CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125327Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	January 12, 2012
From	Patricia Keegan, M.D.
Subject	Division Director Summary Review
BLA #	BL STN 125327
Applicant Name	BTG International, Inc.
Date of Submission	July 18, 2011
PDUFA Goal Date	January 17, 2012
Proprietary Name / Established (USAN) Name	Voraxaze/ glucarpidase
Dosage Forms / Strength	Lyophilized powder for intravenous injection/ 1000 Units per vial
Proposed Indication(s)	"VORAXAZE® (glucarpidase) is indicated for the (b) (4) reduction of toxic methotrexate concentrations due to impaired renal function."
Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Reviews	Erik Laughner (BLA) Kim Rains (carton/container)
Medical Officer Review	Patricia Dinndorf
Pharmacology Toxicology Review	Stacey Ricci; Anne Pilaro (TL)
CMC Review/OBP Review	Akhilesh Nagaich Howard Anderson (DP) Nikolay Spiridonov (Manufacturing process/process validation) Emanuela Lacana (TL)
Product (Immunologic testing)	Laura Salazar-Fontana Susan Kirshner (TL)
Facilities	Mary Farbman Lakshmi Narasimhan Patricia Hughes (TL)
Clinical Pharmacology Review	Lillian Zhang; Hong Zhao (TL)
OPDP	Carole Broadnax
OSI	Jyoti Patel
CDTL Review	Suzanne Demko
OSE/DMEPA	Manizheh Siahpoushan
OSE/DRISK	Manizheh Siahpoushan Zachary Oleszczuk (TL)
MHT	Jeanine Best

OND=Office of New Drugs
OPDP=Office of Drug Promotion
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
MHT=Maternal Health Team

Division Director Summary Review

1. Introduction

BTG, Inc. seeks approval for Voraxaze (glucarpidase), a bacterial enzyme that hydrolyzes methotrexate to produce two inactive metabolites (DAMPA and glutamate), for the treatment of patients with toxic plasma methotrexate levels due to renal impairment.

Demonstration of efficacy is based on a subset of patients with toxic methotrexate concentrations and severely delayed methotrexate clearance due to renal impairment who were enrolled in a historically-controlled, multicenter, single-arm clinical trial. The primary efficacy outcome measure was a rapid (≤ 15 minutes), sustained (≥ 8 days), clinically important reduction (RSCIR) in methotrexate concentration as determined by a centralized laboratory using a validated, sensitive assay. Evidence for efficacy was evaluated in 22 patients, a subset of the patient population enrolled in Study PR001-CLN-rpt006, who met all eligibility criteria and with documentation of appropriate sample handling. These 22 patients received a single dose (n=16) or two doses (n=6) of glucarpidase 50 Units/kg administered intravenously over 5 minutes. Ten of the 22 patients achieved RSCIR [45.5% (95% CI: 26.9, 65.3%)]. However, all 22 patients showed evidence of pharmacodynamic effects with reduction in the plasma methotrexate concentration of ≥97% within 15 minutes, and there was evidence of >95% reduction from pre-treatment methotrexate levels up to 8 days in 20 of the 22 patients. The results of this subset analysis are supported by qualitative evidence of rapid and sustained reduction of methotrexate levels in expanded access programs and in non-clinical studies with both Voraxaze and with a related product (carboxypeptidase manufactured by CAMR).

The safety of glucarpidase was evaluated in 290 patients with elevated methotrexate concentrations and delayed clearance enrolled in two single arm trials, and in two pharmacokinetic trials conducted in a limited number of healthy volunteers and patients with renal failure receiving glucarpidase alone or with leucovorin.

At the time of this review, there are outstanding issues with the manufacturing facility, which are expected to be resolved prior to the action date and outstanding negotiations on PMCs and PMRs. Assuming successful resolution of these outstanding issues, all review team members and their supervisory management recommend approval of this application.

Issues to be considered further in this review are:

- The use of a single-arm trial(s) to establish efficacy and safety
- The use of a pharmacodynamic endpoint for demonstration of clinical benefit
- Reliance on results obtained in a per-protocol rather than an intent-to-treatment population
- The size of the efficacy and safety databases
- Inadequacy of dose-finding

- Drug interactions with other rescue medications (leucovorin)
- Potential for off-label uses where safety and efficacy have not been demonstrated (intrathecal administration for treatment of intrathecal methotrexate doses) and where use may result in harm to patients (compromising effective treatment by administration to patients with normal methotrexate clearance)

2. Background

Product overview and Rationale for Use

Glucarpidase is a homodimeric, carboxypeptidase enzyme with a molecular weight of 83 kDa. It is produced by a genetically-modified *E. coli* containing the gene for carboxypeptidase cloned from *Pseudomonas* straing Rs-16. Carboxypeptidases hydrolyze the carboxyl terminal glutamate residue from folic acid; this class of enzymes also hydrolyzes and inactivates many analogues of folic acid, including methotrexate and leucovorin (citrovorum factor) Glucarpidase hydrolyzes methotrexate and its active metabolite, 7-hydroxymethotrexate, into the inactive metabolites, 4-deoxy-4-amino-N10-methylpteroic acid (DAMPA) and glutamate, which are metabolized by the liver.

Glucarpidase was developed for the treatment of toxic methotrexate levels in patients with delayed methotrexate clearance due to renal impairment. Methotrexate is an inhibitor of dihydrofolate reductase (DHFR) and also directly inhibits the folate-dependent enzymes of *de novo* purine and thymidylate synthesis. Methotrexate is used, as an FDA-approved agent and off-label, as a component of multi-agent chemotherapy regimens for the treatement of sarcomas, leukemias and lymphomas, choriocarcinomas, breast cancer, and cancers of the head and neck. Methotrexate is also used at lower doses, for the treatment of rheumatoid arthritis and other rheumatologic diseases.

Intravenously administered methotrexate is reported to have a triphasic clearance. At low doses (e.g., those administered in rheumatologic diseases), methotrexate is renally excreted with minimal or no *in vivo* metabolism. At higher doses, as used for the treatment of cancer, methotrexate is renally excreted but there is also *in vivo* metabolism to active metabolites. At higher doses, methotrexate is nephrotoxic; in clinical practice, reduction in nephrotoxicity and enhancement of urinary excretion is achieved by vigorous intravenous hydration and urinary alkalinization. It is reported that the risk of renal toxicity that in patients with normal pretreatment renal function who receive high-dose methotrexate, with adequate hydration, urinary alkalinization, and leucovorin rescue is less than 2%. Leucovorin (citrovorum factor) is a metabolically functional form of folic acid that does not require reduction by dihydrofolate reductase and is used to rescue cells from the effects of methotrexate. Leucovorin is administered when plasma methotrexate concentrations at 48 hours post-dosing exceed (or are predicted to exceed) 1 micromol/L, or in accordance with specific treatment regimens utilizing high-dose methotrexate.

Observational reports dating back to the 1970's have characterized the methotrexate excretion curve and have correlated increased risks of methotrexate toxicity with methotrexate C_{max} and

exposure (AUC). The risk of toxicity is increased in patients with "toxic" plasma methotrexate concentrations defined as greater than 1 micromol/L at or beyond 48 hours or more than 2 standard deviations above the mean methotrexate clearance on standard curves derived from patient data; additional criteria based on plasma methotrexate concentrations at other timepoints have been identified for specific high-dose treatment regimens. Delayed excretion of methotrexate, with prolonged exposure to toxic levels, occurs in patients with moderate or severe renal impairment. Removal of methotrexate through continuous-flow hemodialysis is an unsatisfactory alternative, with removal of methotrexate from plasma at approximately 50% of the clearance rate in patients with intact renal function.

More recent reports indicate that, in both sarcomas and hematologic malignancies, antineoplastic activity also correlates with methotrexate exposures and efficacy may be reduced with inadequate exposure. For example, efficacy outcomes in children with acute lymphoblastic leukemia were inversely correlated with the rate of drug clearance and high steady-state levels achieved during methotrexate infusion were associated with a lower leukemia relapse rate (Pui et al., 2004). FDA became aware of unsupported claims on Protherics, Inc. website suggesting uses of glucarpidase that could result in inadequate exposure to methotrexate and impair efficacy of treatment in such patients. On November 14, 2008 the Division of Drug Marketing, Advertising, and Communications (DDMAC), issued a letter to Protherics regarding unsupported or promotional claims on Protherics' website, including the following statements:

- "Voraxaze is a unique drug that allows clinicians to control patient exposure to methotrexate (MTX)."
- "Voraxaze may also prove suitable for more routine adjunctive use ("planned use") with high-dose MTX (HDMTX) to optimize the HDMTX therapy."
- "Protherics believes that Voraxaze could potentially be used as an adjunctive therapy with each cycle of high dose MTX therapy . . ."

Protherics was informed that "These claims are misleading because neither the webpage nor the product fact sheet reveals that there is no data to support the efficacy of the drug for this use or that the risks for routine, planned use are unknown. This is particularly problematic from a public health perspective because routine administration of Voraxaze could have serious safety and efficacy implications. Voraxaze is a protein that is foreign to the body, and the risk of an allergic reaction and/or anaphylaxis may increase following repeat doses. Voraxaze may also become ineffective after repeated doses (i.e., routine use) due to the presence of neutralizing antibodies. Additionally, patients receiving Voraxaze routinely after a cycle of high dose methotrexate may be exposed to a sub-optimal dose of methotrexate, potentially reducing effectiveness of methotrexate for treating or preventing recurrence of certain types of cancer."

Clinical Development Program and Pre-submission Regulatory History

IND 4663, sponsored by the National Cancer Institute (NCI), was submitted August 7, 1992 and inactivated on October 16, 2006. The glucarpidase product administered under this IND was manufactured by the Centre for Applied Microbiology and Research (CAMR). NCI first approached FDA to discussion the possibility of submission of a Product License Application

for glucarpidase in May 1997 based on product administration under a broad access trial. Issues requiring further assessment were identified, which included:

- (b) (4)

In 2002, glucarpidase was acquired by Enact Pharma (Salisbury, UK) and then by Protherics (London, UK & Brentwood, TN) in 2003. Protherics transferred manufacture of the drug substance to Eurogentec SA (Belgium) and of the drug product to Cangene Corporation (Canada) using a re-derived Master Cell Bank.

Jan 22, 2004: NCI submitted a letter of cross-reference for Protherics and notified FDA in subsequent phone conversation on Feb. 6, 2004 that Protherics, Inc. would continue clinical marketing development for glucarpidase.

IND 11630, sponsored by the NCI, was submitted March 30, 2004 and received March 31, 2004. On April 8, 2004, FDA requested, and NCI agreed to provide a protocol for, collection of complete pharmacokinetic data in a minimum 12 patients at selected sites receiving the Protherics-manufactured product up to 48 hours after dosing. Study PR001-CLN-rpt006 (also referred to as the NCI PD study) conducted under this IND, began enrollment in July 2004. By the time of the proposed data cut-off date of November 4, 2005, 68 patients had been enrolled, with at least 27 patients having methotrexate concentrations determined by HPLC and 27 patients with complete (n=13) or partial (n=14) assessment for anti-glucarpidase antibodies. This IND was inactivated on May 11, 2007, subsequent to the removal of the clinical hold for the treatment protocol for glucarpidase under IND 11557.

IND 11557 was submitted Feb. 18, 2004 by Protherics, Inc.

April 13, 2004: End-of phase 2 meeting was held; key advice and agreements reached were:

- 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 manufacturing data presented were 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 were inadequate for confirming comparability of the CAMR product with the commercial product.

June 2004: PR001-NCL-PK001, a single-dose, pharmacokinetic, cross-over study comparing the pharmacokinetics of a lot of glucarpidase manufactured by CAMR (CAMR-004) to a lot manufactured by Protherics, Inc. (at the Eurogentec facility) was initiated. Results demonstrated that these lots were not pharmacokinetically similar, applying strict bioequivalence criteria, based on the upper limit of the 90% confidence interval for both C_{max} and AUC which exceeded 1.25.

In correspondence dated December 5, 2005, the FDA stated that:

- (b) (4)
- More emphasis will be placed on the results of Study PR001-CLN-rpt006 (also referred to as the NCI PD study) conducted under NCI BB-IND 11630; and
- There were deficiencies in the design of Study PR001-CLN-rpt006, specifically with regard to collection of immunogenicity and pharmacokinetic data.

April 28, 2006: pre-BLA meeting. Key agreements reached were:

- The primary analysis population for PR001-CLN-rpt006 would consist of all enrolled patients with impaired methotrexate clearance with methotrexate levels > 1 μmol/L prior to treatment with glucarpidase.
- The primary efficacy endpoint was the proportion of patients who achieved a durable, clinically important reduction (CIR) in plasma methotrexate concentration (pMTX), defined as a reduction of pMTX to ≤1 umol/L in all post-glucarpidase samples. FDA agreed that the point estimate for the CIR rate and 95% confidence intervals should be provided but did not reach prospective agreement on the lower confidence limit.
- Planned subgroup analyses of the "response rates" should be should be conducted on groups determined by
  - baseline methotrexate level (e.g., patients with > 1, >10, or > 100 μmol/L immediately prior to treatment);
  - underlying disease (osteosarcoma vs. other diagnoses), given the differences in eligibility criteria for patients with osteosarcoma; and
  - additional subgroups, if adequate justification provided for the subgroup selection).
- That, as previously communicated to Protherics during the November 9, 2004, meeting, and as confirmed during the April 28, 2006 meeting, "[Protherics] must provide a plan to collect immunogenicity data in at least 100 patients assessed at 28 days post-exposure for anti-glucarpidase binding antibodies. Patients who are seropositive at day 28 will need to undergo additional assessment for neutralizing antibodies and sampling at later time points to characterize the persistence of the immune response to your product." Protherics stated that they did not have the authority to agreed to amend Study PR001-CLN-rpt006, to resume collection of patient samples for immunogenicity testing on days 14, 21, and 28. Protherics agreed to provide all available immunogenicity data and a proposed PMC to collect additional safety information in the original BLA. FDA also advised Protherics that, due to the paucity of immunogenicity assessments, product labeling might be restricted to a single dose.

- Preliminary PK data from the PR001-CLN-rpt011 trial should be submitted in the original BLA with additional data obtained after the submission of the BLA to be provided with the day 120 safety update to the BLA.
- To allow FDA to initiate an earlier review of certain complete sections (such as the toxicology section) of the BLA, Protherics was advised to submit a request for Fast Track designation, which if granted, would allow submission of a "rolling" BLA.

1/5/2007: Designation granted as a Fast Track development program the investigation of glucarpidase for the (b) (4) reduction in toxic methotrexate levels in patients receiving methotrexate who have toxic methotrexate levels due to impaired renal function.

4/10/2007: Treatment protocol titled "An Open-Label Treatment Protocol for the Use of Voraxaze as Adjunctive Treatment for Patients Experiencing or at Risk of Methotrexate Toxicity" was received by FDA. In addition, Protherics submitted a request for cost recovery under 21 CFR 312.7(d).

4/25/07: E-mail transmission requested the following treatment protocol revisions
- The eligibility criteria for the treatment protocol, consistent with the PR001-CLN-rpt006, should be evidence of renal dysfunction and documentation of impaired methotrexate clearance, specifically levels greater than 2 standard deviations above the mean expected methotrexate concentration.
- The protocol should require collection of samples for immunogenicity testing at 7 to 10 days, and 4 to 6 weeks after the dose of glucarpidase.
- The treatment protocol should include a chart providing criteria for 2 standard deviations above the expected mean methotrexate concentration based on methotrexate dose administered and time from administration (as below).

Table 1: Threshold Plasma MTX Concentrations for Glucarpidase Administration

MTX Dose	1 g/m2	2 g/m2	5 g/m2	4 g/m2	8 g/m2	12 g/m2
Infusion Duration	> 24 hours			> 4 hours		
Hours after start of MTX infusion	Threshold plasma MTX concentration (µmol/L)a					
12 hours	≥ 50	≥ 100	≥ 250	≥ 160	≥ 310	≥ 470
24 hours	≥ 50	≥ 100	≥ 250	≥ 25	≥ 50	≥ 75
36 hours	≥ 7.5	≥ 15	≥ 35	≥ 5	≥ 10	≥ 16
42 hours	≥ 3	≥ 6	≥ 16	≥ 3	≥ 6	≥ 9
48 hours	≥ 1.5	≥ 3	≥ 7.5	≥ 2	≥ 4	≥ 6
≥ 60 hours	≥ 1	≥ 1	≥ 2.5	≥ 1	≥ 2	≥ 3

a Values rounded to 1 or 2 significant digits, and predicted values < 1 µmol/L replaced by 1 µmol/L. For dosing with infusion time > 12 hours, values for the 12-hour time point are based on predictions for the end of infusion.

5/17/2007: Letter, providing reasons for the clinical hold on the Treatment Protocol, placed on hold during May 8, 2007 teleconference, pending revisions to the Investigator's Brochure; the

protocol was allowed to proceed on May 24, 2007. Protherics was also notified that FDA had no objection to your intent under 21 CFR 312.7 (d)(2) to charge patients enrolled in this protocol for the cost of the study drug.

Application history

- November 17, 2008: The application (BL STN 125372) was submitted by Protherics, Inc. under 506 (c) of the FD&C Act for review of an incomplete application for a Fast Track Designated Program (rolling BLA). Additional portions of the BLA were submitted on April 30, 2009, May 10, and 11, September 29, and December 16, 2010, and June 30 and July 18, 2011.
- 6/30/11: FDA notified of change in responsible organization for the BLA from Protherics, Inc. to BTG International, Inc.
- February 5, 2010: FDA informed Protherics of major deficiencies with the organization and content of the clinical modules which, if unresolved, could affect a decision to file the application; these issues were addressed through resubmission of the clinical module.
- 4/15/2010 FDA correspondence: informed Protherics that, both the binding and neutralization assays were sufficient to analyze patient samples.
- July 18, 2011: Last portion of the application was received and application deemed complete.

3. CMC

Glucarpidase is a 390 amino acid carboxypeptidase enzyme. The genetic sequence was isolated from *Pseudomonas sp.* RS-16, cloned, and product is manufactured through standard fermentation technology using *Escherichia coli* K12 strain RV308, genetically engineered through recombinant DNA methods to express glucarpidase. The manufacturing process (b) (4) (b) (4). The drug substance is manufactured at Eurogentec (Belgium) and the drug product at Cangene (CBI, US). The material administered for the portion of the trial supporting efficacy in this BLA was distributed to study sites by the Cancer Therapy Evaluation Program (CTEP);Division of Cancer Treatment, and Diagnosis, NCI.

VORAXAZE is supplied as a lyophilized powder containing 1000 Units carboxypeptidase and 10 mg lactose. Upon reconstitution with 1 mL sodium chloride injection USP, each vial contains 1000 U carboxypeptidase per mL. A unit of glucarpidase activity (U) is defined as the quantity of enzyme needed to catalyze the hydrolysis of one micromole of methotrexate in one mL of the reaction mixture at 37°C in one minute.

I concur with the conclusions reached by the OBP and facilities reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Resolution of the lack of data to support proposed specifications for (b) (4), as noted in Dr. Lancana's review, have been satisfactorily addressed through (b) (4) of specifications. I also concur with the conclusions reached by the OBP and facilities reviewers that there are no outstanding clinical microbiology or sterility issues that preclude approval. The manufacturing site inspection for

the drug product was waived based on recent FDA inspections of this facility. The manufacturing site inspection for manufacture of drug substance was generally acceptable however the inspectional findings have not been classified. Commitments, with projected timelines for completion, to satisfactorily address the outstanding cGMP issues are under discussion between the OSI reviewers and the manufacturing facility. It is anticipated that these issues will be successfully resolved prior to the PDUFA goal date. Stability testing supports an expiry of 30 months from the date of manufacture (b) (4) when stored at 2 to 8 ºC. The OBP review staff also recommended that BTG's request for categorical exclusion from environmental assessment be granted.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

As summarized in Dr. Ricci's review, prior human experience with bacterially-derived carboxypeptidase enzymes supported the initial IND trials for glucarpidase rather than traditional non-clinical studies. The toxicology program consisted of a 3-day repeat-dose toxicology study in the rat, a single-dose, dose-escalation toxicology study in the dog, and a 14-day repeat dose toxicology study in the dog. These studies predated the requirements for Good Laboratory Practices and are further limited by the number of animals tested and, for multi-dose studies, the rapid development of anti-glucarpidase antibodies which limited exposure.

In the rat, intravenous doses of glucarpidase of up to 5000 Units/kg daily for 3 days in the rat did not result in adverse effects. Single doses of up to 2500 Units/kg did not result in adverse effects in dogs, however evidence of hepatic and/or renal toxicity based on clinical signs and laboratory findings were observed at doses greater than 2500 Units/kg; no post-mortem assessment of organs or histopathology were conducted in this study. In the 14-day repeat-dose study, 3 dogs/sex/group received 50, 500 or 2500 Units glucarpidase/kg every other day for up to 14 days. Four of the 6 dogs receiving 500 Units/kg and 3 of the 6 dogs receiving 2500 Units/kg dose died prematurely or were sacrified between days 11-13 of the study. The cause of death could not be determined from post-mortem histopathologic evaluation.

Nonclinical proof-of-concept studies were conducted in mice. In two studies, treatment groups were administered high-dose methotrexate (HDMTX) systemically (intraperitoneally), HDMTX followed by leucovorin rescue, or HDMTX with leucovorin rescue and glucarpidase. Cohorts given leucovorin rescue with or without glucarpidase exhibited lower mortality and less morbidity (weight loss) that those receiving HDMTX alone, however there were no apparent differences in morbidity or mortality between cohorts receiving HDMTX with leucovorin and those receiving HDMTX with leucovorin and glucarpidase. There is insufficient information in the application to determine why these proof-of-concept studies failed to demonstrate a treatment effect for intravenously administered glucarpidase. Proof-of-concept studies evaluating the effects of glucarpidase rescue for intrathecal methotrexate

overdose were conducted in rabbits and monkeys. Data from the rabbit study suggested that this is not a good model for assessment of intrathecal drug administration. Data from the proof-of-concept study in 6 monkeys is available only from a published literature report that states that treatment with glucarpidase reduced the concentration of methotrexate in the cerebrospinal fluid.

Based on the indication sought, glucarpidase will be administered only to patients receiving high-dose methotrexate regimens for treatment of cancer, therefore no genetic toxicology, carcinogenicity or reproductive and developmental toxicology studies were conducted, consistent with the recommendations in ICH S6 and S9.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

The pharmacokinetics (PK) of glucarpidase were assessed using two assays – one assessing enzymatic activity and one detecting the carboxypeptidase enzyme (ELISA). The results obtained with the enzymatic and ELISA assays were similar. Pharmacokinetics of glucarpidase at the dose and schedule to be recommended (a single dose of 50 U/kg as an intravenous injection over 5 minutes) were limited to data collected in healthy volunteers (n=8) and individuals with renal impairment (n=4), who were administered only glucarpidase (i.e., did not receive methotrexate or leucovorin), healthy subjects (n=6) enrolled in drug interaction studies who received glucarpidase in combination with leucovorin (but not methotrexate), and two patients with osteogenic sarcoma with normal renal function who received glucarpidase following administration of methotrexate and in combination with leucovorin. The clinical pharmacology reviewer considered the number of subjects in whom the PK of glucarpidase alone, or in combination with leucovorin and the adequacy of sampling times to be sufficient to characterize the PK profile in healthy subjects. The PK data obtained in two patients with osteogeneic sarcoma was not sufficient to fully characterize the PK profile; however the data did not indicate the presence of clinically important difference in PK in patients that would require further evaluation of PK in patients prior to approval in order to develop a product label for safe and effective use.

Pharmacokinetic profile

The pharmacokinetics of a single, intravenous dose of 50 U/kg of glucarpidase were evaluated in a single study of eight healthy subjects. Serum glucarpidase activity levels were measured by an enzymatic assay and serum total glucarpidase concentrations were measured by ELISA.

Based on the enzymatic assay, the mean elimination half-life ($t_{1/2}$) was 5.6 hours, the mean C_{max} was 3.3 µg per mL, and the mean area under the curve ($AUC_{0\text{-}inf}$) was 23.3 µg·h per mL. The mean systemic clearance (CL) was 7.5 mL per min. The mean volume of distribution (V_d) was 3.6 L, suggested that glucarpidase distribution is restricted to plasma volume.

The pharmacokinetic parameters derived from the serum total glucarpidase concentrations were similar to those generated by enzymatic assay with the exception that the calculated half-life was longer, with $t_{1/2}$ of 9 hours.

Administration to Patients receiving high-dose methotrexate

As noted by Dr. Zhang "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

Dr. Zhang's review noted that the mean PK parameters in subjects with severe renal impairment (creatinine clearance <30 mL/min) 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. Based on these data, the pharmacology reviewer concluded that no dose adjustment is needed for patients with renal impairment.

Drug interactions with leucovorin

In a study of cancer patients receiving a high-dose methotrexate (≥1 g per m^2) and leucovorin rescue regimen, intravenous administration of 50 Units per kg VORAXAZE 2 hours before leucovorin reduced (6S)-leucovorin AUC_{0-3h} by 33% and C_{max} by 52%, and also reduced its active metabolite, (6S)-5-methyltetrahydrofolate, AUC_{0-3h} by 92% and C_{max} by 93%.

In Study 010, a double-blind, placebo-controlled, randomized, 2-period crossover pharmacokinetic trial conducted in healthy subjects, the effects of glucarpidase metabolism of leucovorin (5 doses) was detectable at 26 hours after glucarpidase administration. In this trial, subjects were randomized to one of the two treatment periods:

Treatment A: glucarpidase (50 U/kg) as an intravenous injection over 5 minutes for one dose followed by leucovorin (150 mg/m^2) as an intravenous injection over 2.5 minutes every 6 hours for 5 doses at 2, 8, 14, 20, and 26 hours following glucarpidase

Treatment B: placebo (equivalent volume to 50 U/kg glucarpidase) as an intravenous injection over 5 minutes for one dose followed by leucovorin (150 mg/m^2) as an intravenous injection over 2.5 minutes every 6 hours for 5 doses at 2, 8, 14, 20, and 26 hours following placebo

Each treatment period was separated by a washout period of 14 days.

The results for the 6 subjects enrolled in this study are presented in the table below, abstracted from Dr. Zhang's review.

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

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

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

As noted in Dr. Zhang's review: "Despite of these findings, dose adjustment for LV is not necessary because of the following reasons: a) in clinical practice, the dose of LV is guided by the plasma MTX concentrations not by LV's exposure; b) following glucarpidase administration, a rapid and sustained reduction in plasma MTX concentrations occurs; c) the leucovorin dose will still be based on the patient's pre-glucarpidase MTX concentration for 48 hours after glucarpidase administration; d) in addition, after glucarpidase administration, LV dosing will not be stopped and will continuously be given every 3 hours until MTX level below the LV treatment threshold according to the rescue dosing regimen."

Section 5.3 of the product labeling instructs healthcare providers to continue dosing of leucovorin based on the pre-treatment plasma methotrexate contrentration for at least 48 hours following glucarpidase administration, to ensure adequate exposure during this period when some metabolism of leucovorin is expected.

Dose selection

The application stated that dose selection was based on a dose-ranging proof-of-concept trial in non-human primates and prior clinical experience under expanded access programs. The application does not contain data that would allow for an assessment of the relationships between exposure and efficacy or safety since PK data for glucarpidase were not collected in a sufficient number of patients in the primary efficacy trial (006) or in the access trial. However, there is sufficient evidence of efficacy and no concerns regarding safety that would require these data in order to develop a product label for safe and effective use.

Dr. Zhang conducted exploratory analyses assessing the relationship of patient factors and efficacy (RSCIR)in the 22 patients constituting the efficacy population Patient factors included in the exploratory analyses were age, body weight, tumor type, methotrexate (MTX) dose administered, total first dose of glucarpidase, pre-glucarpidase plasma MTX

concentration, and pre-glucarpidase creatinine clearance. Dr. Zhang noted correlations between age, tumor type, and pre-glucarpidase MTX concentration and the likelihood of achieving an RSCIR. However, all of these factors are interrelated, with higher doses of methotrexate (adjusted for weight or mass) being prescribed in specific malignancies (e.g., osteogenic sarcoma) occurring in younger patients. Of these factors, the pre-glucarpidase MTX concentration may be most relevant to healthcare providers as a means of predicting likelihood of achieving RSCIR and therefore, this exploratory analysis was included in product labeling. The following table, from Dr. Zhang's review, displays the results of the relationship between pre-glucarpidase MTX concentration and RSCIR.

Results of an Exploratory Analysis following Glucarpidase Administration

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

Because glucarpidase is a protein, a mass balance study was not provided and will not be required as the metabolism of proteins through degradation into amino acids is well-understood. Similarly, no studies of the PK of glucarpidase in patients with hepatic impairment were conducted or requested by FDA since glucarpidase is eliminated by catabolism not by hepatic metabolism via cytochrome P450 enzymes.

Pharmacodynamic effects resulting in interference with immunoassay measurement of MTX

BTG provided pharmacokinetic data characterizing one of the two primary metabolites of methotrexate; the analyses were confirmed by Dr. Zhang. In addition, BTG included a Warning regarding interference by DAMPA in immunoassays measuring methotrexate concentrations, yielding spurious results (overestimates actual concentration) for 48 hours after glucarpidase. This warning is based on the PK of DAMPA and is considered appropriate.

6. Clinical Microbiology

Assessment of sterility was conducted by the CMC reviewer and is discussed under Section 3 of this summary review.

7. Clinical - Efficacy

The data supporting the efficacy of glucarpidase is derived from the pre-protocol subset of patients treated in a single-arm trial. Given the extensive data, based on more than 40 years of

clinical trials, the methotrexate excretion curves are well-characterized and can be used as an historical control against which the results of this trial can be assessed for efficacy and is sufficient to provide a clear assessment of the treatment effect.

The size of the efficacy dataset, 22 patients, is less than optimal and is insufficient to identify differences in treatment effects that are modest or uncommon within subsets defined by demographic (e.g., age, gender, race) or prognostic characteristics (e.g., chemotherapy regimen, pre-treatment methotexate concentration). Accrual of a larger, more representative study population, which would allow greater ability to extrapolate treatment effects across a broad population was limited by the low incidence of the condition and inability to prospectively identify patients at high risk for this condition. However, given the magnitude of the treatment effect as described below, in the context of the well-defined expected methotrexate clearance, there is sufficient evidence from this trial to establish the existence of a clinically important treatment effect.

The selection of the primary endpoint of a rapid (≤15 minutes) and sustained (≥ 8 days) clinically important reduction is based on (1) the known mechanism of action of the product and (2) historical experience on the clinical relevance of the pharmacologic value identified as clinically relevant. With regard to the mechanisim of action, glucarpidase hydrolyzes methotrexate, generating two inactive metabolites 4-deoxy-4-amino-N^{10}-methylpteroic acid (DAMPA) and glutamate, both of which are metabolized by the liver. The product is characterized in strength and is dosed in potency units. A unit of glucarpidase activity (U) is defined as the quantity of enzyme needed to catalyze the hydrolysis of one micromole of methotrexate in one mL of the reaction mixture at 37°C in one minute. With regard to the threshold value of 1 micromol/L as the plasma methotrexate concentration correlating with clinical benefit, data from clinical trials dating back to the 1970's have repeatedly confirmed that prolonged (more than 48 hours) exposure to plasma methotrexate concentrations above 1 micromol/L are correlated with an increased risk of severe and potentially fatal toxicity. In addition, this threshold value was identified as appropriate based on its correlation with an increased risk of toxicity, and therefore clinically relevant, by a Special Government Employee assisting FDA in the evaluation of this drug development program.

The choice of the primary endpoint required particular attention to the ascertainment of the samples and assay for measurement of the primary endpoint. Because of the integral nature of the primary endpoint to pharmacokinetic assessments, the evaluation of the assay methodology and conduct as well as the statistical analyses of the data were conducted by the clinical pharmacology reviewer. The applicant was required to provide specific information on sample handling and assay procedures in order to assure FDA of the validity of the assay results as an accurate measurement of *in vivo* plasma concentrations. A specific concern, which was adequately addressed in the application, was demonstration that the assay results did not reflect *ex vivo* metabolism of methotrexate.

A limitation of the study design (single-arm trial) is that the effects of a rapid reduction of toxic methotrexate concentrations on duration or severity of methotrexate toxicity and on the risk of death arising from methotrexate toxicity, cannot be determined.

Regulatory history of efficacy trial

The primary efficacy data are derived from patients enrolled in Study PR001-CLN-rpt006 (also referred to as the NCI PD study),which was supported by Protherics, Inc. but conducted under the sponsorship of the Cancer Therapy Evaluation Program of the National Cancer Institute.

Key agreements reached regarding the efficacy trial during the Sept. 8, 2006 pre-BLA meeting were:

- The primary analysis population for PR001-CLN-rpt006 would consist of all enrolled patients with impaired methotrexate clearance with methotrexate levels > 1 μmol/L prior to treatment with glucarpidase.
- The primary efficacy endpoint was the proportion of patients who achieved a durable, clinically important reduction (CIR) in plasma methotrexate concentration (pMTX), defined as a reduction of pMTX to ≤1 umol/L in all post-glucarpidase samples. FDA agreed that the point estimate for the CIR rate and 95% confidence intervals should be provided but did not reach prospective agreement on the lower confidence limit.
- Planned subgroup analyses of the "response rates" should be should be conducted on groups determined by
  - baseline methotrexate level (e.g., patients with > 1, >10, or > 100 μmol/L immediately prior to treatment);
  - underlying disease (osteosarcoma vs. other diagnoses), given the differences in eligibility criteria for patients with osteosarcoma; and
  - additional subgroups, if adequate justification provided for the subgroup selection).

Study Design

The design was a single arm, open-label trial in patients with delayed methotrexate clearance secondary to renal impairment. Key eligibility criteria were

- For patients with osteosarcoma
  - Plasma methotrexate level > 50 μmol/L at 24 hr, >5 μmol/L at 48 hr, or > 2 standard deviations above the mean MTX excretion curve at >12 hours following methotrexate administration
  - Abnormal renal function > 2-fold increase in serum creatinine above pretreatment level.
- For patients with any other diagnosis
  - Plasma methotrexate level > 10 μmol/L for more than 42 hours after start of methotrexate infusion or > 2 standard deviations above the mean methotrexate excretion curve at least 12 hours following methotrexate administration
  - Abnormal renal function defined by serum creatinine > 1.5 times the upper limit of normal or creatinine clearance < 60 mL/min at least 12 hours following methotrexate administration

The treatment plan consisted of glucarpidase administered at 50 Units/kg as an intravenous injection over 5 minutes. Patients with baseline methorexate concentrations of greater than 100 μmol/L at baseline were to receive a second dose glucarpidase at 48 hours following the

first glucarpidase dose. A protocol amendment, effective November 2005, set a maximum treatment dose of 2000 Units glucarpidase. Plasma methotrexate concentrations were assessed in a centralized laboratory using a qualified HPLC assay for patients enrolled between July 2004 and November 2005; by protocol amendment, central laboratory assessment of plasma methotrexate was discontinued.

The main outcome measure was the proportion of patients who achieved a rapid and sustained clinically important reduction (RSCIR) in plasma methotrexate concentration, defined as an attainment of plasma methotrexate concentration ≤1 µmol/L at 15 minutes that was sustained for up to 8 days following the initial injection.

The per-protocol population for determination of the efficacy was defined as those who met the inclusion criteria for the study, had a pre-glucarpidase baseline methotrexate concentration of greater than µmol/L, and had both pre- and post-treatment plasma samples available for determination of methotrexate concentration by a chromatographic method analysis.

Efficacy Results

Study 006 enrolled a total of 184 patients between June 2004 and April 2007; BTG submitted the analyses based on demonstration of RSCIR in 27 of the 68 patients patients enrolled in Study 006 between July 2004 and November 2005. These 27 patients were identified as those have had at least 1 post-glucarpidase MTX concentration measured by an HPLC method. FDA per-protocol population, in which the primary analysis of efficacy was conducted, excluded five of these 27 patients for failure to meet one or more of the following key inclusion criteria: pre-glucarpidase plasma methotrexate concentrations ≤1 µmol/L, normal or mild renal impairment (serum creatinine 2.0 mg/dL).

The demographics and baseline characteristics for the per-protocol population, as defined by Dr. Dinnorf, are presented in the following table abstracted from Dr. Zhang's review.

Baseline Characteristics

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

The following table, abstracted from Dr. Dinndorf's and Dr. Zhang's reviews, presents the primary efficacy analyses in the FDA per-protocol population and as presented by BTG.

Summary of the Primary Efficacy Results

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

All patients exhibited evidence of a large pharmacodynamic effect, with reduction in plasma methotrexate concentration by ≥97% within 15 minutes in all 22 patients. The likelihood of achieving the RSCIR endpoint appeared to be linked to pre-glucarpidase methotrexate concentrations. These data are displayed in the following table abstracted from the product label.

Results of RSCIR and Exploratory Analyses Following the First Dose of VORAXAZE

Pre-VORAXAZE Methotrexate Concentration (µmol/L)	Number of Patients	Patients Achieving RSCIR n (%)	Patients with >95% Rapid Reduction in Methotrexate Concentration and Maintained up to 8 Days n (%)
>1	22	10 (45%)	20 (91%)
>1 to ≤50	13	10 (77%)	11 (85%)
>50 to ≤100	2	0	2 (100%)
>100	7	0	7 (100%)

Five (22.7%) of the 12 patients who failed to achieve RSCIR exhibited a decrease in plasma methotexate concentrations of less than 1 µmol/L that was not durable for 8 days. In these 5 patients, the median time to rebound (plasma methotexate concentrations exceeding 1 µmol/L) was 2 - 3 days and the median increase of plasma methotrexate concentration from the nadir value was 1.4 µmol/L (0.3 to 2.5 µmol/L).

Among the 22 patients in the efficacy analysis, six with pre-treatment plasma methotrexate levels of more than 100 micromol/L received a second dose of glucarpidase 48 hours after the first dose. The impact of the second dose on plasma methotrexate concentrations in this group, as shown in the table abstracted from Dr. Dinndorf's review, was not clinically meaningful and does not support the use of second dose in this population.

Methotrexate Level with Second Dose of Glucarpidase

Patient ID	Pre 2nd Glucarpidase Methotrexate Level	Day 1 Post 2nd Glucarpidase Methotrexate Level
Pt 244)	0.4 µmol/L	0.05 µmol/L
Pt 252 (**Error! Reference source not found.**)	0.05 µmol/L	0.05 µmol/L
Pt 228 ()	3.2 µmol/L	1.8 µmol/L
Pt 245)	2.3 µmol/L	0.5 µmol/L
Pt 243)	2.0 µmol/L	0.4 µmol/L
Pt 224)	3.3 µmol/L	3.1 µmol/L

8. Safety

The size of the safety database was adequate. However given the co-morbidity in the study population due to cancer, renal impairment, and recently administered chemotherapy which included but may not have been limited to high-dose methotrexate, ascertainment of glucarpidase-related toxicity was challenging in light of the lack of an internal control for comparison in the safety studies. Additional sources of safety data considered in this review were the pharmacokinetic studies that were conducted in healthy volunteers; while the number of healthy subjects evaluated were limited, the safety data are relevant since subjects had no co-morbid conditions or concomitant therapy and received glucarpidase at the recommended dose and schedule.

The safety of glucarpidase in patients with cancer consists of data obtained in 290 patients (149 in Study 006 and 141 in Study 016) who received glucarpidase in single-arm, open-label, access trials and for whom safety information. Key eligbility criteria were similar in both trials, including evidence of markedly delayed methotrexate clearance secondary to renal dysfunction.

In both trials, patients received glucarpidase 50 Units/kg as an intravenous infusion over 5 minutes. In study 006, a second dose of glucarpidase was to be administered to patients with pre-Voraxaze plasma methotrexate concentrations of ≥ 100 micromole/L whereas in Study 016, the criteria for administration of a second dose was not specified in the protocol. All patients were to receive continued leucovorin rescue, intravenous hydration, and urinary alkalinization.

In Study 006, VORAXAZE-related adverse reactions were collected on a flow sheet with a daily log of adverse reactions characterized as "glucarpidase toxicity." Additional safety information was collected from clinical records submitted by treating physicians. This information was abstracted and categorized according to NCI CTCAE version 3.

In Study 016, only VORAXAZE-related adverse reactions were collected; events were coded according to NCI CTCAE version 3.

Results

Study 006 enrolled a total of 184 patients between June 2004 and April 2007; of these, post-treatment safety data was submitted for 149 patients, which constitutes the safety database for this trial. Study 016 remains open to accrual; at the time of the data cut-off date for the BLA submission, 244 patients had been enrolled and safety data had been submitted for 141 patients.

The safety population from n Study 006 had a median age of 18 years (1 month to 85 years) 64% were male, and the underlying malignancies were osteogenic sarcoma in 32%, and leukemia or lymphoma in 63% of patients. One (n=106) or 2 (n= 30) doses of VORAXAZE were administered intravenously; the number of doses was not specified in 13 patients. Doses ranged from 18 to 98 Units per kg per dose, with a median dose of 49 Units per kg.

The safety population from Study 016 had a median age of 17 years (6 months to 85 years); 65% were male, and the underlying malignancies were osteogenic sarcoma in 32%, and leukemia or lymphoma in 62% of patients. One (n=122) or 2 (n= 18) doses of VORAXAZE were administered intravenously; the number of doses was not specified for 1 patient. Doses ranged from 6 to 189 Units per kg, with a median dose of 50 Units per kg.

Twenty-one of 290 patients (7%) experienced adverse reactions that were assessed as related to VORAXAZE. The most common adverse events (occurring in >1% of patients) identified by treating physicians as Voraxaze-related were paresthesia, flushing, nausea / vomiting, hypotension and headache. Most of the reported events were Grade 1 or 2 in severity; Grade 3 flushing was reported in a single patient.

Among these 290 patients, there were 8 deaths within 30 days of VORAXAZE exposure that were not related to progressive disease. Dr. Dinndorf carefully assessed case narratives for all patients with serious adverse events (both fatal and non-fatal). In the opinion of Dr. Dinndorf, none were clearly attributable to glucarpidase.

In addition, Dr. Dinndorf assessed the safety experience reported in a limited number of healthy volunteers (n=14) or patients with impaired renal function only (n=4)enrolled in pharmacokinetic studies (Study 005 and 010) or cancer patients (n=7) receiving high-dose methotrexate without renal impairment and toxic methotrexate levels (Study 012 and 017). In these studies, either no adverse reactions or mild adverse reactions attributable to glucarpidase were identified.

QTc effects

A formal thorough QT study was not conducted since glucarpidase is a protein which would not affect the hERG channel. However, assessement of glucarpidase effects on ECGs was assessed in a single study (Study 010), which did not identify clinically important effects on post-treatment ECGs.

Anti-product antibodies

Post-treatment anti-glucarpidase antibodies were detected in 16 (17%) of 96 Voraxaze-treated patients using a validated bridging enzyme-linked immunosorbent assay (ELISA). Anti-glucarpidase antibodies were identified between 7 days to 7 months following exposure to glucarpidase. The incidence of anti-glucarpidase antibodies appeared to be similar in patients receiving one as compared to two doses of glucarpidase. Twelve (15%) of the78 patients who had received a single dose of VORAXAZE and four (22%) of the 18 patients who received two doses of VORAXAZE developed anti-glucarpidase antibodies.

The development of anti-product antibodies is not expected to be clinically important given the rapid (15 minutes) time to maximum pharmacodynamic effect and the recommended dosage regimen which is limited to a single dose.

PMRs and PMCs

Glucarpidase has been administered to a limited number of individual patients on an emergency basis for the treatment of accidental overdose of methotrexate administered intrathecally or via an intraventricular catheter. The BLA contained limited clinical information obtained in nine patients who received glucarpidase for this use, in addition to other supportive care measures which included CSF exchange. The data provided are inadequate to allow a judgment regarding the benefits of such use. The application also contained a publication of a non-human primate study evaluating the role of glucarpidase for treatment of intrathecal methotrexate overdose, however the primary study data were not included in the application.

FDA anticipates future off-label use of glucarpidase, however due to the small number of cases expected (BTG estimates fewer than one case per year) conducting a clinical trial to identify an effective dose/dose range and determine more clearly a population that may derive benefit is not feasible. Therefore, FDA has required BTG to conduct non-clinical studies to establish the safety and efficacy of this use. These PMRs require BTG International to evaluate intrathecal administration of glucarpidase under the "Animal Rule" (21 CFR 601.90 for biological products) to assess the risks and benefits of its use to treat intrathecal methotrexate overdose.

9. Advisory Committee Meeting

This application was not referred for review to the Oncologic Drugs Advisory Committee because the application did not raise significant public health issues regarding the role of the

glucarpidase in the treatment of toxic methotrexate levels in patients with delayed methotrexate clearance.

10. Pediatrics

Orphan drug exclusivity was granted for this indication, therefore the BLA was not subject to the requirements of the Pediatric Research Equity Act (PREA). However the data provided in the application were sufficient to extend labeling to pediatric patients who formed more than half the per-protocol population evaluated for efficacy in Study 006. While some differences in RSCIR rates exist between pediatric and adult patients, comparisons are confounded by the higher pretreatment methotrexate contentrations in pediatric patients compared to adults. Furthermore, evidence of pharmacodynamic effects (≥ 97% reduction in plasma methotrexate concentrations) are similar in older and younger patients. The efficacy findings in pediatric patients, supported by that in adults, is sufficient to support approval in both pediatric and adult patients and as noted in Dr. Dinndorf's review, the incidence of investigator-identified, glucarpidase-related adverse reactions in patients between ages 1 month to 16 years was similar to that in adults (9% in each), with no unique toxicities identified in children.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: The proposed proprietary name was evaluated by DMEPA, OPDP, and OND review staff. There were no objections to the proposed proprietary name based on the potential for medications errors or promotional language.

- Physician labeling (major issues that were discussed, resolved, or not resolved)

  Indications and Usage
  - Revised to include definition of "toxic" methotrexate concentration (>1 micromole/L plasma methotrexate)
  - Revised to accurately reflect population studied, including requirement for evidence of delayed methotrexate excretion.
  - Additionl of a limitation of use to avoid off-label use in patients with acceptable clearance in whom administration of glucarpidase may impair or abrogate the anti-cancer efficacy of methotrexate.

  Dosage and Administration section
  - Revised to delete recommendation (b) (4) (b) (4)

- [redacted]
- Revised to delete the recommendation [redacted]
- Revised to specify minimum interval between administration of leucovorin and glucarpidase added since leucovorin is also a substrate of glucarpidase and a pharmacokinetic interaction between glucarpidase and LV was observed, LV should not be administered within 2 hours before or after glucarpidase injection.
- Extensively revised for brevity
- Deleted redundant sections [redacted] containing information discussed in Warnings and Precautions [redacted]

Dosage Forms and Strength

- Edited for brevity & essential information; statements overlapping with section 11 (Description) were removed.

Contraindications

- Revised to state "none" as the contraindications listed are theoretical.

Warnings and Precautions

- Edited for command language.
- Edited information on allergic reactions to provide specific information on risks in place of language indicating a theoretical risk.
- Removed [redacted] Replaced this language with specific instructions to physicians regarding time-frame for expected interference and directions to use an HPLC assay for MTC concentrations.
- Strenghtened warning (by bolding) to emphasize the need for an interval of at least 2 hours between leucovorin and glucarpidase administration. Added language to clarify that the dose of leucovorin should be based on pre-Voraxaze methotrexate concentrations to ensure adequate exposure given the reduced leucovorin exposure after 5 doses despite a 2-hour interval between glucarpidase and the first of 5 doses of leucovorin.

Adverse Reactions

- Revised for format/consistency with FDA Guidances
- Restricted safety database results to patients receiving BTG/Protherics-manufactured glucarpidase in whom case report forms describing adverse reactions were obtained.
- Revised demographic and adverse reaction data to reflect safety database of 290 patients.
- Added descriptions of the clinical trials from which safety data were obtained
- Limited tabular description to treatment-emergent adverse events in which findings were also reported in health volunteer studies, were temporally-related to glucarpidase infusion, or were not expected in this patient population (i.e., not

previously observed in clinical studies of patients receiving high-dose methotrexate).

Drug Interactions

- Edited for brevity – detailed description of interactions moved to Clinical Pharmacology section
- Deleted (b) (4)

Use in Specific Populations

- Modified Pregnancy section for consistency with 21 CFR 201.57.
- Deleted (b) (4)
- Modified Pediatric use to minimize redundant information (most information is already in the Clinical Studies section).
- Modified Geriatric Use section for consistency with 21 CFR 201.57.
- Deleted subsection on renal impairment to delete (b) (4)
- Edited to contain relevant information only, not exploratory analyses.

Overdosage

- Edited for brevity.

Description

- Edited for brevity.

Clinical Pharmacology

- Mechanism of action subsection revised to remove (b) (4)
- Pharmacodynamics subsection limited to data a brief description of the effects on methotrexate in patients assessed with a validated assay (e.g., 22 patients in efficacy trial (b) (4) and added information on effects on DAMPA levels. Deleted (b) (4)
- Pharmacokinetics subsection limited to data in 8 healthy volunteers who received Protherics-manufactured product and where adequate ascertainment of samples and a validated assay were documented. Brief descriptions of PK results in patients with renal impairment and brief description of drug interactions between leucovorin and glucarpidase.

Nonclinical Toxicology

- Deleted (b) (4)

Clinical Studies

- (b) (4)

- Data from Study 1 limited to the per-protocol population (n=22) (b) (4)
- Data table added to provide concise information on primary endpoint in the per-protocol population, for pre-defined exploratory subgroup analyses defined by baseline methotrexate concentrations, and to provide insight on supportive pharmacodynamic outcomes, based on an exploratory FDA analysis.
- Addition of information on lack of efficacy with second dose of Voraxaze.
- Addition of information on clinical outcomes (mortality attributed to methotrexate toxicity) to provide prescribers with information on potential lack of effect on the ultimate clinical outcome.

References
- Deleted (b) (4)

How Supplied
- Deleted (b) (4)

Patient Counseling Information
- Deleted (b) (4)
- Edited for command language.

- Carton and immediate container labels
  - All FDA-recommended revisions for consistency with applicable regulations and policy have been incorporated into final carton/container labeling.
- (b) (4)

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval is recommended.

- Risk Benefit Assessment
  The proposed indications is for treatment of a serious, and sometimes fatal, condition arising from chemotherapy administered for treatment of cancer. There are no effective alternative therapies as continuous hemodialysis is both morbid and only enhances clearance rates by 50% of that occurring in the absence of dialysis and leucovorin rescue alone will not ameliorate toxicity when methotrexate concentrations are sustained above 1 μmol/L. The results of the clinical trial provide robust evidence of a rapid (15 minutes) and sustained (≥8 days) clinically important reduction (RSCIR) in methotrexate concentration in approximately half the patients treated and ≥97% reduction in methotrexate levels in all patients. These effects were consistent across relevant patient subgroups defined by age and tumor type, however likelihood of attaining RSCIR appears to correlate inversely with pre-treatment methotrexate concentrations. A limitation of the trial design (single-arm trial) is that the effects of a

rapid reduction of toxic methotrexate concentrations on duration or severity of methotrexate toxicity and on the risk of death arising from methotrexate toxicity, cannot be determined. Twenty-one of 290 patients (7%) experienced adverse reactions that were assessed as related to VORAXAZE. The most common adverse events (occurring in >1% of patients) identified by treating physicians as VORAXAZE - related were paresthesia, flushing, nausea / vomiting, hypotension and headache. Most of the reported events were Grade 1 or 2 in severity; Grade 3 flushing was reported in a single patient. All events were transient, self-limited, occurring in temporal association with product infusion. These safety findings were also confirmed in healthy volunteers receiving VORAXAZE at same dose as used in clinical trials in patients. The major safety concerns arise from off-label use in three settings; these are (1) multiple doses with the potential for development of anti-product antibodies leading to loss of the treatment effect and possible increased risk of allergic reactions the proposed dose for approval, (2) administration to patients with normal methotrexate clearance resulting in suboptimal exposure to methotrexate, and (3) intrathecal administration, a setting in which effective doses have not been identified. The first two issues have been addressed through product labeling and the last issue has been addressed through the post-marketing required trials discussed below. In light of the benefits and minimal toxicity, the risk:beneft analysis is positive and favors approval.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  I concur with the recommendations of the review team members that a REMS is not required to ensure safe and effective use of Voraxaze.

- Recommendation for other Postmarketing Requirements and Commitments
  I concur with the recommendations of the clinical reviewer and team leader that post-marketing requirements to conduct an assessment of the risks and benefits of intrathecal glucarpidase for the treatment of intrathecal methotrexate overdose under the Animal Rule is necessary. The PMR is needed to ensure safe use, since this off-label use is anticipated to occur; however due to the low incidence of intrathecal methotrexate overdosage and the immediately life-threatening nature of this condition, clinical trials to assess the risks and benefits of glucarpidase for this use is not feasible.

SIGNATURES PAGE

/Patricia Keegan /s/ January 12, 2012

Patricia Keegan. M.D. Date
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Office of Hematology and Oncology Products
Center for Drug Evaluation and Research