal dysfunction/failure, hepatic dysfunction/failure, mucositis, and infections. Treatment of patients in this setting is an oncologic emergency, and there are no other FDA-approved drugs for this population of patients. Other measures, e.g., renal dialysis, have only variable success in this setting. After a single dose, glucarpidase was successful in rapidly (within 15 minutes) reducing MTX levels in 46% (95% CI: 27, 65) of patients who had elevated levels and sustaining decreased MTX levels of 95% from baseline for up to 8 days after dosing. There are no other medications or medical measures that can achieve these results.

There is a risk that using glucarpidase in any other setting than for patients with severely delayed methotrexate clearance could result in sub-therapeutic exposure to methotrexate and decreased antitumor activity. However, a remedy for this is the limitation of use that will be part of the indication statement.

There is also a risk that an approval for Voraxase will very likely lead to an increase in the use of the enzyme for patients who experience toxicity after accidental administration of inappropriately high doses of MTX by the intrathecal route. A study is to be performed as a postmarketing requirement under the conditions of the so-called "Animal Rule" will evaluate the safety and efficacy of glucarpidase administered by the intrathecal route, as recommended by the Nonclinical review team.

Treatment with glucarpidase failed to prevent fatal methotrexate toxicity in 3% of patients. Additional toxicities were difficult to evaluate because of the baseline adverse events exhibited by the population being studied, and the fact that the safety data are not from a controlled trial. However, the most common adverse events reported from clinical trials as related to glucarpidase administration were paraesthesia, flushing, nausea and/or vomiting, hypotension and headache.

Administration of leucovorin (LV) to patients receiving glucarpidase remains a necessity to protect normal cells from MTX toxicity because glucarpidase cannot counteract the intracellular antineoplastic effects of high dose MTX. Because LV is also a substrate of glucarpidase and a pharmacokinetic interaction between glucarpidase and LV occurs, LV should not be administered within 2 hours before or after glucarpidase injection.

Anti-glucarpidase antibodies (AGAs) were developed by 17% of patients studied in the clinical trials. However, no deleterious effect on glucarpidase pharmacodynamics (PD) was

observed in the registration trial. Due to a short elimination half-life ($t_{1/2}$ 5.7 to 9 hours) of glucarpidase relative to the time needed for AGA formation, the impact of immunogenicity on its pharmacokinetics (PK) is not anticipated.

The benefits of glucarpidase in rapidly reducing toxic MTX levels and sustaining them in the setting of renal impairment outweigh the risks of treatment.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
None

Recommendation for other Postmarketing Requirements and Commitments
Proposed Product PMCs

1) To reevaluate the mixing step for the thawed formulated drug substance (b) (4) (b) (4) to include an upper limit for the mixing time. The revised range for the mixing time of the formulated drug substance will be submitted to the Agency. Final report submitted [Insert date]

2) To characterize the types and amounts of subvisible particulates (b) (4) in the drug product at release and under real time and stress stability conditions and to evaluate the risk to product quality as it may relate to safety and efficacy. The results of these studies, together with a summary of your risk assessment and any proposed risk mitigation strategy will be submitted to the Agency. Final report [Insert date]

3) To update the tryptic and Glu-C peptide mapping specification using new acceptance criteria to reflect control of impurities and product related substances. BTG commits to add the peptide mapping as a drug substance and drug product release and stability test with the new acceptance criteria. The revised specifications for tryptic and Glu-C methods will be submitted to the Agency. Final report submitted [Insert date]

4) To reevaluate CEX-HPLC and iCE specifications to establish acceptance criteria for all major peaks. The revised specifications will be submitted to the Agency. Final report submitted [Insert date]

5) To reevaluate the lower limit of the acceptance criterion for K_m and (b) (4) the acceptance range for drug substance and drug product. The revised specification will be submitted to the Agency. Final report submitted [Insert date]

6) To reevaluate specification for the drug substance and drug product for release and stability testing after [insert number] lots are manufactured and to adjust specifications to reflect clinical and manufacturing experience. The revised specifications will be submitted to the Agency. Final report submitted [Insert date]

7) To provide information on the functional tests performed for the qualification of new batches of critical complex raw materials of biological origin (b) (4)

(b) (4) used in the fermentation process. The functional tests should provide quantitative evaluation of the growth promoting properties of complex raw materials. The study report will be submitted to the Agency. Final report submitted [Insert date]

8) To provide the results of the shipping validation study for the drug substance bulk and QC samples. The study report will be submitted to the Agency. Final report submitted [Insert date]

9) To reevaluate the specificity of the SEC-HPLC method to detect aggregates using an orthogonal method and to include an aggregate control as assay suitability. The study report and revised specifications will be submitted to the Agency. Final report submitted [Insert date]

10) To include in the SDS-PAGE method, a reference standard loaded in amounts near the limit of detection of the assay. The revised specifications will be submitted to the Agency. Final report submitted [Insert date]

11) To develop and implement an enzyme activity potency assay that measures the generation of the product of the enzyme reaction in the drug substance and drug product release and stability programs. The results of the assay development and validation, and proposed specifications will be submitted to the Agency. Final report submitted [Insert date]

12) To reevaluate the sensitivity of the SEC-HPLC and RP-HPLC assays by characterizing the percent recovery of the protein loaded onto RP-HPLC and SEC-HPLC column. The study report will be submitted to the Agency. Final report submitted [Insert date]

13) To reevaluate the specificity of the Host Cell Protein method by qualifying the anti-HCP antibody by two-dimensional electrophoresis. The study report will be submitted to the Agency. Final report submitted [Insert date]

14) To establish a robust testing protocol for the qualification of incoming Host Cell Protein assay kits. The qualification protocol will be submitted to the Agency. Final report submitted [Insert date]

15) To develop a primary reference standard that will be used to qualify future working standard and to revise the reference standard qualification protocol. The revised protocol will be submitted to the Agency before future reference standards, with the exclusion of the current M-CG2-P11 reference standard, are qualified. Final report submitted [Insert date]

16) To develop and implement a more sensitive assay for the measurement of (b) (4) in drug substance. The results of the assay development and validation,

and proposed specifications will be submitted to the Agency. Final report submitted [Insert date]

17) To increase the number of vials sampled for the cake appearance testing. The revised sampling testing strategy will be submitted to the Agency. Final report submitted [Insert date]

Proposed Facility PMCs

17) To submit shipping validation report to support shipping conditions of drug substance to the drug product manufacturing site. The report should be submitted as a product correspondence by March 2012.

18) To complete the qualification of the bioburden assay using two additional batches of drug substance. The final qualification report should be submitted as a product correspondence by June 2013.

19) To validate the integrity of container closure for the Voraxaze drug product using worst case crimping parameters (b) (4) for the capper. Validation information and summary data of the ingress test should be submitted in a CBE-0 by January 2013.

20) To revise the post approval stability program for microbiological testing. The sterility tests should be performed (b) (4) (b) (4) Alternatively, revise the stability program to include a container closure integrity testing of finished product vials in lieu of sterility testing. Please report the revised post approval stability program in the annual report by January 2013.

21) To provide information and data for low temperature worst case shipping validation study for finished drug product in a CBE-30 by June 2012.

Proposed Immunogenicity PMC

22) To analyze patient serum samples from the Voraxaze pivotal studies for the presence of anti-glucarpidase antibodies with neutralizing activity using a validated assay. The final report will be submitted by XX/XXXX

Proposed Nonclinical PMR

23) To conduct an animal safety and efficacy study to evaluate Voraxaze treatment of IT MTX overdose under the conditions of the "Animal Rule" (21 CFR 601.90 for biological products). A draft protocol will be submitted on XX/XXXX. A final protocol will be submitted on XX/XXXX. The final study report will be submitted on XX/XXXX.

Proposed Nonclinical PMC

24) To conduct a single dose toxicology study to evaluate the safety of intravenous administration of (b) (4) alone and in the presence of Voraxaze, at the lot release specification limit set for (b) (4)

Additional Comments to Applicant
None