

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125327Orig1s000

Trade Name: Voraxaze

Generic Name: glucarpidase

Sponsor: BTG International, Inc.

Approval Date: January 17, 2012

Indications: Provides for the treatment of toxic plasma methotrexate concentrations (>1 micromole per liter) in patients with delayed methotrexate clearance due to impaired renal function.

CENTER FOR DRUG EVALUATION AND RESEARCH

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125327Orig1s000

APPROVAL LETTER



Our STN: BL 125327/0

BLA APPROVAL

January 17, 2012

BTG International Inc.
Attention: Carol Clark-Evans
Vice President, Regulatory Affairs
5214 Maryland Way #405
Brentwood, TN 37027

Dear Ms. Clark-Evans:

Please refer to your Biologics License Application (BLA) dated July 18, 2011, received July 18, 2011, submitted under section 351 of the Public Health Service Act for Voraxaze (glucarpidase).

We acknowledge receipt of all subsequent amendments received through January 17, 2012.

We have approved your BLA for glucarpidase effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, glucarpidase under your existing Department of Health and Human Services U.S. License No. 1861. Glucarpidase is indicated for the treatment of toxic (>1 micromole per liter) plasma methotrexate concentrations in patients with delayed methotrexate clearance due to impaired renal function. Glucarpidase is not indicated for use in patients who exhibit the expected clearance of methotrexate (plasma methotrexate concentrations within 2 standard deviations of the mean methotrexate excretion curve specific for the dose of methotrexate administered) or those with normal or mildly impaired renal function because of the potential risk of subtherapeutic exposure to methotrexate.

Under this license, you are approved to manufacture glucarpidase drug substance at Eurogentec S.A, Liege Science Park, Seraing, Belgium. The final formulated product will be filled, and packaged at Cangene bioPharma Inc., (CBI) in Baltimore, MD. You may label your product with the proprietary name Voraxaze and market it in vials containing 1,000 Units of lyophilized product.

The dating period for glucarpidase shall be 30 months from the date of manufacture when stored at 2 to 8 °C. The date of manufacture shall be defined as [REDACTED] (b) (4)

[REDACTED] The dating period for your drug substance shall be [REDACTED] (b) (4)

Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including results of stability studies from the first three production lots. The stability protocol in your license application is considered approved for the purpose of extending the expiration dating period of your drug product as specified in 21 CFR 601.12.

You currently are not required to submit samples of future lots of glucarpidase to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of glucarpidase or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

ADVISORY COMMITTEE

Your application for glucarpidase was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of glucarpidase in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

CONTENT OF LABELING

We are approving this application for use as recommended in the enclosed agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. For administrative purposes, please designate this submission “**Product Correspondence – Final SPL for approved BLA STN 125327/0.**”

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and carton and immediate container labels submitted on January 10, 2012 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)”. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Product Correspondence – Final Printed Carton and Container Labels for approved BLA STN 125327/0.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of neurologic impairment related to intrathecal administration of Voraxaze administered for accidental methotrexate overdose.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1. To conduct a pilot study to evaluate the safety and pharmacodynamic (PD) effects of a range of Voraxaze doses administered in a relevant animal model of intrathecal methotrexate overdose.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: January 2015

2. To use the results from PMR #1 to conduct an animal study to evaluate and establish the relative safety of an effective dose of Voraxaze in an animal model of intrathecal Voraxaze treatment of intrathecal methotrexate overdose. In this model, demonstration of PD effects alone will not suffice to establish that a non-toxic dose is relatively safe.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Draft Protocol Submission: September 2015
Final Protocol Submission: December 2015
Final Report Submission: January 2018

Submit protocols to your IND, with a cross-reference letter to this BLA. Submit all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3. 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 timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: June 2012

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4. To re-evaluate the mixing step for the thawed formulated drug substance (b) (4) to include an upper limit for the mixing time based on historical batch experience. A revised range for the mixing time of the formulated drug substance will be submitted to your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: February 2012

5. To evaluate and monitor subvisible particulates in the range of (b) (4) for lots of drug product at release, and on real time and under stressed stability conditions. The results of the evaluation, a risk assessment and a proposed control strategy will be submitted to your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: July 2013

6. To update the tryptic and Glu-C peptide mapping specification using new acceptance criteria to reflect control of impurities and product related substances and 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 your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: December 2013

7. To re-evaluate CEX-HPLC and iCE specifications to establish acceptance criteria for all major peaks. The revised specifications will be submitted to your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: December 2013

8. To re-evaluate 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 your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: June 2012

9. To re-evaluate specifications for the drug substance and drug product for release and stability testing after 6 lots are manufactured and to adjust specifications to reflect clinical and manufacturing experience. The revised specifications will be submitted to your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: December 2013

10. To provide information on the functional tests performed for the qualification of new batches of critical complex raw materials of biological origin (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 your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: December 2012

11. To provide the results of the shipping validation study for the drug substance bulk and QC samples. The study report will be submitted to your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: March 2012

12. To re-evaluate 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 your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: September 2013

13. To include in the SDS-PAGE method, a reference standard loaded in amounts near the limit of detection of the assay. The revised system suitability specifications will be submitted to your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: June 2012

14. 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, if feasible. The results of the assay development and validation, and proposed specifications will be submitted to your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: December 2013

15. To re-evaluate 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 your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: December 2013

16. To re-evaluate the specificity of the Host Cell Protein (HCP) method by qualifying the anti-HCP antibody by two-dimensional electrophoresis. The study report will be submitted to your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: June 2012

17. To establish a robust testing protocol for the qualification of incoming HCP assay kits. The qualification protocol will be submitted to your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: September 2012

18. To develop a primary reference standard that will be used to qualify future working standards and to revise the reference standard qualification protocol. The revised protocol will be submitted to your BLA in accordance with 21 CFR 601.12 before future reference standards, with the exclusion of the current M-CG2-P11 reference standard, are qualified.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: June 2013

19. 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, along with a justification based on non-clinical data, will be submitted to your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: June 2013

20. To increase the number of vials sampled for the cake appearance testing. The revised sampling testing strategy will be submitted to your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: September 2013

21. To complete the qualification of the bioburden assay using two additional batches of drug substance. The final qualification report will be submitted to your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: June 2013

22. 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 will be submitted to your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: January 2013

23. To revise the post approval stability program for microbiological testing. The sterility tests should be performed (b) (4). Alternatively, revise the stability program to include a container closure integrity testing of finished product vials in lieu of sterility testing. The revised post approval stability program will be submitted to your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: January 2013

24. To provide information and data for a low temperature worst case shipping validation study for finished drug product. The report will be submitted to your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: June 2012

25. To conduct a single dose toxicology study to evaluate the intravenous administration of (b) (4) alone and in the presence of Voraxaze, in order to qualify a new lot release specification limit for (b) (4). The results of this study will be submitted to your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on January 17, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: August 2012

Submit clinical protocols to your IND 11557 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA. If applicable under 21 CFR 601.70, you should include a status summary of each commitment in your annual progress

report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at

<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Erik S. Laughner, M.S., RAC (US), Senior Regulatory Health Project Manager, at (301) 796-1393.

Sincerely,

/Richard Pazdur/
Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Carton and Container Labeling