CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Director Decisional Memo for Regulatory Action

Date	January 17, 2012
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
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**
Division Director Summary Review	Patricia Keegan
Regulatory Project Manager Reviews	Erik Laughner (BLA) Kim Rains (carton/container)
Medical Officer Review & CDTL Review	Patricia Dinndorf, Suzanne Demko
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

1. Introduction & Background

On July 18, 2011, BTG, Inc. submitted the last portion of this Biologics Licensing Application (BLA) under the Fast Track Designation Program (rolling review), completing the application for review under PDUFA timeframes.

BTG, Inc. is seeking approval for Voraxaze (glucarpidase) for the treatment of patients with toxic plasma methotrexate levels due to renal impairment.

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 treatment 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.

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 is 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.

2. CMC

OBP and facilities reviewers have recommended an overall acceptability of the manufacturing of the drug product and drug substance. They have also determined 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. 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.

3. Nonclinical Pharmacology/Toxicology

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 sacrificed between days 11-13 of the study. The cause of death could not be determined from post-mortem histopathologic evaluation.

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.

4. Clinical Pharmacology

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/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 PK trial conducted in healthy subjects, the effects of glucarpidase metabolism of leucovorin (5 doses) was detectable at 26 hours after glucarpidase administration. 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.

5. Clinical Microbiology

See Section 2.

6. Clinical - Efficacy

The primary efficacy data were derived from Study PR001-CLN-rpt006—a single arm, open-label trial in patients with delayed methotrexate clearance secondary to renal impairment.

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 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).

Efficacy was established in 22 patients with delayed methotrexate clearance (more than 2 standard deviations above the average indicated on standard nomograms) secondary to renal dysfunction. The efficacy assessment was limited to patients having pre- and post-treatment plasma samples collected and handled according to a validated procedure to yield reliable methotrexate measurements by HPLC.

All patients received glucarpidase, 50 Units/kg, as an intravenous injection over 5 minutes. Patients with pre-glucarpidase methotrexate concentrations >100 µmol/ L were to receive a second dose of glucarpidase 48 hours after the initial dose. All patients received vigorous intravenous hydration, urinary alkalinization, and leucovorin rescue.

Ten of the 22 patients met the criteria for RCSIR [45% (95% CI: 27, 65)]. Efficacy was dependent on pre-treatment methotrexate levels. Ten of 13 patients (77%) who had baseline methotrexate levels between 1-50 µmol/L achieved an RSCIR, however, none of the 9 patients with pre-glucarpidase methotrexate concentrations > 50 µmol/L attained this endpoint. All evaluable patients exhibited more than 95% reduction in methotrexate concentration from pre-treatment baseline levels that was maintained for up to 8 days following glucarpidase therapy.

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%)

7. Safety

Safety data were evaluated in 290 patients treated in two single-arm, open-label, multicenter trials. These trials enrolled patients who had markedly delayed methotrexate clearance secondary to renal dysfunction. The median age was 17 years (1 month to 85 years), 64% were male, 32% had osteogenic sarcoma or sarcoma and 63% had leukemia or lymphoma. The most common adverse reactions (incidence >1%) were paraesthesias, flushing, nausea and/or vomiting, hypotension and headache.

QTc effects

A formal thorough QT study was not conducted since glucarpidase is a protein which would not affect the hERG channel. However, assessment 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 the 78 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.

8. 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.

9. 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).

10. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

11. 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): There are no outstanding issues that preclude approval.

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval.

- Risk Benefit Assessment
  The proposed indication 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. In light of the benefits and minimal toxicity, the risk:beneft analysis is positive and favors approval. In addition, review staff for this application, including Dr. Patricia Keegan recommend approval, and I concur with their recommendation.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  None.

- Recommendation for other Postmarketing Requirements and Commitments
  See action letter for Postmarketing Requirements and Commitments.

/Richard Pazdur/s/ January 17, 2012

Richard Pazdur, MD Date

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