CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125327Orig1s000

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Therapeutic Proteins

Amendment to the Quality TL Executive Summary dated 12/23/2011

From: **Emanuela Lacana, PhD** Emanuela Lacana 1/13/2012
Division of Therapeutic proteins (DTP)

Through: **Barry Cherney, PhD** Barry Cherney 1-13-2012
Deputy Division Director, DTP
Amy Rosenberg, MD
Division Director, DTP Amy Rosenberg 1-13-2012

BLA Number: **125327**
Product: **Glucarpidase (VORAXAZE)**
Sponsor: **BTG International**

Date of Review: **1/11/2012**

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

On 12/23/2011, after discussion with DTP upper management, concerns were raised regarding the presence of detectable amounts of (b) (4) in all recently manufactured lots. (b) (4) (b) (4) (b) (4) While it is unlikely that the presence of (b) (4) will result in a serious safety risk, DTP requested advice on the toxicology of (b) (4) from the Pharm/Tox group. A consult request was provided on 12/22/2011 through Erik Laughner. At that time, given that at least one lot containing detectable levels of (b) (4) had been used clinically, and that no adverse events appear to pertain to its use, DTP recommended approval pending a satisfactory assessment from the Pharm/Tox group.

While the oral toxicity dose evaluated by the antifoam manufacturer and documented by the sponsor is quite high, the Pharm/Tox group was unable to retrieve intravenous toxicity data on (b) (4)

The following points resulted from a discussion with the review team following the findings of the Pharm/Tox group:

1. While a lot with detectable amounts of (b) (4) was used in the treatment IND, the safety data provided were acquired under a treatment IND and not as a result of a well controlled study therefore the information is not as rigorous as one expects.

2. The release test for (b) (4) was implemented later in product development, and the lots manufactured prior to implementation of the assay, which include the lot used in the pivotal clinical trial, were not tested at release. In fact, these older lots were tested well after the manufacturing expiration date. The pivotal clinical trial lot was at least five years old at the time of testing and had no detectable amounts of (b) (4) Since the manufacturing process has not changed throughout product development, it is likely that the (b) (4) might have been present at the time of manufacturing and subsequently degraded during storage. However, this is an extrapolation based on the consistency of the quality of the product manufactured over the years.

3. The Pharm/Tox group proposed a single dose toxicity study to address potential safety issues with (b) (4) This was subsequently submitted as PMC to the firm.

4. DTP proposed to revise the specification for (b) (4) to (b) (4) to conform to the quality characteristics of the pivotal clinical trial material. DTP had already proposed a PMC to increase the sensitivity of the assay and proposed to further modify this PMC to specify that the proposed acceptance criteria should be based on appropriate non clinical data.

5. The firm agreed with the non clinical PMC (to be completed by August 2012) and with the CMC PMC (to increase assay sensitivity and provide a specification with a justification based also on appropriate non clinical data, to be completed by June 2013). The firm also agreed to revise the (b) (4) specification to "(b) (4)" and to include in the system suitability a concentration of (b) (4) at the limit of detection of the assay.

Based on the above review team discussion and agreements with the sponsor, DTP recommends approval of BLA 125327.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Therapeutic Proteins

The Quality Team Leader's Executive Summary

From:	**Emanuela Lacana, PhD** **Division of Therapeutic proteins (DTP)**
Through:	**Barry Cherney, PhD** **Deputy Division Director, DTP** **Amy Rosenberg, MD** **Division Director, DTP**
BLA Number:	**125327**
Product:	**Glucarpidase (VORAXAZE)**
Sponsor:	**BTG International**
Date of Review:	**12/20/2011**
Due Date of Memo:	**12/24/2011**

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

As of 12/23/2011, The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of BLA125327 for glucarpidase (VORAXAZE) manufactured by BTG International. The data submitted in this application are adequate to support the conclusion that the manufacture of glucarpidase is well controlled, and leads to a product that is pure and potent. It is recommended that this product be approved for human use (under conditions specified in the package insert).

However, after discussion with DTP upper management, concerns were raised regarding the presence of detectable amounts of (b) (4) (b) (4) While it is unlikely that the presence of (b) (4) will result in serious safety risk, DTP requested advice on the the toxicology of from the Pharm/Tox group, A consult request was provided on 12/22/2011 through Erik Laughner. Given that at least one lot containing detectable levels of (b) (4) has been used clinically, and that no adverse events appear to pertain to its use, it is doubtful that our recommendation for approval will change.

An amendment to this review will be written after input is received from the Pharm/Tox group.

II. APPROVAL LETTER INFORMATION

Under this license, you are approved to manufacture Voraxaze (glucarpidase) drug substance at Eurogentec S.A, Liege Science Park, Seraign, Belgium. The final formulated product will be manufactured, filled, and packaged at Cangene Biopharma Inc (CBI) in Baltimore, MD, USA. 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 Voraxaze (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 (b) (4)
The dating period for your drug substance shall be (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 21CFR 601.12.

You currently are not required to submit samples of future lots of Voraxaze (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.

III. POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS

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

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

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

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

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

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

7) BTG commits to provide information on the functional tests performed for the qualification of new batches of critical complex raw materials of biological origin [redacted] (b) (4) used in the fermentation process. The functional tests should provide quantitative evaluation of the growth promoting properties of complex raw materials. The study report will be submitted to the Agency. Final report submitted [Insert date]

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

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

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

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

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

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

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

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

16) BTG commits to develop and implement a more sensitive assay for the measurement of (b) (4) in drug substance. The results of the assay development and validation, and proposed specifications will be submitted to the Agency. Final report submitted [Insert date]

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

IV. LIST OF DEFICIENCIES TO BE COMMUNICATED

Not Applicable.

V. EXECUTIVE SUMMARY

A. Description of PRODUCT

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

Environmental Assessment Or Claim Of Categorical Exclusion

The sponsor provided a claim for categorical exclusion from filing an environmental assessment under 21CFR 25.31 (c). Glucarpidase is a recombinant protein, naturally present in the environment because it is expressed by bacteria of the *Pseudomonas* (b) (4) (b) (4) (b) (4) Most of the protein will be administered to patients and will be metabolized. Thus, manufacturing will not significantly alter the distribution of the substance. Based on the above, the Division of Therapeutic proteins recommend that categorical exclusion from environmental assessment be granted.

B. Clinical Trial Information

Voraxaze is indicated for the treatment of acute methotrexate toxicity in renal-impaired patients and is intended as a single dose treatment. Voraxaze provides an alternate non-renal pathway for methotrexate elimination in patients with renal dysfunction during high-dose methotrexate treatment. Clinical studies have demonstrated that methotrexate is rapidly cleared from the bloodstream, within 15 minutes of administration, and reduction of methotrexate is sustained over an 8 days period. Voraxaze should be administered in a single intravenous injection of 50 Units per /kg. 476 patients have received at least one dose of Voraxaze, and a small

percentage has received two during the clinical studies. The safety evaluation is based on 290 patients. The 476 patients treated were divided in subgroups for the purpose of the efficacy analysis. Pooling each subgroup, about 65% achieved a Clinically Important Reduction (CIR) in methotrexate blood levels. Twenty-two patients experienced adverse events, of which the most common (incidence > 1%) were paraesthesias, flushing, nausea and/or vomiting, hypotension and headache. The link between the product's biological activities and these adverse events is unclear. The clinical studies provided support the safety and efficacy of Voraxaze.

C. Stability

Glucarpidase drug substance is stored (b) (4) The proposed shelf-life is (b) (4) albeit the sponsor has accumulated up to 12 months data on one lot. Additionally, lot M-CG2-P10 was filled with drug substance that was 9 months old. The stability time point reached for this lot is (b) (4) and the sponsor will continue to monitor stability up to 36 months, as per stability protocol. Drug substance has been filled into drug product at various ages, from two to nine months, averaging 5 months. The sponsor is not proposing to extend the shelf life of drug substance past (b) (4) The data provided by the sponsor is sufficient and there is no need for additional cumulative stability studies. The proposed shelf-life for drug product is 30 months at 2-8°C from the time of (b) (4). The sponsor submitted supportive data on development lots for up to 60 months. Stability of the drug product was assessed by robust set of analytical tools that monitored major degradation products observed under a variety of stress conditions. The drug product, a lyophilized formulation, is remarkably stable at the proposed storage conditions, with only a limited increase in moisture content that plateaus at (b) (4) Under accelerated conditions, the pyroglucarpidase peak decreases and the glucarpidase peak increases for the first three months (b) (4) At the six month time point, there is an increase in the RP-HPLC impurity profile (b) (4) and a decrease in the glucarpidase peak, while the pyroglucarpidase peak is unaffected. Specific activity, K_m and k_{cat} are unchanged, suggesting that, although the sponsor has not characterized the impurities, there is no impact on the potency of the product. No other change is detected with any of the other assays. (b) (4) product degradation was detected by most stability assays. The only change observed in the drug substance under the recommended storage conditions over the shelf life is a shift in the proportion (b) (4) detected by CEX-HPLC and iCE that corresponds to an increase in pyroglucarpidase. These assays were implemented at the time the process validation was executed and the firm has accumulated data on four lots of material. As of December 2011, two of these lots have reached the stability time points of 30 months. BTG also provided stability data up to 60 months for the clinical lots. The stability testing program was not as extensive as the program developed for the most recent lots, but the data provided suggested that the product is very stable and supports the requested expiry of 30 months.

The sponsor conducted an extensive in-use stability study. In summary, samples of drug product aged 0, 3, 6 and 12 months stored at 2-8°C, or aged 0, 3 and 6 months stored at 25°C/60%RH, were reconstituted in WFI and stability was evaluated for up to 48 hours at ambient temperature. The sponsor employed the entire battery of stability assays. No product

degradation was observed on any of the samples tested. Although the stability profile of the product is adequate, the sponsor did not perform microbial tests during the in-use study to determine the ability of microbes to grow in the finished drug product formulation, therefore the package insert recommends use within 4 hrs of reconstitution.
BTG conducted a photostability study using recommended ICH conditions as well as stronger (3X and 5X ICH) lighting conditions. The product degraded under 3X and 5X ICH only. Under recommended ICH conditions, the product was stable and a recommendation to protect from light was not included in the package insert.
No agitation studies were performed. However, considering that the drug substance is stored and shipped frozen and the drug product is stored and shipped lyophilized, agitation is highly unlikely to negatively affect product quality in terms of protein aggregation.
The forced degradation studies conducted by the sponsor are also very extensive. Glucarpidase was subjected to stress induced by acid and base treatment, heat, agitation, light, freeze-thaw, oxidation, pyroglutamation, deamidation and Maillard reaction (lactosylation). For the drug product, additional conditions of heat and high humidity were also explored. Some degree of degradation was observed under all conditions. Oxidation, acid and base hydrolysis, heat/humidity combination and Maillard reaction caused the most rapid and extensive degradation, with changes detected by all methods employed. Pyroglutamation induced by acetic acid treatment, light and heat treatment induced degradation only after prolonged treatment conditions. Deamidation induced by incubation with 0.1M TRIS, and freeze-thaw caused minimal changes in the product. Only a modest reduction in the main SEC-HPLC peak was detected, after the sample was agitated for 9 days.
In conclusion, the assays that are used to monitor the stability of the product are suitable to detect production degradation induced by a variety of stress conditions.
The small reduction in the SEC-HPLC main peak could be due to the fact that large aggregates could not be adequately recovered from the column. In fact, the sponsor has not performed studies aimed at demonstrating that there is a high recovery of the protein loaded onto the analytical SEC-HPLC column. Furthermore, analytical ultracentrifugation has not been conducted on aggregated samples, to cross-validate SEC-HPLC. **These issues will be addressed by a PMC.**

D. Complexity

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

Glucarpidase is a carboxypeptidase that hydrolyzes the carboxy terminal glutamate residue from folic acid and its analogues including methotrexate (MTX). It cleaves the MTX molecule into two inactive metabolites, 4-deoxy-4-amino-N10-methylpteroic acid (DAMPA) and

glutamate. The affinity Constant (Km) for glucarpidase with MTX is approximately (b) (4) the catalytic Rate (kcat) is approximately (b) (4)

BTG provided extensive drug substance characterization data. BTG evaluated primary and secondary structure, charge profile, purity and impurities profiles and potency of glucarpidase.

Primary Structure: The primary structure of Glucarpidase has been analyzed using the following test methods:

- Intact molecular weight analysis by LC/MS
- N-terminal sequencing
- C-terminal sequencing
- Amino acid composition
- Experimental extinction coefficient
- RP-HPLC-MS for Tryptic peptide mapping
- RP-HPLC-MS for Glu-C peptide mapping

Analysis of the intact molecular weight, N and C-terminal sequencing and peptide mapping followed by Mass Spec sequencing has provided >98% protein sequence coverage. Signatory peptides are identified in each of the peptide mapping methods (8 for the tryptic digest and 6 for the Glu-C digest) and are used in the system suitability for comparison to the reference standard. BTG uses the peptide mappings mainly as identity methods. Albeit BTG claims these methods for purity as well, there are no quantitative acceptance criteria. Peptide mapping is a useful orthogonal technique for the assessment of purity and BTG should avail itself of these methods for the purpose of evaluating purity and impurities. **This issue can be addressed by PMC.**

Secondary and Tertiary Structure: The secondary and tertiary structure was analyzed solely by circular dichroism (CD). The sponsor provided circular dichroism profiles. The method is not quantitative and only provides an estimate of the proportion of higher order structures present in the protein.

Purity and characterization of aggregates: The purity of Glucarpidase as well as the aggregation profile was evaluated using the following methods:

- SDS-PAGE (reduced)
- RP-HPLC
- SEC-HPLC
- SEC-MALLS
- SV-AUC

(b) (4)

(b) (4) In glucarpidase, the N-terminal glutamic acid cyclizes and converts to pyroglutamate. The two

(b) (4)

BTG detected only a very limited amount of aggregated product (less than 1%) by SEC-HPLC. SEC in conjunction with MALLS and Refractive Index detectors detected the presence of small amounts of glucarpidase in a tetrameric form. However, the technique is not quantitative and did not provide information on the relative amounts of tetramer. Analytical ultracentrifugation evaluations also confirm that a small percentage of glucarpidase is present as tetramer (about 4%). No higher order aggregates were detected either by SEC-MALLS or analytical ultracentrifugation. The results were similar and in the same order of magnitude obtained with SEC-HPLC (about 1%for SEC-HPLC and about 4% for AUC). However, BTG did not analyze samples stressed to induce aggregation to demonstrate and cross-validate the routine use of SEC-HPLC for measurement of aggregates. **This issue will be addressed as PMC.**

Charge profile: The charged isoforms of glucarpidase were analyzed by the following test methods:

- Isoelectric Focusing (IEF)
- CEX-HPLC
- Imaging capillary electrophoresis (iCE)

IEF separation resolved three to five bands on Coomassie stained gel that run between the pI of 7.4 and 6. BTG maintains that they were unable to validate the method from a quantitative perspective; therefore, it will only be used to determine identity. IEF is not an identity method, but the sponsor uses it in combination with the two peptide mappings, which are adequate to determine identity. Considering that the sponsor is implementing CEX-HPLC and iCE, the fact that IEF is not used as a quantitative method is not an issue.

(b) (4)

(b) (4)

Potency: The potency was evaluated by the following test methods.

- Enzyme Activity
- Enzyme kinetics

Both enzyme activity and kinetic parameters are measured using the same assay, which consists of measuring the loss of methotrexate at 320 nm. Both the enzyme activity measured in Units/ml and the specific activity (measure in Units/mg of protein) were very consistent throughout the history of product, ranging from (b) (4) for specific activity and (b) (4) (b) (4) for the activity measured in Units/ml. The kinetic parameters K_m and k_{cat} showed a higher degree of variability, with about (b) (4) in K_m. This degree of variability is common for this type of measurement, where the values are extrapolated using linear regression analysis.

Release and stability specifications: The table below summarizes the release and stability specifications for the drug substance and the drug product. Based on the results of the characterization and forced degradation and stability studies, BTG established release and stability specifications, summarized in the table below. The table also reports the results of release testing conducted on lots used in clinical trials. (b) (4) For ease of review, although drug product has different naming and numbering convention, in the table I assigned the same name to drug substance and drug product.
The exact names are as follows:

Drug substance	(b) (4)
M-CG2-P01	
M-CG2-P03	
M-CG2-P10	

The first two lots have both been used in the pivotal clinical trial (PR001-CLN006), as well as in an open label treatment protocol that is currently ongoing (PR001-CLN016). The third lot has been introduced in the open label treatment protocol only, as of March 2011.
Unless otherwise indicated, release and stability specifications are the same.

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VI. SIGNATURE BLOCK (BLA ONLY)

Name and Title	Signature and Date
Amy Rosenberg, MD, Director Division of Therapeutic Proteins Barry Cherney, Ph.D Deputy Director Division of Therapeutic Proteins	Amy Rosenberg 12-23-11 Amy Rosenberg for Barry Barry 12-23-11
Emanuela Lacana, Ph.D Associate Laboratory Chief, Laboratory of Chemistry, Division of Therapeutic Proteins	Emanuela Lacana 12/23/2011

BLA 125327

Glucarpidase

BTG International

Division of Therapeutic Proteins

Name and Title
Emanuela Lacana, Ph.D

Signature and Date
Emanuela Lacana Dec 19, 2011

Team Leader, Associate Laboratory Chief,
Laboratory of Chemistry,
Division of Therapeutic Proteins
Office Of Biotechnology Products
CDER

Akhilesh K. Nagaich, Ph.D — Akagaich Dec 19, 2011

Howard Anderson, Ph.D — Howard Anderson Dec 19, 2011

Nikolay Spiridonov, Ph.D — Nikolay Spiridonov. Dec. 19, 2011.

Primary Reviewer (s)
Division of Therapeutic Proteins
Office Of Biotechnology Products
CDER

OBP CMC Review Data Sheet

1. **BLA#:** 125327

2. **REVIEW DATE:** December 12, 2011

3. **PRIMARY REVIEW TEAM:**
Medical Officer:
Pharm/Tox:
Product Quality Team:
Akhilesh K. Nagaich, Ph.D, (Reviewed drug substance section except for manufacture, container closure and adventitious agents)
Nikolay Spiridonov, Ph.D (Reviewed drug substance manufacture, drug substance container closure, drug substance shipping validation and adventitious agents)
Howard Anderson, Ph.D, (Reviewed drug product and reference standard)

BMAB or Facilities: Mary Farbman and Lakshmi Narasimhan
Clinical Pharmacology: Lillian Zhang
Pharm/Tox: Stacey Ricci
Statistics: None
OBP Labeling: Kimberly Rains
RPM: Erik Laughner

4. **MAJOR GRMP DEADLINES**
Filing Meeting: September 8, 2011
Mid-Cycle Meeting: October 31, 2011
Wrap-Up Meeting: December 20, 2011
Primary Review Due: December 20, 2011
Secondary Review Due: December 24, 2011

CDTL Memo Due:
PDUFA Action Date:

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
Information request	8/12/2011
Information request	11/4/2011
Information request	12/7/2011
Information request	12/12/2011

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
BLA125327/0004	9/29/2010	Yes

BLA125327/0006	6/30/2011	Yes
BLA125327/0009	9/16/2011	Yes
BLA125327/0015	11/30/2011	Yes
BLA125327/0016	12/7/2011	Yes
BLA125327/0017	12/12/2011	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary Name: Voraxaze
   b. Trade Name:
   c. Non-Proprietary/USAN: Glucarpidase
   d. CAS name:
   e. Common name:
   f. INN Name: Glucarpidase
   g. Compendial Name:
   h. OBP systematic name:
   i. Other Names: Carboxypeptidase G2, CPG2

8. **PHARMACOLOGICAL CATEGORY:** carboxypeptidase
9. **DOSAGE FORM:** Lyophilized cake
10. **STRENGTH/POTENCY:** 1,000U/vial
11. **ROUTE OF ADMINISTRATION:** intravenous

12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
	(b) (4)	(b) (4)		Acceptable - Sufficient information in application
				Acceptable - Sufficient information in application

13. **INSPECTIONAL ACTIVITIES**

DTP (Ralph Bernstein) participated in inspectional activities conducted at the drug substance manufacturing site (Eurogentec, Seraign, Belgium) with Mary Farbman from BMAB. Deficiencies were identified and the firm received a 483 form with 9 citations. For detailed analysis of the inspection, refer to the Establishment Inspection Report. The drug product (fill and finish) facility inspection was waved, and other facilities supporting the application were inspected by the field.

14. **CONSULTS REQUESTED BY OBP**

NONE

15. **QUALITY BY DESIGN ELEMENTS**

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
	Design of Experiments
	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. PRECEDENTS

NONE

17. ADMINISTRATIVE

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PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

BLA/NDA Number:	Applicant:	Stamp Date:
125327	BTG International, Inc	July 18, 2011
Established/Proper Name: Glucarpidase/Voraxaze	**BLA/NDA Type:** BLA, 21 CFR Part 601	

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

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y✓ N	
Form 356h completed including list of all establishment sites and their registration numbers	Y ✓ N Y ✓ N	Eurogentec registration (in-process)
Comprehensive Table of Contents	Y✓ N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y✓ N	
Labeling: ❑ PI –non-annotated ❑ PI –annotated ❑ PI (electronic) ❑ Medication Guide ❑ Patient Insert ❑ package and container ❑ diluent ❑ other components ❑ established name (e.g. USAN) ❑ proprietary name (for review)	Y ✓ N Y ✓ N Y ✓ N Y ✓ N Y N Y N Y ✓ N Y N Y N Y ✓ N Y ✓ N	 Not applicable Not applicable Not applicable, no diluent is used No other components

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y✓ N	
❑ legible	Y ✓ N	
❑ English (or translated into English)	Y ✓ N	
❑ compatible file formats	Y ✓ N	
❑ navigable hyper-links	Y ✓ N	
❑ interpretable data tabulations (line listings) & graphical displays	Y ✓ N	
❑ summary reports reference the location of individual data and records	Y ✓ N	
❑ all electronic submission components usable (e.g. conforms to published guidance)	Y ✓ N	
Companion application received if a shared or divided manufacturing arrangement	Y N	Not applicable

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y ✓ N	
Introduction to the summary documents (1 page) [2.2]	Y ✓ N	
Quality overall summary [2.3]	Y✓ N	
❑ Drug Substance	Y✓ N	
❑ Drug Product	Y✓ N	
❑ Facilities and Equipment	Y✓ N	
❑ Adventitious Agents Safety Evaluation	Y✓ N	
❑ Novel Excipients	Y✓ N	
❑ Executed Batch Records	Y✓ N	
❑ Method Validation Package	Y✓ N	
❑ Comparability Protocols	Y N	None submitted

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y✓ N	
Drug Substance [3.2.S]		
❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties	Y✓ N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y✓ N	
❑ description of manufacturing process and process control o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping	Y✓ N	
❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing	Y✓ N	
❑ control of critical steps and intermediates o justification of specifications o stability	Y✓ N	

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CTD Module 3 Contents	Present?	If not, justification, action & status
❑ process validation (prospective plan, results, analysis, and conclusions)	Y✓ N	
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y✓ N	
❑ characterization of drug substance	Y✓ N	
❑ control of drug substance		
o specifications	Y✓ N	
o justification of specs.	Y✓ N	
o analytical procedures		
o analytical method validation	Y✓ N	
o batch analyses	Y✓ N	
❑ reference standards	Y✓ N	
❑ container closure system		
❑ stability	Y✓ N	
❑ summary	Y✓ N	
❑ post-approval protocol and commitment	Y✓ N	
❑ pre-approval		
o protocol		
o results		
o method validation		
Drug Product [3.2.P] [Dosage Form]	Y✓ N	
❑ description and composition	Y✓ N	
❑ pharmaceutical development	Y✓ N	
o preservative effectiveness	Y✓ N	
o container-closure integrity	Y✓ N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y✓ N	
❑ batch formula	Y✓ N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y✓ N	
❑ controls of critical steps and intermediates	Y✓ N	
❑ process validation including aseptic processing & sterility assurance:	Y✓ N	
o Filter validation	Y N✓	Available on Request (VOR/ESR/005, VOR/ESR/006,VOR/ESR/007 and VOR/ESR,009)

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CTD Module 3 Contents	Present?	If not, justification, action & status
○ Component, container, closure depyrogenation and sterilization validation	Y✓ N	
○ Validation of aseptic processing (media simulations)	Y✓ N	
○ Environmental Monitoring Program	Y✓ N	
○ Lyophilizer validation	Y✓ N	
○ Other needed validation data (hold times)		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y✓ N	
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y✓ N	
❑ reference standards or materials	Y✓ N	
❑ container closure system [3.2.P.7]	Y✓ N	
○ specifications (vial, elastomer, drawings)		
○ availability of DMF & LOAs		
○ administration device(s)		
❑ stability	Y✓ N	
❑ summary		
❑ post-approval protocol and commitment		
❑ pre-approval		
○ protocol		
○ results		
○ method validation		
Diluent (vials or filled syringes) [3.2P']	Y N	No diluent is supplied with the product. Not applicable
❑ description and composition of diluent	Y N	
❑ pharmaceutical development	Y N	
○ preservative effectiveness	Y N	
○ container-closure integrity	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	

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CTD Module 3 Contents	Present?	If not, justification, action & status
❑ batch formula	Y✓ N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y✓ N	
❑ controls of critical steps and intermediates	Y✓ N	
❑ process validation including aseptic processing & sterility assurance:		
o Filter validation	Y N✓	
o Component, container, closure depyrogenation and sterilization validation	Y✓ N	
o Validation of aseptic processing (media simulations)	Y N	
o Environmental Monitoring Program	Y✓ N	
o Lyophilizer sterilization validation	Y✓ N	
o Other needed validation data (hold times)		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y✓ N Y✓ N	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y✓ N	
❑ reference standards	Y✓ N	
❑ container closure system	Y✓ N	
o specifications (vial, elastomer, drawings)		
o availability of DMF & LOAs		
❑ stability		
❑ summary	Y✓ N	
❑ post-approval protocol and commitment		
❑ pre-approval		
o protocol		
o results		
Other components to be marketed (full		

CTD Module 3 Contents	Present?	If not, justification, action & status
description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	 Y N✓ Y N✓	
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	Y✓ N (facilities and equipment) Y✓ N (adventitious agents) Y N✓ (novel excipients)	No novel excipients used
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y✓ N Y✓ N Y N✓	 None submitted
Literature references and copies [3.3]	Y✓ N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y✓ N	
Includes data demonstrating consistency of manufacture	Y✓ N	
Includes complete description of product	Y✓ N	

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Examples of Filing Issues	Yes?	If not, justification, action & status
lots and manufacturing process utilized for clinical studies		
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y✓ N	
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y✓ N	
Certification that all facilities are ready for inspection	Y✓ N	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y✓ N	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility	Y✓ N Y✓ N Y N✓ Y✓ N	 Product manufactured in bacteria, mycoplasma test not applicable
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y✓ N	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y✓ N	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y✓ N	

PRODUCT QUALITY (Biotechnology)
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IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? (Yes) No

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

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

A Hagaich — 08/09/2011
Product Quality Reviewer(s) — Date

Emanuela Lacana — 08/09/2011
Branch Chief/Team Leader/Supervisor — Date

Barry Chen — 8-10-11
Division Director — Date