CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125327Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125327 | Supplement Number: _____ | NDA Supplement Type (e.g. SE5): _____

Division Name: DBOP | PDUFA Goal Date: 01/17/2012 | Stamp Date: 7/18/2011

Proprietary Name: VORAXAZE

Established/Generic Name: glucarpidase

Dosage Form: powder for injection

Applicant/Sponsor: BTG International Inc. (formerly Protherics Inc)

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): ____
(Attach a completed Pediatric Page for each indication in current application.)

Indication: for the (b) (4) reduction of toxic methotrexate concentrations due to impaired renal function.

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☒ indication(s); ☒ dosage form; ☒ dosing regimen; or ☒ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

* ***Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit*	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients

in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

. ediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

dditional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is ppropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other ediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product e sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

ediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

3. DEBARMENT CERTIFICATION

BTG International Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Carol Clark-Evans
Vice President, Regulatory Affairs

2 May 2011
Date

Debarment Certification Statement

The National Cancer Institute (NCI) hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with the product Voraxaze™ (Glucarpidase), formerly known as Carboxypeptidase-G2 or CPG2.

Authorized representative of the NCI:

Sherry Singer Ansher
SAFE-BIOPHARMA, Location:
Date: 2011.03-08 14:22:23
-0500
[1] Facsimile of Original Digital Signature

Sherry S. Ansher, Ph.D.

Associate Chief

Agreement Coordination Group

Regulatory Affairs Branch

Cancer Therapy Evaluation Program

Division of Cancer Treatment and Diagnosis

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # BLA # 125327	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: VORAXAZE Established/Proper Name: glucarpidase Dosage Form: lyophilized powder for injection		Applicant: BTG International Inc. Agent for Applicant (if applicable):
RPM: Erik Laughner		Division: Division of Oncology Products 2

NDAs:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 01/17/12	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics[2]	

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

☒ Fast Track
☒ Rolling Review
☒ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates 01/03/12
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No
Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other ASCO BURST, OCP BURST

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[3]	YES
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval 01/17/12
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	01/17/12
• Original applicant-proposed labeling	06/30/11
• Example of class labeling, if applicable	N/A

[3] Fill in blanks with dates of reviews, letters, etc.

Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	N/A
• Original applicant-proposed labeling	N/A
• Example of class labeling, if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	01/10/12
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	10/11/11 LTR 10/11/11 Review
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 09/09/11 ☒ DMEPA 10/04/11 ☐ DRISK ☒ DDMAC 12/01/11 ☐ SEALD ☐ CSS ☒ Other reviews OBP 01/03/12 MHT 10/25/11
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	09/08/11 Filing Mtg/RPM Checklist ☐ Not a (b)(2) ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC N/A Pediatric Page just provided If PeRC review not necessary, explain: ORPHAN • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	01/17/12 labeling email (final) 01/17/12 PMC_PMR email (final) 01/12/12 labeling email 01/10/12 PMC_PMR email 01/09/12 labeling email 01/05/12 CMC tcon 01/05/12 PMR tcon 01/03/12 PMC_PMR tcon 12/27/11 nonclinical IR email 12/23/11 labeling advice email 12/23/11 Immuno Advice email 12/22/11 PMC email 12/20/11 PMC_PMR email 12/19/11 CMC tcon 12/16/11 CMC IR email 12/14/11 CMC Advice email 12/13/11 container labeling email 12/13/11 labeling email 12/13/11 Clinical IR email 12/12/11 labeling email 12/12/11 CMC IR email 12/12/11 Clinical IR email 12/09/11 labeling IR email 12/08/11 labeling advice email 12/07/11 CMC IR email 12/06/11 labeling email 12/05/11 CMC IR email 12/02/11 CMC IR email 12/01/11 Clinical IR email 11/30/11 Clinical IR email 11/30/11 CMC IR email 11/23/11 Immuno advice email 11/21/11 CMC IR email 11/17/11 CMC IR email #2 11/17/11 CMC IR email 11/04/11 CMC IR email 10/14/11 CMC IR email 10/06/11 CMC advice email 10/04/11 CMC IR email 09/22/11 Clin Pharm IR email 09/20/11 Clin Pharm IR email 09/16/11 Filing Letter 09/02/11 Clin Pharm IR email 08/17/11 CMC IR email 08/17/11 CMC IR email #2 08/12/11 CMC IR email 07/27/11 Ack Letter 07/26/11 Nonclnical IR email 07/20/11 Fac. Inspection IR email 05/13/11 tcon (CMC) 03/30/10 tcon 03/30/10 advice email 03/17/10 tcon

	02/05/10 IR Letter 12/11/08 Ack Letter (rolling unit)
❖ Internal memoranda, telecons, etc.	12/19/11 Wrap-up Mtg 12/1/11 Label Wrap up Mtg 11/14/11 Fourth Labeling Mtg 11/08/11 Third Labeling Mtg 11/04/11 Second Labeling Mtg 10/31/11 Midcycle Mtg 10/28/11 First Labeling Mtg 10/07/11 Monthly Team Mtg 07/21/11 Planning Mtg
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 04/28/06 (issued minutes 05/24/06)
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	06/04/07 Type C (issued minutes 07/03/07)
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 01/17/12
Division Director Summary Review *(indicate date for each review)*	☐ None 01/12/12
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 01/09/12
PMR/PMC Development Templates *(indicate total number)*	☐ None 26
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	TL is CDTL (see CDTL review)
• Clinical review(s) *(indicate date for each review)*	12/19/11 (with TL concurrence) 08/11/11 Filing Checklist
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See page 9 of 12/19/11 Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None 12/19/11
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable

[5] Filing reviews should be filed with the discipline reviews.

❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None co-signed with 12/21/11 review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 12/21/11(co-signed with TL) 09/08/11 Filing Checklist
DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None 10/31/11
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None 01/09/12
• Supervisory Review(s) *(indicate date for each review)*	☐ None 12/22/11
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 12/21/11 (co-signed by Supervisor) 09/08/11 Filing Checklist
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None DTP Division Director concurrence in TL review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 01/13/12 Addendum (with DTP Division Director concurrence) 12/23/11
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 12/19/11 (co-signed by TL) 08/10/11 Filing Checklist
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☒ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 01/05/12 Drug Substance (co-signed by Branch Chief) 12/29/11 Drug Product (co-signed by Branch Chief) 09/07/11 Filing Checklist
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None 01/06/12 nonclinical consult review
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	see page 5 of 12/23/11 team leader review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☒ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: 01/13/12 Acceptable 12/22/11 Request ☒ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 01/17/12 Esc 01/19/12

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Final FDA Package Insert Draft

---

Telecon Memo: Carol Clark-Evans at BTG was advised after receipt of this label via the email below to be sure and "bold" the contents main section headings of **FULL PRESCRIBING INFORMATION:CONTENTS**.

Email:

From: Laughner, Erik
Sent: Tuesday, January 17, 2012 1:40 PM
To: 'Carol Clark-Evans'
Subject: Minor Final Edits; Package Insert STN 125327

Carol,

Please see final minor package insert changes/comments. Please provide a final clean version for the action.

Thanks,

Erik

STN 125327 FDA Final Draft 011...

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 01/17/12 01/17/12

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); FINAL language/milestones for PMRs_PMCs

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From: Laughner, Erik
Sent: Tuesday, January 17, 2012 9:11 AM
To: 'Carol Clark-Evans'
Subject: Final language/list of PMR/PMCs for STN 125327
Importance: High

Carol,

Please see final language/list of PMR/PMCs for STN 125327. Please review and confirm agreement with all milestone dates.

If you can provide back to me by 11AM I would appreciate.

Erik

011712 FINAL
NGUAGE PMC_PMR.

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

FINAL PMR/PMC LANGUAGE/MILESTONES STN 125327

PMRs

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

PMCs

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

4. To re-evaluate the mixing step for the thawed formulated drug substance [redacted] 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 sub visible particulates in the range of [redacted] 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) (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 XX 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, 2012tates 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) (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, 2012states 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) (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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 01/12/12 ESC 01/12/12

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); FDA proposed draft package insert labeling

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From: Laughner, Erik
Sent: Thursday, January 12, 2012 12:20 PM
To: 'Carol Clark-Evans'
Subject: STN 125327; 01/12/12 FDA Labeling Revision
Importance: High

STN 125327 FDA 011212 Label.do...

Hello Carol,

Please see FDA label in response to your most recent revision. Please review and perform final QC for spelling, PLR format, content, etc. If you can provide back by tomorrow morning, that would be ideal.

Please confirm receipt.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 01/10/12 ES 01/10/12

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); FDA revisions to select PMCs and PMRs; FDA additional PMC

From: Laughner, Erik
Sent: Tuesday, January 10, 2012 9:15 AM
To: 'Carol Clark-Evans'
Subject: STN 125327; FDA revisions to select PMC/PMRs and new PMC
Importance: High

Carol,

Please see the following attachment which contains several revised PMCs as well as revisions to the PMRs. In addition, a new PMC is proposed per our 01/05/12 tcon discussion.

We ask that you provide a response back by this afternoon.

Please confirm receipt.

Erik

FDA Revised
1C_PMR 011012.doc

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
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http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 01/09/12 ES 01/09/12

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); FDA proposed draft package insert labeling

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From: Laughner, Erik
Sent: Monday, January 09, 2012 5:18 PM
To: 'Carol Clark-Evans'
Subject: STN 125327; FDA Proposed Package Insert 01/0912 Red-Line
Importance: High

Carol,

Please see FDA proposed package insert. Please review and provide back a response label by Wednesday Noon ET. If there is any need for discussion, please let me know tomorrow.

Note: I turned off the "authorship" using the tools/options security tab function in word. When you send back, please provide with this function removed so that we may clearly see your edits (if any).

Please confirm receipt.

Thanks,

Erik

STN 125327 FDA revised red-lin...

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 01/05/12 ESC 01/05/12

From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Advice/Information Request; CMC

FDA Attendees:

Erik Laughner, RPM
Patricia Keegan, Director
Anne M. Pilaro, Pharm/Tox Supervisor
Stacey Ricci, Pharm/Tox Reviewer
Patricia Dinndorf, Medical Reviewer
Emanuela Lacana, Product Team Leader (DTP)
Barry Cherney, Deputy Director (DTP)

BTG Attendees:

Debbie Lloyd, Head of Quality and Technical Services
Sam Elcomb, Quality Manager
Chiron Howell, Process Development Lead
Zainab Bascal, Senior Manager of Non-clinical Development
Janet Rush, VP Clinical Development
Carol Clark-Evans, VP Regulatory Affairs

Discussion:

FDA informed BTG that the current lot release specification for [redacted] (b) (4) is not acceptable. There was insufficient information to qualify [redacted] (b) (4) as safe when given intravenously.

FDA recommended that BTG revise their release specification to [redacted] (b) (4) and update the analytical method by including, in the system suitability of the assay, concentrations of [redacted] (b) (4) at the limit of detection [redacted] (b) (4) to ensure the assay consistently detects this amount of [redacted] (b) (4) BTG could release a lot for commercial use provided the amount of [redacted] (b) (4) in the lot did not exceed the limit of detection [redacted] (b) (4)

In order to raise the release specification limit above the limit of detection, BTG would need to conduct a single-dose toxicology study with 14-days of follow-up to qualify the upper limit of

(b) (4) that is acceptable for intravenous use. The toxicology study design should include full histopathology and clinical pathology results. FDA suggested that BTG include dose groups that receive (b) (4) at the desired level for setting the proposed revised specification as well as at least one dose lower and possibly one dose level higher. FDA also advised BTG to include dose groups that receive these doses of (b) (4) added to Voraxaze to evaluate whether the presence of glucarpidase alters the safety (b) (4).

BTG asked FDA to confirm their understanding that if they did not wish to revise their current specification to "none detected" the toxicology data would be required for pre-approval review. FDA concurred.

FDA noted that given the short time remaining on the current review clock, should BTG decide to adjust the release specification and add the system suitability test to the analytical method, a formal amendment containing the revised specification limit and detection assay would need to be submitted to the BLA as soon as possible. BTG acknowledged their understanding.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 01/05/12 EEL 01/05/12

From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Advice; PMR for intrathecal route

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FDA Attendees:

Erik Laughner, RPM
Patricia Keegan, Director
Anne M. Pilaro, Pharm/Tox Supervisor
Stacey Ricci, Pharm/Tox Reviewer
Patricia Dinndorf, Medical Reviewer
John Leighton, Director (DHOT)

BTG Attendees:

Guenter Janhofer, Head of Development & Chief Medical Officer
Janet Rush, VP Clinical Development
Joanne Bedwell, VP Non-clinical Development
Carol Clark-Evans, VP Regulatory Affairs
Russell Hagan, Voraxaze Project Leader

Discussion:

BTG requested a tcon to discuss FDA's rationale behind the PMR to investigate the intrathecal use of Vorxaze following inadvertent methotrexate overdose. BTG noted that only two patients in the last 5 years had been given intrathecal Voraxaze under emergency IND and inquired why FDA was requiring a study for an "ultra-orphan indication." FDA noted that the practicing oncology community believes that emergency use of Voraxaze through the intrathecal route is useful. The only way for FDA to evaluate the safety and efficacy of intrathecal Voraxaze administration is by conducting an animal study, and following the provisions of the Animal Rule regulations for approval. FDA clarified that the clinical data that BTG previously provided was not sufficient to support the safety and efficacy of intrathecal Voraxaze in this setting, and was confounded on multiple levels.

(b) (4)

(b) (4)

was likely. BTG stated they felt that expense seemed disproportionate to the likely

number of cases of intrathecal methotrexate overdose. (b) (4) [redacted] (b) (4) [redacted] (b) (4) [redacted] the only way to evaluate the safety and efficacy of intrathecal Voraxaze use following intrathecal methotrexate overdose was through the provisions of the Animal Rule and that FDAAA regulations allow a PMR to be required. FDA advised BTG to carefully consider their proposed timeframes (milestones) for completing the PMR to allow for efforts to obtain financing and complete the study. FDA noted that BTG should demonstrate good faith efforts toward this development program, and that this topic could be discussed at a future ODAC if needed.

FDA clarified that while it might be possible to use a non-primate model other than the monkey (such as marmoset), the physiology of an appropriate animal model should have a vertical spine with similar CSF flow kinetics as humans, to appropriately represent the distribution of both methotrexate and Voraxaze. Using an animal model with a horizontal spinal configuration would not effectively model the human situation. In addition, FDA clarified that the endpoint for the pivotal study must be reflective of clinical safety and efficacy, as per the Animal Rule.

(b) (4) [redacted] (b) (4) [redacted] FDA acknowledged and agreed that BTG could come back to FDA after completing their pilot study to discuss the findings prior to starting the pivotal study. However, both PMRs are still needed, and BTG must provide milestone dates. BTG agreed to provide the revised PMR language within 24hrs for FDA review.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 01/03/11 01/03/11

From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Advice; PMC and PMR

Carol Clark-Evans called to provide an update on when they intended to respond to the PMC_PMR list provided by FDA. Carol noted that most of the PMCs had been reviewed, but that all PMCs had to be cost evaluated by the company. Carol proposed providing the final list back to FDA by Friday morning given the clearance process still under way at BTG. A few proposed edits to the language would be included. I indicated that there was very little time remaining on the current review clock and that the final list should be provided no later than Friday morning.

Carol also noted that BTG had reviewed the IND advice letter regarding the needed development plan intrathecal study under the Animal Rule as a PMR. Carol noted that FDA's advice had dramatically escalated the cost of this study and that BTG was not likely able to commit to a PMR given the predicted commercial revenues Voraxaze could generate with the current intented use. Carol also expressed concern on the ethics involved with doing such an animal study. Carol requested that FDA reconsider the need for a PMR and consider addressing any concerns on intrathecal use through revised/ restrictive labeling. Carol agreed to provide an email outlining this concern to me by the end of the day. I acknowledged and agreed to forward to the appropriate FDA staff.

Carol also noted that the outstanding nonclinical information request regarding the use of the [redacted] (b) (4) would be provided via email by the end of the day.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/27/11

From: Norma Griffin, RPM DOP2/OHOP /CDER/FDA 12/27/2011

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Nonclinical Information Request

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From: Griffin, Norma [Norma.Griffin@fda.hhs.gov]
Sent: Tuesday, December 27, 2011 1:54 PM
To: Carol Clark-Evans
Cc: Laughner, Erik
Subject: RE: STN 125327 (Voraxaze); Nonclinical Information Request

Carol,

The Reviewers have just asked, is it possible to respond by close of business January 3rd, 2012?

Thanks,

Norma S. Griffin
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Norma.Griffin@fda.hhs.gov
Telephone 301.796.4255

From: Carol Clark-Evans [mailto:Carol.Clark-Evans@btgplc.com]
Sent: Tuesday, December 27, 2011 2:39 PM
To: Griffin, Norma
Subject: Re: STN 125327 (Voraxaze); Nonclinical Information Request

Received, thanks.

Best wishes,
Carol

From: Griffin, Norma <Norma.Griffin@fda.hhs.gov>
To: Carol Clark-Evans
Cc: Laughner, Erik <Erik.Laughner@fda.hhs.gov>
Sent: Tue Dec 27 14:34:30 2011
Subject: RE: STN 125327 (Voraxaze); Nonclinical Information Request

Good Afternoon Carol,
I know you are out on holiday, but just in case you answer emails, please see the following request from our Nonclinical Reviewer:

Please send (as soon as possible), any animal safety information (including its intravenous use) you may have regarding (b) (4) (b) (4) used in the manufacture of Voraxaze.

Kindly respond to confirm receipt of this email.

Norma S. Griffin
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Norma.Griffin@fda.hhs.gov
Telephone 301.796.4255

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/23/11 ESC 12/23/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); FDA additional PMC

From: Laughner, Erik <Erik.Laughner@fda.hhs.gov>
To: Carol Clark-Evans
Sent: Fri Dec 23 14:18:44 2011
Subject: RE: STN 125327 (Voraxaze); 12/20/11 FDA Proposed PMC_PMR list; additional 12/23/11 PMC

Hello Carol,

One last CMC PMC to review (please collate with the others in your response document):

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]

Please confirm receipt.

Erik

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/23/11 ESL 12/23/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); FDA Revised Draft Carton Labeling

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From: Laughner, Erik
Sent: Friday, December 23, 2011 11:18 AM
To: 'Carol Clark-Evans'
Subject: STN 125327 (Voraxaze); Additional 12/23/11 FDA Carton Revisions

Hello Carol,

The revised vial label you provided in the 12/20/11 BLA amendment is acceptable.

However, we have the following further requested revisions to the carton labeling:

1. Relocate the 'Rx only' statement to the lower portion of the principal display panel. As currently presented, the 'Rx only' statement can distract from the route of administration statement.

2. Relocate the statement 'To be reconstituted with 1 mL 0.9% Sodium Chloride Injection USP. Diluent Not Included' to the side panel to minimize crowding of the label and to provide space for other revisions.

3. Add the statement 'Single use vial. Discard unused portion' to the principal display panel. This statement may replace the 'To be reconstituted with 1 mL.....', after relocating to the side panel.

Please revise the carton and provide both the "final draft" carton and vial labeling together as a formal amendment in early January.

Please confirm receipt.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/23/11 ESC 12/23/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Immuno (collection of samples)

From: Laughner, Erik
Sent: Friday, December 23, 2011 9:47 AM
To: 'Carol Clark-Evans'
Subject: RE: Proposal to Cease Collection of Voraxaze Antibody Samples

Hello Carol,

The immuno review team and the clinical team agree that new sample collection can be ceased.

Please confirm receipt.

Erik

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/22/11 ESC 12/22/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); FDA additional PMC; and Revised PMCs

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From: Laughner, Erik
Sent: Thursday, December 22, 2011 3:56 PM
To: 'Carol Clark-Evans'
Subject: RE: STN 125327 (Voraxaze); 12/20/11 FDA Proposed PMC_PMR list; additional 12/22/11 FDA revisions

Carol,

Per the original PMC list I provided your on 12/20/11, the Facility group made a few language revisions to PMC numbers 18-20 for your consideration. Please review and incorporate these revisions into your response document.

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

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

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

Please confirm receipt.

Thanks,

Erik Laughner, RPM

From: Laughner, Erik
Sent: Thursday, December 22, 2011 8:40 AM

To: 'Carol Clark-Evans'
Subject: RE: STN 125327 (Voraxaze); 12/20/11 FDA Proposed PMC_PMR list- additoinal PMC 12/22/11

Carol,

Please see the following additional PMC (please add to the list you send back):

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, based in part on clinical experience, will be submitted to the Agency. Final report submitted [Insert date]

Please confirm receipt.

Thanks,

Erik

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/20/11 E\ L 12\20\11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); FDA Proposed PMC_PMR list

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From: Laughner, Erik
Sent: Tuesday, December 20, 2011 4:19 PM
To: 'Carol Clark-Evans'
Subject: STN 125327 (Voraxaze); 12/20/11 FDA Proposed PMC_PMR list

Carol,

Please see proposed PMC_PMR list. Please review with your team and provide a response back with milestones (where needed or where a counter-proposal date may be needed).

Please confirm receipt.

Sincerely,

Erik

STN 125327
2011 FDA PMC_PMR

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
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http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 20, 2011
From: Erik Laughner, M.S., DOP2/OHOP/CDER
Subject: FDA Request for Information; BLA STN 125327 (Voraxaze); List of Proposed PMCs (and one PMR)

PROPOSED PMC/PMR LIST STN 125327 (VORAXAZE) 12/20/11

[Insert date] = Propose Month/Year (no actual day of month)

Proposed Product PMCs:

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

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

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

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

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

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

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

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

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

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

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

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

13) To reevaluate the specificity of the Host Cell Protein method by qualifying the anti-HCP antibody by two-dimensional electrophoresis.

The study report will be submitted to the Agency. Final report submitted [Insert date]

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

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

Comment [I1]: Per 12/19/11 telecon discussion

Proposed Facility PMCs

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

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

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

19) To revise the post approval stability program for microbiological testing. The sterility tests should be performed (b) (4) Please submit an updated post approval stability program in the annual report by January 2013.

20) To develop an appropriate container closure integrity test to replace the sterility test for the post approval stability program. Please report the implementation of the container closure testing of the stability samples in lieu of sterility in the annual report by January 2013.

Proposed Immunogenicity PMC

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

Proposed Nonclinical PMR

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/19/11 ESL 12/19/11

From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Information request; CMC (reference standard)

FDA Attendees:

Emanuela Lacana (TL, DTP)
Howard Anderson (reviewer, DTP)
Akhilesh Nagaich (reviewer, DTP)
Barry Cherney (Deputy Director, DTP)
Erik Laughner, (RPM, DOP2)

BTG Attendees:

Carol Clark-Evans
Richard Branton

Background:

On December 14, 2011, FDA provided the following information request/advice to BTG:

C. Your proposed revisions to The Reference Standard (Ref Std) qualification protocol are not adequate. FDA suggests that BTG withdraw the Ref Std qualification protocol from the application. If the BLA is approved, establishment of a new Ref Std would require either a prior approval supplement (PAS) containing the results of your qualification study or a PAS with a revised qualification protocol, with submission of the data in the BLA Annual Report(AR). The RS qualification protocol when submitted should include the following;

1) Acceptance criteria for release specifications should be appropriate for the intended use of the Std. In general the criteria would be expected to be tighter than routine product release to prevent potential drift in product attributes when future RS are used and should be justified in your application.

2) It is critical that the acceptance criteria for the phase III lot be considered when establishing acceptance criteria for the reference standard qualification protocol.

3) The number of samples used in analytical testing should be justified in terms of assay precision. In general more samples should be used to qualify new reference standards to increase the precision of the assay. Where appropriate, acceptance criteria

for the variability in the estimate of the true value (95% confidence) of the standard should be established.

4) For further information, you can consult the public information posted on the IABS website (http://www.iabs.org) related to a recent meeting being held on the characterization of reference standards.

On December 17, 2011, BTG provided the following email response:

BTG acknowledges the request to withdraw the reference standard qualification protocol and the concerns raised leading to the request. This document summarizes BTG's rationale for continuing with the current reference standard qualification strategy at this point in time.

1) Current Reference Standard Expiry

BTG is currently replacing the working reference standard which is due to expire at the end of December 2011. The new working reference standard is required in order to release the launch batch of Voraxaze should the product be approved, as well as support the ongoing stability studies for drug substance and drug product. Withdrawal of the current protocol will prevent the new working reference standard being qualified in order to support these activities.

2) Infrequency of Manufacture and Limited Availability of Data

BTG intends to manufacture approximately (b) (4) batches of Voraxaze drug substance each year and the proposed drug substance shelf life is (b) (4) months; therefore, the working reference standard for Voraxaze is the drug product, which will have an anticipated shelf life of (b) (4) months at the time of approval. As such, the reference standard will need replacing relatively frequently compared to the numbers of batches of Voraxaze manufactured. BTG will be unable to select the batch that is laid down as a reference due to the infrequency of manufacture and the anticipated reference standard shelf life.

The limits proposed for qualification of the reference standard have been based on the Phase 3 clinical batches and the subsequent full scale development batches, including the conformance lots (n = 7). Application of 95% confidence limits on a small data set is likely to lead to qualification criteria failure. In combination with the infrequency of manufacture, this presents a risk to continued supply of the product. Increased replication in testing can be applied to minimize analytical variation, but it is likely that true batch variation would cause reference standard qualification failures.

3) Use of the Reference in Release and Stability Testing

The purpose of the reference standard varies depending on the analytical method in which it is used. Many of the assays do not include the product reference standard, a further subset use the reference as a system suitability test and a small number involve some comparison to the reference. A detailed description of the use of the standard was provided in response to the request for information dated 04 November 2011 (Q10e). The reference is used to compare signatory peptides in the peptide mapping identity methods based on matching relative retention times. Each new reference standard incorporates characterization to confirm identity of these signatory peaks by LC-MS. The IEF method employs a visual comparison with the reference standard. The CEX-HPLC

and iCE methods also provide quantitative information on charged species and, therefore, provide orthogonal information to support IEF.

The only method that includes a correction based on a numerical value from the working reference standard is the glucarpidase activity assay. In an individual release or stability test, the activity value is normalized by a concurrently tested reference standard value in order to reduce occasion to occasion analytical variability. In order to establish the true value for a new working reference standard, the analysis of activity is carried out at increased replication including different operators, different equipment and different occasions. As such, it is considered that adequate control is in place to qualify new working reference standards.

Given additional experience of manufacture, it is acknowledged that the criteria for qualification of a reference standard could be tightened. BTG would like to discuss whether the current proposal to qualify a working reference standard could be implemented with a commitment to review as more batch data become available.

DISCUSSION DURING THE TELECONFERENCE:

BTG clarified that the working reference standard will expire at the end of December 2011 and that a new working reference standard is required in order to release the April 2011 launch batch (PV4 = P11) of Voraxaze should the product be approved as well as to support the ongoing stability studies for drug substance and drug product. BTG stated that they would like to release PV4 for commercial launch based on the current reference standard. BTG confirmed that the actual data for the lot was already submitted to FDA for review. More data would be available for review regarding the new reference standard in early January. FDA acknowledged and noted there were concerns with the qualification protocol but the main concern was for potency.

FDA noted that the current review clock, per the 21rst century milestones, was nearly complete and that it would be difficult to review any new data submitted at the end of year. However, it may be possible to allow an exception for the P11 batch as the reference standard. BTG could commit as a PMC to revise the reference standard qualification protocol for FDA review and approval prior to any use of new reference standards.

BTG also clarified that until the April launch date, the Treatment Protocol under the IND would remain active.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

ESL 12/19/11

Date: December 19, 2011
From: Erik Laughner, DOP2/OHOP/CDER
Subject: BLA STN 125327; Voraxaze; Wrap-Up Team Meeting

Regulatory Management
Erik Laughner
Greg Reaman
Patricia Keegan

Clinical
Patricia Dinndorf
Suzanne Demko (CDTL/TL)

Nonclinical
Stacey Ricci
Anne Pilaro (TL)

Clinical Pharmacology
Lillian Zhang
Hong Zhao (TL)

Product
Akhilesh Nagaich
Howard Anderson
Emanuela Lacana (TL)
Kim Rains

Product-Immuno Assay Review
Laura Salazar-Fontana
Susan Kirshner (TL)

Facilities
Mary Farbman
Lakshmi Narasimhan
Bo Chi

DOP2 Safety Team
Jeff Summers- DDS

OSE
Manizheh Siahpoushan
Zachary Oleszczuk (TL)
Robert Pratt
Sue Kang
Corrinne Kulick

OPDP
Carole Broadnax

OSI- Clinpharm inspection
Jyoti Patel

Discussion: Participants were present from all disciplines. This review wrap-up meeting reviewed any remaining items to complete prior to taking an action on the BLA. In addition, OSE attended and was briefed by the Division on the overall safety, efficacy and quality of this drug and its intended use.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/16/11 Esl 12/16/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); CMC Information Request

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From: Laughner, Erik
Sent: Friday, December 16, 2011 12:43 PM
To: 'Carol Clark-Evans'
Subject: STN 125327; CMC Information Request

Carol,

See the following information request:

In the Quality Overall Summary (2.3.P) section 2.6 conclusion, which was amended and submitted on 12 Dec 11 (eCTD sequence 017) you state that. (b) (4) (b) (4) Please update the Quality Overall Summary to reflect the proposed labeling changes for the reconstitution hold time. **The hold time is limited to 4 hours at 2-8°C.**

Please confirm receipt.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/14/11 ESL 12/14/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); CMC Advice

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From: Laughner, Erik
Sent: Wednesday, December 14, 2011 10:29 AM
To: 'Carol Clark-Evans'
Subject: RE: STN 125327; 12/12/11 CMC AI Request

Carol,

CMC has indicated that based on the response, there is no need for different tables.

Erik

From: Carol Clark-Evans [mailto:Carol.Clark-Evans@btgplc.com]
Sent: Tuesday, December 13, 2011 4:44 PM
To: Laughner, Erik
Subject: RE: STN 125327; 12/12/11 CMC AI Request

Erik,

We are working on these responses and have a question about the first one. The stability specifications for DS and DP do not differ to the proposed release specifications in Sections 3.2.S.4.1 and 3.2.P.5.1, respectively, with the exception of pH for drug substance and water content for drug product. Different end of shelf life limits are proposed for these parameters and are already included in 3.2.S.4.1 and 3.2.P.5.1 (see attached). Is it necessary to generate separate tables for end of shelf life limits given that they will be identical except for one parameter in each?

Thanks,
Carol

Carol Clark-Evans

VP Regulatory Affairs, Site Manager
BTG International Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/13/11 SSC 12/13/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Draft Carton/Container Labeling

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From: Laughner, Erik
Sent: Tuesday, December 13, 2011 11:30 AM
To: 'Carol Clark-Evans'
Subject: STN 125327; Preliminary Carton/Container Edits
Importance: High

Carol,

Here our preliminary carton/container edits. Please review and provide revised labeling back by next Monday. Please provide as a formal amendment to the BLA.

Please confirm receipt.

Erik

125327 121311
Carton_Container...

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
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http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/13/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Preliminary FDA Carton/Container Comments

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1. Container label

a. Add the US License number per 21 CFR 610.60 (a)(2).

b. Under 21 CFR 601.2, this is a recombinant DNA derived biological product. Revise the placement and prominence of the trade name and proper name to comply with 21 CFR 201.10. *See recommended format below.

c. CDER is working to standardize the presentation of biologics to include the dosage form and route of administration with the primary presentation of the trade name and proper name.

*See recommended format below.

d. Remove all reconstitution information from the vial label to increase readability and create space for other revisions.

e. Add the statements, "Single-use vial; Discard unused portion." to decrease the potential for vial re-use in the absence of a preservative.

f. The "Rx Only" designation has greater prominence than other required statements. Please decrease the prominence of the "Rx Only" designation per 21 CFR 201.15. And relocate 'Rx Only' to appear at the end of the other information.

g. Please indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60 (e).

h. The applicant (per 356h form) is the manufacturer for biologic products. The complete address should be listed, along with the U.S. license number. "Manufactured by: BTG International Inc., Brentwood, TN 37027. US License No. 1861

*Recommended format:

Voraxaze®

Comment [A1]: If room permits, can modify per 12/13/11 email discussion regarding presentation on package insert.

Comment [A2]: Ensure the size of the established name is at least half as large as the letters comprising the proprietary name and has a prominence consistent with the proprietary name (type, size, color, font) in accordance with 21 CFR 201.10 (g)(2).

(Glucarpidase)
For Injection

1000 Units/ vial
For Intravenous Injection

Comment [A3]: If space permits, relocate the route of administration statement 'For intravenous injection to the principal display panel under the product strength presentation, and make the statement prominent by bolding it.

2. Carton label

It is not clear which of the proposed panels is intended to be the principal display panel (PDP) of the carton labeling.

a. Add the statement "no preservatives" per 21 CFR 610.61(e) near the ingredient listing.

b. Add the statement, "No U.S. Standard of Potency" per 21 CFR 610.61(r) near the ingredient listing.

c. Revise storage information to "Store vial at ...." And remove the statement, (b) (4) (b) (4)

d. Remove the statement, (b) (4) from the primary panel and the statement, (b) (4) (b) (4) Complete reconstitution directions are located in the Prescribing Information.

e. Per 21 CFR 201.100, please list the corresponding amounts of each inactive ingredient in the following format: ingredient (amount).

f. Under 21 CFR 601.2, this is a recombinant DNA derived biological product.. Revise the placement and prominence of the trade name and proper name to comply with 21 CFR 201.10. **See recommended format below.

g. The agency is working to standardize the presentation of biologics to include the dosage form and route of administration with the primary presentation of the trade name and proper name. See recommended format for the primary display panel:

Single Vial NDC XXXXXX

Voraxaze®
(Glucarpidase)
For Injection

1000 Units/ vial
For Intravenous Injection

Rx Only

Comment [A4]: If space permits, relocate the route of administration statement 'For intravenous injection to the principal display panel under the product strength presentation, and make the statement prominent by bolding it.

h. The applicant (per 356h form) is the manufacturer for biologic products. The complete address should be listed, along with the U.S. license number. "Manufactured by: BTG International Inc., Brentwood, TN 37027. US License No. 1861

3. Vial cap and ferrule

a. Please provide all proposed printed information on the vial cap and/or ferrule.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/13/11 ESL 12/13/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Labeling Advice

---

From: Laughner, Erik
Sent: Tuesday, December 13, 2011 11:25 AM
To: 'Carol Clark-Evans'
Subject: RE: Voraxaze Labeling

Carol,

The presentation as suggested below would work; however, you need to add the U.S. License Number under the manufactured by: section

Manufactured by: (per front page of 356h form).
BTG International Inc.
Brentwood, TN 37027
U.S. License No. 1861

Distributed by:
BTG International Inc.
West Conshohocken, PA 19428

Erik

From: Carol Clark-Evans [mailto:Carol.Clark-Evans@btgplc.com]
Sent: Monday, December 12, 2011 3:25 PM
To: Laughner, Erik
Subject: Voraxaze Labeling

Hi Erik,

At the end of the Voraxaze package insert, we originally proposed the following, which is consistent with what CBER recently approved for CroFab and DigiFab when we changed our company name:

(b) (4)

In the FDA's labeling comments of Sep 2011, the agency changed this to:

Manufactured by:

BTG International Inc.
Brentwood, TN 37027

The agency referred to the CFR definition of Manufacturer in 600.3(t), which refers to an applicant that takes responsibility for manufacturing done by a contractor, so we agree with changing the 'for' to 'by'; (b) (4)

The agency changed the address to Brentwood, TN citing the requirement that the address match the 356h form; however, it is our understanding from communications with CBER that we can have our corporate address in the product labeling while specifying a different office location on the application form as the contact for FDA correspondence. If CDER agrees, then we would propose to change the address in the labeling (b) (4) If not, then would it be acceptable to add the distributor information (see below) since it is our PA office that is responsible for marketing the product, not Brentwood, TN?

Manufactured by:
BTG International Inc.
Brentwood, TN 37027

Distributed by:
BTG International Inc.
West Conshohocken, PA 19428

If we get a response by tomorrow, then we can include this in our labeling response.

Thanks,
Carol

Carol Clark-Evans | VP Regulatory Affairs, Site Manager
BTG International Inc.
5214 Maryland Way, Suite #405, Brentwood, TN 37027 USA
Main: +1 615 327 1027 | (b) (4)
Email: carol.clark-evans@btgplc.com | **Web:** www.btgplc.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/13/11 ESL 12/13/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Clinical Information Request

---

From: Laughner, Erik
Sent: Tuesday, December 13, 2011 9:28 AM
To: 'Carol Clark-Evans'
Subject: STN 125327; Clinical Information Request

Carol,

Please see the following clinical reviewer information request:

In my early review of the application I read a discussion of a study conducted in UK in which patients received repeat doses of glucarpidase as a component of methotrexate therapy. This study was terminated early. Can you direct me to the section of the application this study was discussed? I can not currently locate it.

Please confirm receipt.

Thanks,

Erik

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/12/11 ESL 12/12/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); FDA proposed draft package insert labeling; Clinical pharmacology revision

---

From: Laughner, Erik
Sent: Monday, December 12, 2011 10:34 AM
To: 'Carol Clark-Evans'
Subject: RE: STN 125327 (Voraxaze); FDA Proposed Label 12/06/11; slight edit from clinical pharmacology 12/12/11
Importance: High

Carol,

The clinical pharmacology group had the following minor edits to the 12/06/11 label we provided. See red-lined version below. If you can incorporate into your response back that would be great.

Please confirm receipt.

Thanks,

Erik

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/12/11 ESL 12/12/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Information request; CMC

From: Laughner, Erik
Sent: Monday, December 12, 2011 10:39 AM
To: 'Carol Clark-Evans'
Subject: STN 125327; 12/12/11 CMC AI Request
Importance: High

Carol,

Please see the following CMC AI requests:

1) Provide a table with a specification for stability for both DS and DP

2) Revise SEC-HPLC specifications to include "no new peaks above X%"

3) Revise RP-HPLC to include "no new peaks above X%"

4) Please clarify when the dating period for DP begins (b) (4) (b) (4)

Please confirm receipt and respond ASAP.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/12/11 ESL 12/12/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Clinical Information Request

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From: Laughner, Erik
Sent: Monday, December 12, 2011 7:10 AM
To: 'Carol Clark-Evans'
Subject: STN 125327; Clinical AI
Importance: High

Hello Carol,

Please see the following clinical information request;

For the NCI study CLN 002 and Study CLN 003, what data set has a flag for the subjects that comprise the safety population?

Please confirm receipt.

Thanks,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
301-796-1393
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http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/09/11 ESL 12/09/11

From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Information Request; vial label

---

From: Laughner, Erik
Sent: Friday, December 09, 2011 9:17 AM
To: 'Carol Clark-Evans'
Subject: STN 125327; Vial Label

Carol,

When the vial label is attached to the vial, can you advise if a sufficient area of the container shall remain uncovered for its full length of circumference to permit inspection of the contents? Do you have a photo of this?

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
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erik.laughner@fda.hhs.gov
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/09/11

From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Advice Clinical Pharmacology

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From: Laughner, Erik
Sent: Friday, December 09, 2011 11:55 AM
To: 'Carol Clark-Evans'
Subject: RE: STN 125327 (Voraxaze); FDA Proposed Label 12/06/11

Carol,

Our response to 1:

Since the distribution of body surface area (BSA) between the treatment group (Arm A) and the control group (Arm B) was not balanced, with a higher median BSA in the treatment group than that in the control group (2.06 m^2 *vs* 1.12m^2), the dose-normalized PK parameters for (6S)-LV and (6S)-5-MeTHF, were generated based on the total LV dose (mg) received rather than the LV dose in mg/m^2 used in the BTG's analysis. The results of the analysis are reflected in Section 12.3 of the labeling.

Please confirm receipt.

Erik

From: Carol Clark-Evans [mailto:Carol.Clark-Evans@btgplc.com]
Sent: Thursday, December 08, 2011 12:41 PM
To: Laughner, Erik
Subject: RE: STN 125327 (Voraxaze); FDA Proposed Label 12/06/11

Hi Erik,

We have reviewed the FDA re-write of the package insert and have the following questions:

1. Please provide explanation and results of analysis of Study 017 referred to by the text included in *Section 12.3 Drug Interactions* of the label
2. Please confirm the "22 treatment-evaluable patients" referred to in *Section 14*, paragraph 1 of the label is comprised of the following patients from Study 006:
    - 0223
    - 0224
    - 0226
    - 0228
    - 0232
    - 0233

- 0235
- 0239
- 0240
- 0243
- 0244
- 0245
- 0252
- 0255
- 0259
- 0263
- 0265
- 0270
- 0279
- 0280
- 0284
- 2670

Thanks,
Carol

Carol Clark-Evans

VP Regulatory Affairs, Site Manager
BTG International Inc.

Please consider the environment before printing this
From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Tuesday, December 06, 2011 8:54 AM
To: Carol Clark-Evans
Subject: STN 125327 (Voraxaze); FDA Proposed Label 12/06/11
Importance: High

Carol,

Please find a proposed FDA draft label of the package insert. I have provided a clean version given the extensive revisions/edits that were made by FDA.

Please review and provide a response back to FDA (both clean and red-line word files) via email by COB Tuesday 12/13. The response should also be provided as a BLA amendment.

Carton/container revisions are targeted to be provided to you next week.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
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http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/08/11 12/8/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Advice; Label Information

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From: Laughner, Erik
Sent: Thursday, December 08, 2011 1:25 PM
To: 'Carol Clark-Evans'
Subject: RE: STN 125327 (Voraxaze); FDA Proposed Label 12/06/11

Hello Carol,

With respect to number 2, the clinical reviewer confirms the patient numbers as correct. An answer to number 1 will be provided as soon I hear back from the clinical pharmacology team.

Thanks,

Erik

From: Carol Clark-Evans [mailto:Carol.Clark-Evans@btgplc.com]
Sent: Thursday, December 08, 2011 12:41 PM
To: Laughner, Erik
Subject: RE: STN 125327 (Voraxaze); FDA Proposed Label 12/06/11

Hi Erik,

We have reviewed the FDA re-write of the package insert and have the following questions:

1. Please provide explanation and results of analysis of Study 017 referred to by the text included in *Section 12.3 Drug Interactions* of the label
2. Please confirm the "22 treatment-evaluable patients" referred to in *Section 14*, paragraph 1 of the label is comprised of the following patients from Study 006:
    - 0223
    - 0224
    - 0226
    - 0228
    - 0232
    - 0233
    - 0235
    - 0239
    - 0240
    - 0243
    - 0244
    - 0245

- 0252
- 0255
- 0259
- 0263
- 0265
- 0270
- 0279
- 0280
- 0284
- 2670

Thanks,
Carol

Carol Clark-Evans

VP Regulatory Affairs, Site Manager
BTG International Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/07/11 ESL 12/07/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Information request; CMC

From: Laughner, Erik
Sent: Wednesday, December 07, 2011 3:42 PM
To: 'Carol Clark-Evans'
Subject: STN 125327; 12/07/11 CMC Information Request

Carol,

Please see the following CMC information requests, a response by next Tuesday (COB) 12/13 is requested:

1. You have not provided sufficient information to evaluate the specificity of the HCP method. Specifically you provided an inactive link for the validation report P7709.00 that evaluates the specificity of the ELISA assay using 2D electrophoresis gels and Western-Blots. Please update your BLA by providing an active link for the validation report.

2. Please clarify the information presented in table 35 of the characterization section. In the table lot ECG2-P07/a showed (b) (4) Clarify if (b) (4) is an actual value or a typographical error.

3. Please update the BLA with drug substance and product specification tables containing your revised specifications.

Please confirm receipt.

Thanks,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/06/11 12/06/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); FDA proposed draft package insert labeling

---

From: Laughner, Erik
Sent: Tuesday, December 06, 2011 9:54 AM
To: 'Carol Clark-Evans'
Subject: STN 125327 (Voraxaze); FDA Proposed Label 12/06/11
Importance: High

Carol,

Please find a proposed FDA draft label of the package insert. I have provided a clean version given the extensive revisions/edits that were made by FDA.

Please review and provide a response back to FDA (both clean and red-line word files) via email by COB Tuesday 12/13. The response should also be provided as a BLA amendment.

Carton/container revisions are targeted to be provided to you next week.

Please confirm receipt.

Sincerely,

Erik

STN 125327 Label
FDA revised C...

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
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http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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Center for Drug Evaluation and Research

Memorandum

Date: 12/05/11 ESL 12/05/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); CMC Information Request

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From: Laughner, Erik
Sent: Monday, December 05, 2011 8:55 AM
To: 'Carol Clark-Evans'
Subject: STN 125327 12/5/11 CMC Information Request

Hello Carol,

Please see the following AI request:

Drug Substance Microbiology Product Quality Information Request:

1. You have proposed to determine whether additional in-process limits are necessary following monitoring of bioburden and endotoxin at key intermediates for the next three and five batches, respectively. Please justify and set interim in-process limits for bioburden and endotoxin based on current knowledge of process capability. (b) (4)

2. You stated that the shipping validation report for shipment of drug substance to the drug product manufacturing site would be completed by year's end. Has this report been completed? If so, please submit it to the BLA.

A response by this Thursday COB is requested. Please confirm receipt.

Thanks,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
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http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/02/11 ESL 12/02/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); CMC Information Request

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-----Original Message-----
From: Laughner, Erik
Sent: Friday, December 02, 2011 8:48 AM
To: 'Carol Clark-Evans'
Subject: RE: STN 125327; FDA CMC Information Request 11/4/11

Carol,

I have been informed that this is acceptable. Please make sure the amendment coverletter spells this out.

Thanks,

Erik

-----Original Message-----
From: Carol Clark-Evans [mailto:Carol.Clark-Evans@btgplc.com]
Sent: Thursday, December 01, 2011 6:20 PM
To: Laughner, Erik
Subject: RE: STN 125327; FDA CMC Information Request 11/4/11

Hi Erik,

We are working on the electronic submission for the response we emailed on 30 Nov and have a question. In response to FDA's request 7, we have proposed revised drug substance and drug product specifications and, for the convenience of the reviewers, we are going to include in the electronic submission updated Sections 2.3.S.4/3.2.S.4.1 (DS specs) and 2.3.P.5./3.2.P.5.1 (DP specs), which tabulate the limits in a couple of pages.

The sections that discuss the justification of specifications (3.2.S.4.5 and 3.2.P.5.6) are much longer and involved to update, so we would like to know if it would be acceptable to update those once we have agreed the final specifications to avoid multiple iterations of the datasets and dataplots that the specifications are based on. Would this be okay?

Thanks,
Carol

Carol Clark-Evans

VP Regulatory Affairs, Site Manager
BTG International Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 12/01/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Clinical Information Request

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From: Laughner, Erik
Sent: Friday, December 02, 2011 9:01 AM
To: 'Carol Clark-Evans'
Subject: RE: STN 125327; Clinical Information Request

Hello Carol,

This answer is sufficient and a formal amendment is not needed.

Thanks,

Erik

From: Carol Clark-Evans [mailto:Carol.Clark-Evans@btgplc.com]
Sent: Thursday, December 01, 2011 3:36 PM
To: Laughner, Erik
Subject: RE: STN 125327; Clinical Information Request

Erik – Does this need to be submitted formally (electronically) or is this email clarification sufficient?

Thanks,
Carol

From: Carol Clark-Evans
Sent: Thursday, December 01, 2011 2:25 PM
To: 'Laughner, Erik'
Subject: RE: STN 125327; Clinical Information Request

Hi Erik,

For study 006 the total dose in grams per m2 of methotrexate that patients received prior to treatment with glucarpidase can be found in the study 006 analysis dataset "ADEX" in variable "EXDOSEN" (Label: Normalized Dose per Administration), when the variable "EXTRT" (Label: Name of Actual Treatment) = "Methotrexate". The units for variable "EXDOSEN" can be found in variable "EXDOSNU" (Label: Normalized Dose Units). The variable "EXDOSEN" in the "ADEX" analysis dataset is derived from the original raw dataset "MTXDOSE", as the sum of bolus and continuous dose variables ("BOLDOSE" and "INFDOSE", respectively) converted to 'g/m2' according to the rules specified in the Comments section of the "ADEX" define file for variables "EXTRT" and "EXDOSEN".

For example, for Patient 0223, the total methotrexate dose in grams per m2 is given in analysis dataset "ADEX" as 6.72 g/m2. This is derived from the sum of the bolus and continuous doses given in the raw dataset "MTXDOSE" (1200 mg/m2 and 5.52 g/m2, respectively, ie, as 1.20 g/m2 + 5.52 g/m2).

Please let us know if you need any further information.

Best wishes,
Carol

Carol Clark-Evans

VP Regulatory Affairs, Site Manager
BTG International Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 1, 2011 ESL 12/01/11
From: Erik Laughner, DOP2/OHOP/CDER
Subject: BLA STN 125327 Voraxaze; Wrap-Up Labeling Meeting/Monthly Team Meeting

Attendees:

Regulatory Management
Erik Laughner
Patricia Keegan (Director)
Karen Jones (CPMS)
Greg Reaman

Clinical
Patricia Dinndorf
Suzanne Demko (TL)

Clinical Pharmacology
Lillian Zhang
Hong Zhao (TL)

Nonclinical
Stacey Ricci
Anne Pilaro (TL)

Product
Howard Anderson
Akhilesh Nagaich
Emanuela Lacana (TL)
Laura Salazar-Fontana (immuno)
Susan Kirshner (TL immuno)

Facility
Lakshmi Narasimhan
Mary Farbman
Patricia Hughes (TL)

OSE
Manizheh Siahpoushan
Zachary Oleszczuk (TL)

This meeting was convened to allow complete team review of the complete FDA proposed package insert prior to sending to the applicant for consideration. In addition, reviewers/teams were reminded of the remaining review clock milestones and given the opportunity to discuss review status of BLA.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 11/30/11 ESL 11/30/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Clinical Information Request

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From: Laughner, Erik
Sent: Wednesday, November 30, 2011 3:13 PM
To: 'Carol Clark-Evans'
Subject: STN 125327; Clinical Information Request

Carol,

I have the following clinical information request:

identify the dataset for study 006 that provides the total dose in grams per m2 of Methotrexate patients received prior to treatment with glucarpidase. Equivalent to the dose found in study 016 dataset "MX" in column "MXDOSE" (Notes MTX DOSE (G/M2).

Please confirm receipt.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
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http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

Rd, Building 3, Upper Level, Oxford, CT 06478 USA

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 11/30/11 EJL 11/30/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); CMC Information Request

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From: Laughner, Erik
Sent: Wednesday, November 30, 2011 12:24 PM
To: 'Carol Clark-Evans'
Subject: RE: STN 125327; 11/21/11 CMC AI request; Response to DMF Letter

Hello Carol,

This is fine. Please submit to the BLA. When submitting the BLA amendments of all these email 'advance" responses, please state in the coverletter that the information contained in the amendment is identical to that provided to FDA via email on XX,XX, etc.

Thanks,

Erik

From: Carol Clark-Evans [mailto:Carol.Clark-Evans@btgplc.com]
Sent: Tuesday, November 29, 2011 2:08 PM
To: Laughner, Erik
Subject: RE: STN 125327; 11/21/11 CMC AI request; Response to DMF Letter

Hi Erik,

(b) (4) have provided the attached validation summary in response to the FDA's request. Please let me know if this is sufficient. If so, we will incorporate it in the appropriate BLA sections when we submit it electronically.

Thanks,
Carol

Carol Clark-Evans

VP Regulatory Affairs, Site Manager
BTG International Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 11/23/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Immuno Advice

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From: Laughner, Erik
Sent: Wednesday, November 23, 2011 1:46 PM
To: 'Carol Clark-Evans'
Subject: RE: Proposal to Cease Collection of Voraxaze Antibody Samples

Hello Carol,

Please continue collecting immunogenicity samples until FDA finishes their review and determines whether continued sample collection is necessary for adequate characterization.

Happy Thanksgiving,

Erik

From: Carol Clark-Evans [mailto:Carol.Clark-Evans@btgplc.com]
Sent: Tuesday, November 22, 2011 4:58 PM
To: Laughner, Erik
Subject: Proposal to Cease Collection of Voraxaze Antibody Samples

Hi Erik,

The 120-day safety update that we submitted to the BLA last week contains antibody data on >100 patients; therefore, we believe we have fulfilled our agreement with FDA at the 28 April 2006 pre-BLA meeting to collect data characterizing the immune response of glucarpidase in 100 patients. We would like to request confirmation that the FDA agrees and that it would be acceptable for us to discontinue the collection of these samples in the ongoing treatment protocol, which is an inconvenience to patients.

Happy Thanksgiving,
Carol

Carol Clark-Evans | VP Regulatory Affairs, Site Manager
BTG International Inc.
5214 Maryland Way, Suite #405, Brentwood, TN 37027 USA
Main: +1 615 327 1027 | (b) (4)
Email: carol.clark-evans@btgplc.com | **Web:** www.btgplc.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 11/21/11 11/21/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); CMC Information Request

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From: Laughner, Erik
Sent: Monday, November 21, 2011 4:10 PM
To: 'Carol Clark-Evans'
Subject: STN 125327; 11/21/11 CMC AI request; Response to DMF Letter
Importance: High

Hello Carol,

Please see following CMC information request- a response by 12/5 is requested:

FDA had requested clarification on the stopper part # and an updated LOA for DMF (b) (4) which includes (b) (4) If the reference to this DMF is being deleted, FDA would like the firm to provide the information and summary data for (b) (4)

In your response (email dated November 17) to FDA Request dated 26 Oct 2011 (DMF Letter) you state that DMF (b) (4) in Table 1 is not applicable to (b) (4)

Please provide the information and summary data for (b) (4) of the drug product.

Please confirm receipt.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 11/17/11 11/17/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); CMC Information Request #2

From: Laughner, Erik
Sent: Thursday, November 17, 2011 4:14 PM
To: 'Carol Clark-Evans'
Subject: STN 125327; CMC Information Request; 11/17/11
Importance: High

Hello Carol,

We have the following CMC information requests:

Please provide:

a. Summary of microbiological monitoring data including the excursions obtained during the following media fill runs, CR349, CR350, CR351, CR356, CR360, and CR360 performed to support PV4 lot (M-CG2-P11).
b. Information and summary data of [redacted] (b) (4)

A response by COB 11/28 is requested.

Please confirm receipt.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 11/17/11 11/17/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); CMC Information Request

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-----Original Message-----
From: Laughner, Erik
Sent: Thursday, November 17, 2011 10:33 AM
To: 'Carol Clark-Evans'
Subject: RE: STN 125327; FDA CMC Information Request 11/4/11

Carol,

The CMC team advises that BTG's plan to revise the conformance lot protocol to include the 30 month, and maintain the post-approval stability protocol as described in 3.2.P.8.2 is acceptable.

Erik

-----Original Message-----
From: Carol Clark-Evans [mailto:Carol.Clark-Evans@btgplc.com]
Sent: Wednesday, November 16, 2011 5:01 PM
To: Laughner, Erik
Subject: RE: STN 125327; FDA CMC Information Request 11/4/11

Hi Erik,

We have another question about request 11. We have agreed that we will include the amended stability protocol with the 30-month time point in our response. We only intend to include this extra test interval in the protocol for the 4 conformance lots as a way of addressing the logistics issue in launching the product with sufficient shelf-life remaining. The post-approval stability protocol for our annual stability commitment will contain conventional testing at 0, 3, 6, 9, 12, 18, 24 and 36 months (no 30-month testing) as currently presented in 3.2.P.8.2 in the BLA.

In 3.2.P.8.1, we will revise the stability protocol for the conformance lots to include 30 months and update the shelf-life extension plan to specify our intention to follow this protocol and extend to 30 and then 36 months as acceptable real-time data become available and report it in the annual report. Our question is whether we need to include the stability protocol with the 30-month testing in 3.2.P.8.2 alongside the post-approval protocol (no 30-month testing) or is it sufficient to have it only located within 3.2.P.8.1.

I ask because I was not sure if it was required to be in 3.2.P.8.2 to allow the annual reporting mechanism.

Thanks,
Carol

Carol Clark-Evans

VP Regulatory Affairs, Site Manager
BTG International Inc.

Please consider the environment before printing this email.

-----Original Message-----
From: Carol Clark-Evans
Sent: Monday, November 14, 2011 9:35 AM
To: 'Laughner, Erik'
Subject: RE: STN 125327; FDA CMC Information Request 11/4/11

Thank you Erik. Yes, it will be included in the next BLA amendment in response to request 11 of the 4 Nov CMC RFI, which we will email this Friday and submit electronically 1 week later.

Have a great day,
Carol

Carol Clark-Evans

VP Regulatory Affairs, Site Manager
BTG International Inc.

Please consider the environment before printing this email.

-----Original Message-----
From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Monday, November 14, 2011 8:29 AM
To: Carol Clark-Evans
Subject: RE: STN 125327; FDA CMC Information Request 11/4/11

Carol,

The proposal to update the stability protocol with the 30 month time-point is acceptable with our CMC review team. Can you confirm/advise that this will be submitted in the next amendment to the BLA?

Erik

-----Original Message-----
From: Carol Clark-Evans [mailto:Carol.Clark-Evans@btgplc.com]
Sent: Thursday, November 10, 2011 4:10 PM
To: Laughner, Erik
Subject: RE: STN 125327; FDA CMC Information Request 11/4/11

Hi Erik,

Normally (b) (4) would be acceptable. The issue is purely a logistical one of having a batch of Voraxaze available to supply to the market with sufficient remaining shelf life to be commercially acceptable to hospital purchasers to stock the product. If the BLA is approved in January, the most recent conformance lot (PV4) would be used for commercial launch planned for April, but by then, it would have less than 6 months shelf-life if the dating period was (b) (4)

If submitting the 30-month data in mid-Dec will be problematic for the reviewers, another option would be for us to amend the stability protocol in the BLA to include the 30-month test interval, which, if approved, would allow us to extend the dating period to 30 months based on real-time data and report it in the annual report. If that is an acceptable alternative, then we will include the amended stability protocol with our response to request 11.

Thanks,
Carol

Carol Clark-Evans

VP Regulatory Affairs, Site Manager
BTG International Inc.

From: Laughner, Erik [Erik.Laughner@fda.hhs.gov]
Sent: Wednesday, November 09, 2011 1:15 PM
To: Carol Clark-Evans
Subject: RE: STN 125327; FDA CMC Information Request 11/4/11

Carol,

See the following CMC response from FDA:

For protein products, the pertinent guidance is ICHQ5C "Stability Testing of Biotechnological/Biological Products". The recommendation in the guidance is that the dating period of a biotechnology product be established based on real-time real temperature data. Protein products often do not follow linear degradation kinetic and extrapolation of the dating period is therefore not appropriate.

FDA does not understand why [redacted] (b) (4) is not an acceptable dating period. Can clarification be provided on this point?

Please confirm receipt.

Thanks,

Erik

-----Original Message-----
From: Carol Clark-Evans [mailto:Carol.Clark-Evans@btgplc.com]
Sent: Wednesday, November 09, 2011 1:33 PM
To: Laughner, Erik
Subject: RE: STN 125327; FDA CMC Information Request 11/4/11
Importance: High

Hi Erik,

We have another query regarding the attached RFI. With regard to request 11, in the BLA we project a maximum [redacted] (b) (4) shelf life for the product, but are currently proposing only 30 months based on the 24-month real-time data submitted in SN006 in June 2011. Our interpretation of ICH guidance Q1E is that a 6-month extrapolation from the available real-time data is permissible for refrigerated protein products provided that the real-time data do not show any trend or variability, which we consider applies to the Voraxaze data. Can the FDA confirm that this will be acceptable?

If we are not able to extrapolate, then in order to have a commercially acceptable shelf-life, we need to pull extra samples and conduct additional testing on two of the conformance lots to support the proposed 30-months; however, the data would not be available to submit to the BLA until mid-Dec. Can these data be submitted in mid-Dec without impacting the PDUFA review clock?

Since we have to inform our contract lab right away if we want them to do the extra stability testing, it would be great if we could get a response to these two questions today, if possible.

Thanks so much,
Carol

Carol Clark-Evans | VP Regulatory Affairs, Site Manager BTG International Inc.
5214 Maryland Way, Suite #405, Brentwood, TN 37027 USA
Main: +1 615 327 1027 | [redacted] (b) (4)
Email: carol.clark-evans@btgplc.com | Web: www.btgplc.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 14, 2011 ESL 11/14/11
From: Erik Laughner, DOP2/OHOP/CDER
Subject: BLA STN 125327 Voraxaze; Fourth Labeling Meeting

Attendees:

Regulatory Management
Erik Laughner

Clinical
Patricia Dinndorf

Nonclinical
Stacey Ricci
Anne Pilaro

Product
Howard Anderson
Emanuela Lacana (TL)

Facility
Lakshmi Narasimhan

OSE
Manizheh Siahpoushan

This labeling meeting was convened to discuss the "DOSAGE & ADMINISTRATION, DOSAGE FORMS & STRENGTHS, HOW SUPPLIED/STORAGE & HANDLING, and DESCRIPTION" sections of the proposed package insert label.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

ESV 11/8/11

Date: November 8, 2011
From: Erik Laughner, DOP2/OHOP/CDER
Subject: BLA STN 125327 Voraxaze; Third Labeling Meeting

Attendees:

Regulatory Management
Erik Laughner

Clinical
Patricia Dinndorf
Suzanne Demko (CDTL)

Clinical Pharmacology
Lillian Zhang

Product
Akhilesh Nagaich

OSE
Manizheh Siahpoushan

This labeling meeting was convened to discuss the "CLINICAL PHARMACOLOGY, DRUG INTERACTIONS and USE IN SPECIFIC POPULATIONS (no pregnancy or nursing mothers) sections of the proposed package insert label.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 11/4/11 11/4/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); CMC Information Request

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From: Laughner, Erik
Sent: Friday, November 04, 2011 1:19 PM
To: 'Carol Clark-Evans'
Subject: STN 125327; FDA CMC Information Request 11/4/11
Importance: High

Hello Carol,

Please see the following CMC information requests. A response by Friday 11/18 is requested.

Please confirm receipt.

Erik

STN 125327
0411 CMC AI Reque

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 4, 2011
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125327 (Voraxaze); CMC Deficiencies/Information Requests

Information Request BLA 125327 (Glucarpidase)

1. Please provide information on the functional tests performed for the qualification of new batches of critical complex raw materials of biological origin (b) (4) (b) (4) used in the fermentation process. The functional tests should provide quantitative evaluation of the growth promoting properties of complex raw materials.

2. Regarding control of the manufacturing process:

(b) (4)

d. Please provide the results of the shipping validation study for the drug substance bulk and QC samples.

e. Your BLA does not contain sufficient information on (b) (4) Please obtain a DMF number from the manufacturer and submit the information to the BLA.

f. Please provide the results of (b) (4) (b) (4) or provide a scientific justification and risk assessments as to why these studies are not necessary.

(b) (4)

plasmid sequence analysis for the (b) (4) Master Cell Bank and (b) (4) Working Cell Bank.

4. In regard to your drug substance characterization and stability, please provide following information and clarification:

a. Glucarpidase separates into five charge variants on CEX-HPLC and iCE. We note a trend of reduced enzymatic activity associated with (b) (4) (b) (4) (b) (4) Please comment. Additionally, indicate whether aged lots of drug substance have been used to manufacture drug product used in the clinical trial. If so, please provide the drug product lot numbers.

b. Glucarpidase predominantly exists in a homodimeric form. Please comment on the enzymatic activity associated with the monomeric form of Glucarpidase and how pyroglutamate formation affects monomer/dimer equilibrium of Glucarpidase.

c. In your IEF gel image (figure 49, lanes 2 and 8, section 3.2.S.3), the Voraxase standards show different IEF profiles than samples (lanes 3-7). Please explain this observation.

5. In regards to the analytical procedures and their validation, please provide the following information and clarification:

a. The specific activity of Glucarpidase is calculated based on the enzymatic activity and protein concentration. Please comment on how sample matrix of in-process analysis samples affects the specific activity determination of Glucarpidase.

b. The acceptance criteria for measuring protein concentration at A_{280} (SOP M2006) has been set to (b) (4) Please provide the scientific rationale leading to the setting up of these values and provide data supporting the linearity of the protein concentration assay.

c. Your proposed specification for affinity constant (Km) is (b) (4). However, the lowest concentration of Methotrexate used in the affinity constant measurement (b) (4) method number M4011) is (b) (4) Please comment as to why lower concentrations of Methotrexate are not included in your standard curve, to determine Km values in your proposed range of (b) (4)

d. The intermediate precision of Km and Kcat measurement is [redacted] (b) (4) [redacted] (b) (4) Please comment.

e. Please provide representative raw data for the enzyme activity assay validation. Additionally, we note that the enzyme activity assay is not optimal, since loss of substrate is a less sensitive readout than generation of product. Please comment, and provide an update on the status of the validation of your LC-MS/MS method.

6 Please provide gels and/or chromatograms pertaining to SDS-PAGE, RP-HPLC, SEC-HPLC, and CEX-HPLC and iCE data on the commercial lot M-CG2-P11.

7. In regard to your drug substance and drug product release and stability program, we recommend that you revise the specifications, as follows:

a. Tighten the acceptance criteria for enzyme activity, specific activity and k_{cat}. Specifically, the lower limit should be revised.

b. Establish acceptance criteria for all peaks resolved using RP-HPLC, SEC-HPLC, CEX-HPLC and iCE.

c. You are using peptide mapping solely to determine identity. Peptide mapping is a relevant assay to assess purity as well as identity, and the information gained through this assay should be incorporated in your release and stability programs. Furthermore, it appears that the baseline in the chromatographic profiles of both Glu-C and trypsin peptide mapping is increasing and this is affecting the resolution of the peaks. Please provide an explanation and a plan to improve the resolution of the peptide peaks.

d. The acceptance criteria for many of the assays (IEF, Glu-C and trypsin peptide map) is comparable to reference standard by visual inspection. Please revise your acceptance criteria by establishing numerical value(s) for reference peaks and IEF bands.

8. Your annual stability program for drug substance and drug product provides for one lot of drug substance and one lot of drug product to be entered in the stability program at the proposed storage conditions. However, the purpose of the annual stability program is to confirm stability at the intended storage conditions, and to demonstrate that routine changes such as rotation of operators or minor equipment changes do not have a significant impact on the product. Stability studies conducted under the recommended storage conditions (-20°C and 2-8°C) are not adequate to address this issue because little or no degradation is likely to occur under these conditions even when there is a problem with product quality. The data should be compared to historical trends and an action plan should be developed to investigate out of trend results. We recommend that you revise your annual stability program for drug substance and drug product to include accelerated and stressed conditions.

9. Because large protein aggregates in therapeutic protein products may enhance immune responses these product-related variants should be appropriately characterized and controlled. While USP method <788>, monitors particulates that are greater then 10 µm in size, particulates that are smaller then 10 µm are not evaluated by this test. Although there is a gap in current analytical technology for quantification of sub-visible particulates between [redacted] (b) (4), suitable techniques such as light obscuration can quantify particles in the [redacted] (b) (4) range an should be employed in your assessment of product quality. We therefore recommend that you evaluate the risk to product quality with regard to these particulates. Please provide a risk assessment strategy and a plan to evaluate sub-visible particles in the [redacted] (b) (4) µm range.

10. You are proposing a qualification program for your reference standard that only includes release testing assays. Additionally, the acceptance criteria you have established for the qualification program are the same acceptance criteria you are using for release testing. In our view, the reference standard chosen should be suitable for its intended purpose, which in many cases would translate to ensuring the quality characteristics that the product is expected to possess. This is particularly important when results of an analytical method are expressed as a percentage of the reference standard. In such cases, the product attribute of the new standard must be highly similar to the previous standard in order to prevent a drift in that product characteristic over time. Please revise the qualification protocol as per the recommendations of ICH Q6B and the following points:

a. The reference standard should also be calibrated against a primary reference material. The primary reference standard should be stored under conditions where the protein is most stable (e.g. vapor phase liquid nitrogen).

b. The reference standard acceptance criteria should be established to ensure that the lot is representative of the material used in the pivotal phase III trial. Therefore the acceptance criteria for the reference material should be tighter than that used for release of the drug product to prevent drifts in product attributes over time. Please revise and justify your acceptance criteria for the reference standard.

c. The reference standard should be tested extensively and additional characterization assays that are also relevant to evaluate the physiochemical properties of this standard should be incorporated in the qualification protocol.

d. The qualification program should include a stability protocol for your reference standard that is aligned with the above principles.

e. Please include a detailed description of how the reference standard will be used. Furthermore, please note that it may be necessary to have multiple standards, each specifically designed for its intended purpose.

11. You propose a [redacted] (b) (4) expiry but only provide two years of real-time stability data for Voraxaze. Expiry dating for protein products is based on real time data. Please provide additional stability data or revise the current expiry.

12. In regard to your immunogenicity assays:

a. Please provide information on the status of the validation for your LC-MS/MS based assay for the detection of neutralizing antibodies. If the method is already validated, please submit the final validation report together with the data on neutralizing antibodies in those clinical samples that tested positive for binding anti-glucarpidase antibodies.

b. Please submit the SOPs for your immunogenicity assays.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 4, 2011 ES 11/4/11
From: Erik Laughner, DOP2/OHOP/CDER
Subject: BLA STN 125327 Voraxaze; Second Labeling Meeting

Attendees:

Regulatory Management
Erik Laughner

Clinical
Patricia Dinndorf
Suzanne Demko (CDTL)
Patricia Keegan
Greg Reaman

Nonclinical
Stacey Ricci
Anne Pilaro (TL)

Clinical Pharmacology
Lillian Zhang
Hong Zhao (TL)

Product
Susan Kirshner
Kim Rains
Laura Salazar-Fontana

OSE
Zachary Oleszczuk (TL)
Manizheh Siahpoushan

This labeling meeting was convened to discuss the "ADVERSE REACTIONS, and PATIENT COUNSELING" sections of the proposed package insert label.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 31, 2011 ESL 10/31/11
From: Erik Laughner, DOP2/OHOP/CDER
Subject: BLA STN 125327 Voraxaze; Mid-Cycle Meeting

A mid-cycle meeting was held.

Objectives of the meeting were to:

- Present key findings of all core reviews and inspections.
- Identify any issues that could preclude an approval action.

Participants were present from all disciplines. The following disciplines gave slide presentations to OHOP:

- Erik Laughner, RPM
- Patricia Dinndorf, Clinical
- Lillian Zhang, Clinical Pharmacology
- Akhilesh Nagaich, CMC
- Mary Farbman, Facility
- Stacy Ricci, Nonclinical

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 28, 2011 ESL 10/28/11
From: Erik Laughner, DOP2/OHOP/CDER
Subject: BLA STN 125327 Voraxaze; First Labeling Meeting

Attendees:

Regulatory Management
Erik Laughner

Clinical
Patricia Dinndorf
Suzanne Demko (CDTL)

Nonclinical
Stacey Ricci
Anne Pilaro (TL)

Clinical Pharmacology
Lillian Zhang
Hong Zhao (TL)

OSE
Zachary Oleszczuk (TL)
Manizheh Siahpoushan

This labeling meeting was convened to discuss the "INDICATION AND CLINICAL STUDIES" sections of the proposed package insert label.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 10/14/11 ESL 10/14/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Information request; CMC

From: Laughner, Erik
Sent: Friday, October 14, 2011 11:44 AM
To: 'Carol Clark-Evans'
Subject: STN 125327; CMC Information Request

Hello Carol,

Please see the attached CMC information request.

A response by 10/21 is requested.

STN 125327
1411 CMC AI Reque

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products (OHOP)
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 14, 2011
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125327 (Voraxaze); CMC Deficiencies/Information Requests

Please provide the following:

1. With regard to Labeling, Instructions for use section states that reconstituted Voraxaze® should be used immediately (b) (4) (b) (4)
2. With regard to the new capper introduced prior to PV4, please clarify if worst case crimping parameters (b) (4) were evaluated using the dye ingress test. If so, please provide the information and summary data.
3. Please provide a comparison of the qualification and production operating parameters for the (b) (4)
4. (b) (4)
5. With regard to media fills:
   a. Clarify if the process validation lots manufactured will be marketed for commercial use. If so, please provide the summary data for 3 consecutive media fills performed to qualify the process validation lots.
   b. State how often the media fill requalifications are performed. (b) (4)
   d. Provide the duration of the interventions qualified as a part of media fill.
   e. Clarify whether a growth promotion study performed for media filled vials. If so, please provide the summary results of this study. (b) (4)
6. With regard to lyophilization: (b) (4)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

BLA 125327

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

BTG International Inc.
5214 Maryland Way #405
Brentwood, Tennessee 37027

ATTENTION: Carol Clark-Evans
Vice President, Regulatory Affairs

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 Glucarpidase, 1000 Units/vial.

We also refer to your July 18, 2011, correspondence, received July 18, 2011, requesting review of your proposed proprietary name, Voraxaze. We have completed our review of the proposed proprietary name, Voraxaze and have concluded that it is acceptable.

The proposed proprietary name, Voraxaze, will be re-reviewed 90 days prior to the approval of the BLA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your July 18, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Erik Laughner at (301) 796-1393.

Sincerely,

Carol Holquist 11-OCT-2011

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 7, 2011 ESL 10/07/11
From: Erik Laughner, DOP2/OHOP/CDER
Subject: BLA STN 125327 Voraxaze; Monthly Team Meeting

Attendees:

Regulatory Management
Erik Laughner
Deanne Varney

Clinical
Patricia Dinndorf
Suzanne Demko (CDTL)

Clinical Pharmacology
Lillian Zhang
Hong Zhao (TL)

Product
Akhilesh Nagaich
Howard Anderson
Kim Rains (carton/container)
Emanuela Lacana (TL)
Laura Salazar-Fontana (immuno)

Facilities
Mary Farbman
Lakshmi Narasimhan
Patricia Hughes (TL)
Bo Chi

OSE
Zachary Oleszczuk (TL)
Manizheh Siahpoushan

This monthly standing meeting provided reviewers/teams opportunity to discuss review status of BLA.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 10/06/11 ESL 10/06/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Advice; CMC

From: Laughner, Erik
Sent: Thursday, October 06, 2011 3:48 PM
To: 'Carol Clark-Evans'
Subject: RE: STN 125327; FDA Inspection of CBI

Dear Carol,

I have confirmed with the facility group that FDA will not require a pre-approval inspection of CBI for the review of this BLA.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology Oncology Products (OHOP)
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

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From: Carol Clark-Evans [mailto:Carol.Clark-Evans@btgplc.com]
Sent: Tuesday, October 04, 2011 3:10 PM
To: Laughner, Erik
Subject: STN 125327; FDA Inspection of CBI

Hi Erik,

The glucarpidase drug substance that will be manufactured at Eurogentec this month during the FDA pre-approval inspection must be converted to drug product within 6 months (drug substance shelf-life), so we need to commit to a production slot at Cangene bioPharma Inc. (CBI), our drug product contract manufacturer. We currently have a slot tentatively scheduled on 27 Jan 2012, which is after the BLA action date of 17 Jan, which raises the following question, which we need the agency to answer so that we can confirm plans at CBI for the next batch:

Will the FDA conduct a pre-approval inspection at CBI prior to the action deadline of 17 Jan and if so, will we be required to be in production of glucarpidase drug product?

Thanks,
Carol

Carol Clark-Evans | VP Regulatory Affairs, Site Manager

BTG International Inc.
5214 Maryland Way, Suite #405, Brentwood, TN, 37027, USA
(b) (4) | **Main:** +1 615 327 1027
Email: carol.clark-evans@btgplc.com | **Web:** www.btgplc.com

Please consider the environment before printing this email.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 10/04/11 ESV 10/4/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Information request; CMC

From: Laughner, Erik
Sent: Tuesday, October 04, 2011 11:37 AM
To: 'Carol Clark-Evans'
Subject: STN 125327; FDA information requests; CMC
Importance: High

Hello Carol,

Please see attached additional FDA information requests regarding CMC.

A response by October 31, 2011 is requested.

Please confirm receipt.

Sincerely,

Erik

STN 125327
0411 CMC AI Reque

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 4, 2011
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125327 (Voraxaze); CMC Deficiencies/Information Requests

Drug Substance Microbiology Product Quality Information Request:

Process Controls:

(b) (4)

Process Validation:

(b) (4)

(b) (4)

Specifications:

(b) (4)

Analytical Methods:

(b) (4)

Shipping:

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 09/22/11 EL 09/22/11

From: Erik Laughner, RPM DOP2/OHOP/CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Information request; Regulatory & Nonclinical

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Carol Clark-Evans called to discuss whether the Division had determined whether an ODAC was needed as part of the BLA review. I indicated that at this time an ODAC was not planned. I did note that FDA would likely handle the intrathecal administration route investigation under the Animal Rule as a PMR and that BTG should still provide the information requested in our July 27, 2011 email. Carol acknowledged and agreed to provide this information.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 09/20/11 ESL 09/20/11

From: Erik Laughner, RPM DOP2/OHOP /CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Information request; clinical pharmacology

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From: Laughner, Erik
Sent: Tuesday, September 20, 2011 11:23 AM
To: 'Carol Clark-Evans'
Cc: Chris Lewis
Subject: STN 125327; FDA Clinical Pharmacology Information Request

Good Morning Carol:

1. To follow up with your e-mail response of September 16, 2011, please submit the following:

   a. Bioanalytical data report for Trial PR001-CLN-002 including:

      - data for daily variation of calibration parameters;
      - individual and mean concentrations, bias and precision of calibration standard (Cs), and acceptance criteria for Cs in each run; and
      - individual and mean concentrations, bias and precision of quality control (QC) samples, and acceptance criteria for QC samples in each run.

   b. Bioanalytical data report for Trial PR001-CLN-003 including:

      - data for daily variation of calibration parameters;
      - individual and mean concentrations, bias and precision of calibration standard (Cs) and acceptance criteria for Cs in each run; and
      - individual and mean concentrations, bias and precision of quality control (QC) samples and acceptance criteria for QC samples in each run.

   c. Bioanalytical validation report for Trial PR001-CLN-003

   The reason for requesting the above reports is that: 1) for Trial PR001-CLN-002, the bioanalytical report PR001-CLN-BA006 submitted is the HPLC method validation report rather than the bioanalytical data/study report; 2) for Trail PR001-CLN-003, you only referenced an article (Buchen 2005) for the technical description of the HPLC assay. However, the bioanalytical validation report and the bioanalytical data/study report should be submitted.

   For submission of the above requested bioanalytical data reports, you can follow the format of the bioanalytical report (PR001 CLN-BA011 for trial PR001-CLN-001) included in your BLA submission.

2. For trial PR001-CLN-006, you submitted Raw HPLC Patient Data on June 30, 2011 (SN0006). Please provide information on acceptance criteria for calibration standard and QC samples in each run and a bioanalytical data report if available.

3. Please submit stability data and/or study reports for blood samples analyzed by the central HPLC assay.

Please submit the above requested information by September 30, 2011.

Please confirm receipt.

Erik Laughner, RPM

From: Chris Lewis [mailto:Chris.Lewis@btgplc.com]
Sent: Friday, September 16, 2011 2:13 PM
To: Laughner, Erik
Cc: Carol Clark-Evans
Subject: RE: STN 125327; FDA Clinical Pharmacology Information Request

Hi Erik,

Please find our response to the 02 Sep RFI regarding Clinical Pharmacology attached. We will be updating the BLA (and activating the links) with this information accordingly. These updates will be completed and uploaded through the gateway by 28 Sep. If you have any questions, please do not hesitate to contact me.

Sincerely,

Chris Lewis

Manager of Regulatory Affairs
BTG International Inc.

Please consider the environment before printing this email.
From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Friday, September 02, 2011 1:53 PM
To: Carol Clark-Evans
Cc: Chris Lewis
Subject: STN 125327; FDA Clinical Pharmacology Information Request

Dear Carol and Chris,

Please see the following information request; a response by 09/16/11 is requested:

Please submit the central HPLC bioanalytical study report(s) for clinical studies PR001-CLIN-002, PR001-CLIN-001, and PR001-CLIN-003 and provide the corresponding acceptance criteria for selectivity, accuracy, and precision of the assay run.

Please confirm receipt.

Sincerely,

Erik Laughner, RPM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125327/0

FILING COMMUNICATION
September 16, 2011

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

Dear Ms. Clark-Evans:

This letter is in regard to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your application dated July 18, 2011 for Voraxaze to determine its acceptability for filing. Under 21 CFR 601.2(a), we have filed your application today. The user fee goal date is January 17, 2012. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

At this time, we have not identified any potential review issues. Our filing review is only a preliminary review, and deficiencies may be identified during substantive review of your application. Following a review of the application, we shall advise you in writing of any action we have taken and request additional information if needed.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 20, 2011.

We have completed a preliminary review of the proposed labeling submitted in this application and provide, as an attachment to this letter, a preliminary revision that contains comments. We request that you resubmit labeling (in clean and red-line MS WORD versions) by October 14, 2011. This resubmitted labeling will be used for further labeling discussions.

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because the biological product for this indication has orphan drug designation, you are exempt from this requirement.

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

Sincerely,

/Patricia Keegan/
Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology Oncology Products
Center for Drug Evaluation and Research

Enclosure: FDA preliminary labeling comments

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 8, 2011 ESC 09/08/11
From: Erik Laughner, DBOP/OODP/CDER
Subject: BLA STN 125327 Voraxaze; Filing Meeting

Attendees:

Regulatory Management
Erik Laughner
Patricia Keegan (Director, DBOP)
Joseph Gootenberg (Deputy Director, DBOP)
Anthony Murgo (Associate Director, Regulatory Science)

Clinical
Patricia Dinndorf
Suzanne Demko (CDTL)

Nonclinical
Stacey Ricci
Anne Pilaro (TL)

Clinical Pharmacology
Lillian Zhang
Hong Zhao (TL)

Product
Akhilesh Nagaich
Howard Anderson
Kim Rains (carton/container)
Emanuela Lacana (TL)
Susan Kirshner (TL immuno)
Laura Salazar-Fontana (immuno)

Facilities
Mary Farbman
Lakshmi Narasimhan
Patricia Hughes (TL)
Bo Chi

OSE
Sue Kang
Manizheh Siahpoushan

OSI
Jyoti Patel
Yuong M. Choi

Filing meeting was held.

Participants were present from all disciplines. The filing review checklists were reviewed by each discipline to determine whether application should be filed. All needed consults were also finalized/confirmed. Review milestones for the application and upcoming internal meetings were discussed.

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # BLA# 125327	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: VORAXAZE Established/Proper Name: glurcarpidase (INN name) Dosage Form: lyophilized powder for injection Strengths: 1000 unit vial		
Applicant: BTG International Inc Agent for Applicant (if applicable):		
Date of Application: Rolling BLA; PDUFA clock started with 07/18/11 submission Date of Receipt: 07/18/11 Date clock started after UN:		
PDUFA Goal Date: 01/17/12	Action Goal Date (if different):	
Filing Date: 09/16/2011	Date of Filing Meeting: 09/08/11	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication: indicated for the (b) (4) reduction of toxic methotrexate concentrations due to impaired renal function.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.***		☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☐ Standard ■ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ■		Resubmission after refuse to file? ☐
Part 3 Combination Product? ■ No. ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

■ Fast Track Rolling Review Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 4663, 11630	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			Applicant undergoing name change with existing BLAs from Protherics Inc. to BTG International Inc. Once CBER updates existing product, this pending BLA will reflect BTG as applicant
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☐ Paid ■ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ■ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*				
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?				
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ■ All electronic ☐ Mixed (paper/electronic) ■ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	X			

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

■ legible ■ English (or translated into English) ■ pagination ■ navigable hyperlinks (electronic submissions only) **If no**, explain.			√ Jurisdiction correct box X	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			X	

Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included. **Forms** include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?			X	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:** Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			

Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."*	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:			X	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		X		Orphan

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?				
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	■ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ■ Carton labels ■ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	■ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			OSI, Maternal Health
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 04/13/04 EOP2 ***If yes, distribute minutes before filing meeting***		X		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 04/28/06 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 09/08/11

BLA/NDA/Supp #: 125327/0

PROPRIETARY NAME: VORAXAZE

ESTABLISHED/PROPER NAME: glucarpidase

DOSAGE FORM/STRENGTH: lyophilized powder for injection; 1000 unit vial

APPLICANT: BTG International Inc.

PROPOSED INDICATION: indicated for the (b) (4) reduction of toxic methotrexate concentrations due to impaired renal function.

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Erik Laughner	Y
	CPMS/TL:	Karen Jones	N
Cross-Discipline Team Leader (CDTL)	Suzanne Demko		Y
Clinical	Reviewer:	Patricia Dinndorf	Y
	TL:	Suzanne Demko	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Lillian Zhang	Y
	TL:	Hong Zhao	Y
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Stacey Ricci	Y
	TL:	Anne Pilaro	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	Laura Salazar-Fontana	Y
	TL:	Susan Kirshner	Y
Product Quality (CMC)	Reviewers:	Akhilesh Nagaich Howard Anderson (DP) Nikolay Spiridonov (Manufacturing process/process validation)	Y Y Y Y
	TL:	Emanuela Lacana	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:	Kim Rains (OBP)	
	TL:		
Facility Review/Inspection	Reviewer:	Mary Farbman Lakshmi Narasimhan	N Y
	TL:	Patricia Hughes	Y
OSE/DMEPA (proprietary name)	Reviewer:	Manizheh Siahpoushan	Y
	TL:	Zachary Oleszczuk	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		

OC/DCRMS (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers DDMAC Maternal Health OSI	Carole Broadnax Jeanine Best Jyoti Patel Young Choi		N N Y Y
Other attendees	Anthony Murgo Sue Kang		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	■ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	■ YES ☐ NO
• Electronic Submission comments **List comments**: None	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ■ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: Rationale will be in clinical review.	☐ YES ■ NO
• Advisory Committee Meeting needed?	☐ YES Date if known:

Comments: ***If no, for an original NME or BLA application, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	■ NO ☐ To be determined Reason: the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease
• Abuse Liability/Potential **Comments:**	■ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments:**	■ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments:**	■ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments:**	☐ Not Applicable ■ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	■ YES PK efficacy endpoint ☐ NO
BIOSTATISTICS **Comments:** No stats reviewer needed; clinical pharmacology endpoint determines efficacy	■ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL	☐ Not Applicable

(PHARMACOLOGY/TOXICOLOGY) **Comments:**	■ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments:** assays approved and validated under IND.	☐ Not Applicable ■ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments:**	☐ Not Applicable ■ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments:**	☐ Not Applicable ■ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments:**	☐ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments:** New BLA; Facility group does initial EER per inspection determination; final EER will be requested near action.	☐ Not Applicable ■ YES ☐ NO ☐ YES ■ NO

Facility/Microbiology Review (BLAs only) **Comments:**	☐ Not Applicable ■ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments:**	 ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Office Director

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
■	The application, on its face, appears to be suitable for filing. The applicant was provided CMC information requests prior to the filing deadline. Those responses were deemed adequate for purposes of filing. The official amendment will be submitted on September 16, 2011 to the BLA. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ■ Priority Review

ACTIONS ITEMS

■	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
■	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).

■	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
■	BLA/BLA supplements: If filed, send 60-day filing letter
■	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
■	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
■	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 8, 2011 ESC 09/08/11
From: Erik Laughner, DBOP/OODP/CDER
Subject: BLA STN 125327 Voraxaze; Filing Meeting

Attendees:

Regulatory Management
Erik Laughner
Patricia Keegan (Director, DBOP)
Joseph Gootenberg (Deputy Director, DBOP)
Anthony Murgo (Associate Director, Regulatory Science)

Clinical
Patricia Dinndorf
Suzanne Demko (CDTL)

Nonclinical
Stacey Ricci
Anne Pilaro (TL)

Clinical Pharmacology
Lillian Zhang
Hong Zhao (TL)

Product
Akhilesh Nagaich
Howard Anderson
Kim Rains (carton/container)
Emanuela Lacana (TL)
Susan Kirshner (TL immuno)
Laura Salazar-Fontana (immuno)

Facilities
Mary Farbman
Lakshmi Narasimhan
Patricia Hughes (TL)
Bo Chi

OSE
Sue Kang
Manizheh Siahpoushan

OSI
Jyoti Patel
Yuong M. Choi

Filing meeting was held.

Participants were present from all disciplines. The filing review checklists were reviewed by each discipline to determine whether application should be filed. All needed consults were also finalized/confirmed. Review milestones for the application and upcoming internal meetings were discussed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 09/02/11 ES 09/02/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Information request; nonclinical

---

From: Laughner, Erik <Erik.Laughner@fda.hhs.gov>
To: Carol Clark-Evans
Cc: Chris Lewis
Sent: Fri Sep 02 14:53:26 2011
Subject: STN 125327; FDA Clinical Pharmacology Information Request

Dear Carol and Chris,

Please see the following information request; a response by 09/16/11 is requested:

Please submit the central HPLC bioanalytical study report(s) for clinical studies PR001-CLIN-002, PR001-CLIN-001, and PR001-CLIN-003 and provide the corresponding acceptance criteria for selectivity, accuracy, and precision of the assay run.

Please confirm receipt.

Sincerely,

Erik Laughner, RPM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 08/17/11 ESL 08/17/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Information request; CMC

From: Laughner, Erik
Sent: Wednesday, August 17, 2011 3:28 PM
To: Carol Clark-Evans
Subject: STN 125327; FDA information requests; additional CMC
Importance: High

Hello Carol,

Please see attached additional FDA information requests regarding CMC.

A response by August 26, 2011 is requested.

Please confirm receipt.

STN 125327
1711 CMC AI Reque

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 17, 2011
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125327 (Voraxaze); CMC Deficiencies/Information Request

The following data and information for the validation of the (b) (4) (b) (4) (b) (4) are missing in Section 3.2.P.3.5. A response by August 26, 2011 is requested.

Please provide the following:

1. Vial washer Validation:

(b) (4)

2. Process validation data and information for the sterilization of containers, closure and equipment in contact with sterile product:

(b) (4)

(b) (4)

3. Process validation data and information for the (b) (4) of containers in the (b) (4)

(b) (4)

4. Submit data and information on the sterilization validation of the SIP process for the lyophilizer.

5. Submit the (b) (4) validation reports: VOR/ESR 005, VOR/ESR 006, VOR/ESR 007, VOR/ESR 019. The documents should include information and data on the retentivity of microorganisms and the compatibility of the (b) (4) used for the specific product.

6. Submit a summary of the recent media fill simulation studies (3 runs) using the same filling line used for the drug product, lyophilization and the environmental monitoring data during filling. Include the following information for each media fill run described:

(b) (4)

(b) (4)

7. Provide a summary of the environmental monitoring program for routine production

8. Provide a description and summary data of the shipping validation studies:

    a. Submit the validation shipping report (GEN/SVR/225).
    b. Provide details of shipping validation study (minimum, maximum load size and worst case conditions used) and data to support transport of DP to (b) (4) and Protherics, UK.

9. Insufficient information is provided for the Container Closure Integrity (CCI) test:

(b) (4)

10. Bioburden method qualification data is missing in Section 3.2.P.5:

    a. Provide the details of bioburden method validation and data summary from 3 drug product lots.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 08/17/11 ES 08/17/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Information request; CMC

From: Laughner, Erik
Sent: Wednesday, August 17, 2011 2:05 PM
To: Carol Clark-Evans
Subject: RE: STN 125327; FDA information requests; CMC

Carol,

We have the following comments:

From the product reviewer point of view, FDA would like to see the report ***VOR/PVR/062*** that provides scientific justification for selected process ranges of the Voraxase DS manufacturing process; all others documents could be reviewed at the time of inspection.

From the facility reviewer point of view, FDA would like to review the FER-16 qualification on inspection. FDA does not expect to review the other documents on inspection (but would look at them if GMP issues relating to those areas arise during the course of the inspection).

Hope this helps,

Erik

From: Carol Clark-Evans [mailto:Carol.Clark-Evans@btgplc.com]
Sent: Tuesday, August 16, 2011 1:44 PM
To: Laughner, Erik
Subject: RE: STN 125327; FDA information requests; CMC

Hi Erik,

We need clarification on one of the CMC requests. With reference to your request for information dated 12 August 2011, Question 1b:

The table in Appendix I references nine reports, only one of which was provided in the BLA submission (VOR/PVR/061, provided in sequence 0004). Accordingly, only VOR/PVR/061 was linked in the table. BTG would like clarification whether the agency now requests that all of the other reports are submitted as it is not possible to make active links without also providing the documents themselves. Of note, D500 FER-16 Q1-11/2005 is a sizeable document comprising multiple binders, which is not currently available in

an electronic format. It was our intention to make each of the cross referenced documents available during inspection should they be required.

Thanks,
Carol

Carol Clark-Evans

VP Regulatory Affairs, Site Manager
BTG International Inc.

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Friday, August 12, 2011 12:23 PM
To: Carol Clark-Evans
Subject: STN 125327; FDA information requests; CMC
Importance: High

Hello Carol,

Please see attached FDA information request regarding CMC. A 30-day timeframe is requested.

Please confirm receipt.

Sincerely,

Erik

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 08/12/11 ESL 08/12/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Information request; CMC

From: Laughner, Erik
Sent: Friday, August 12, 2011 1:23 PM
To: Carol Clark-Evans
Subject: STN 125327; FDA information requests; CMC
Importance: High

Hello Carol,

Please see attached FDA information request regarding CMC. A 30-day timeframe is requested.

Please confirm receipt.

Sincerely,

Erik

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 12, 2011
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125327 (Voraxaze); CMC Deficiencies/Information Requests

During our filing review of your application, we identified the following Chemistry, Manufacturing and Controls (CMC) potential deficiencies/information requests to be addressed within 30 days.

1. In regard to your drug substance process validation, please provide the following information and clarification:

   a. You have established in-process controls and operating and performance parameters based on an evaluation of your historical results. However, your submission did not include the data you used to support your proposal. Please provide graphs summarizing the historical results of your in-process tests and operating and performance parameters.

   b. The Table in Appendix 1 of your development report VOR-PDR-049 does not provide active links to all reports referenced. Please provide active links for all the reports listed in the table.

   c. You have provided summary tables to support the hold-time limits (b) (4) (b) (4) (b) (4) However, you have not provided data to support the proposed hold-time limits. Please provide hold time study reports and relevant raw data (e.g. SDS-PAGE).

   d. Provide information on holding containers and: 1) the results of studies conducted to evaluate extractable and leachable materials from the containers and 2) an assessment on their potential impact on product quality. Alternatively, provide a justification as to why these studies are not necessary.

   e. Provide information on how the temperature of the (b) (4) during (b) (4) If the reported temperature is an average of

several measurements, the range of temperatures recorded and the frequency of measurement should be reported.

2. In regards to your drug-substance characterization, please provide following information and clarification:

a. (b) (4)

b. (b) (4)

c. (b) (4)

d. (b) (4)

e. [redacted] (b) (4)

f. [redacted] (b) (4)

g. [redacted] (b) (4)

3. In regards to your drug-substance stability analysis, please provide the following information and clarification:

a. [redacted] (b) (4)

b. [redacted] (b) (4)

c. [redacted] (b) (4)

4. Please provide standard operating procedures and assay transfer reports for all the assays transferred from [redacted] (b) (4) to Eurogentech.

5. Please submit the shipping validation studies of drug substance to the drug product manufacturing site. Shipping studies should be conducted under worst case conditions for temperature and duration. Submit information on allowable excursions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125327/0

BLA ACKNOWLEDGEMENT

July 27, 2011

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 rolling Biologics License Application (BLA) submitted under Section 351 of the Public Health Service Act and to your November 17, 2008, April 30, 2009, May 10, 2010, May 11, 2010, September 29, 2010, December 16, 2010, and June 30, 2011, submissions which contained required portions. We also refer to your July 18, 2011, submission notifying us that manufacturing facilities are ready for inspection. Your BLA is now considered complete for FDA filing review:

Name of Biological Product: Voraxaze (glucarpidase)

Our Submission Tracking Number (STN): BL 125327/0

Proposed Use: for the (b) (4) reduction of toxic methotrexate concentrations due to impaired renal function.

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of revised 21 CFR 201.56-57.

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application.

If you have any questions, please contact the Senior Regulatory Health Project Manager, Erik Laughner, at (301) 796-1393.

Sincerely,

/Karen D. Jones/
Karen D. Jones, on behalf of Patricia Keegan
Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 07/26/11 ES 07/26/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: STN 125327 and IND 11557; BTG rolling BLA. Glucarpidase (Voraxaze); Information request; nonclinical

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From: Laughner, Erik
Sent: Tuesday, July 26, 2011 12:39 PM
To: 'Carol Clark-Evans'
Subject: STN 125327; FDA information comment and request- nonclinical

Hello Carol,

Please see the following information request:

FDA advises BTG International that the need for a post-marketing requirement to assess the safety and efficacy of the off-label use of Voraxaze™ administered by the intrathecal route of administration for treatment of intrathecal methotrexate overdose may be discussed at an upcoming FDA/CDER Oncology Drugs Advisory Committee meeting. Provide a synopsis of your overall nonclinical development plan to designed to assess the risks and benefits of intrathecal administration of Voraxaze under "the Animal Rule" (see 21 CFR 601.90 for biological products) as an amendment to your IND no later than October 10, 2011. Your development plan should include relevant background information including a discussion of the toxicities of intrathecally administered glucarpidase, a summary of the acute and chronic toxicity resulting from intrathecal methotrexate overdose in humans and the selected species, and the relative physiology, spinal orientation and cerebrospinal fluid dynamics of the test animal species as compared to humans, as part of the justification for the selected species. Also include a draft protocol synopsis for a feasibility study to demonstrate that the selected animal species is/are appropriate to model the expected efficacy and toxicities for use of Voraxase in humans for this specific indication.

Please refer to the Draft Guidance for Industry: Animal Models--Essential Elements to Address Efficacy Under the Animal Rule (January 2009) (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078923.pdf) for additional information.

Please confirm receipt.

Sincerely,

Erik
Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 21, 2011 ESS 07/21/11
From: Erik Laughner, DBOP/OODP/CDER
Subject: BLA STN 125327 Voraxaze; First Committee/Planning Meeting

Attendees:

Regulatory Management
Erik Laughner
Patricia Keegan (Director, DBOP)
Joseph Gootenberg (Deputy Director, DBOP)

Clinical
Patricia Dinndorf
Suzanne Demko (CDTL)

Nonclinical
Stacey Ricci
Anne Pilaro (TL)

Clinical Pharmacology
Lillian Zhang
Hong Zhao (TL)
Ruby Leong

Product
Akhilesh Nagaich
Emanuela Lacana (TL)
Susan Kirshner (TL Immuno)

Facilities
Mary Farbman
Lakshmi Narasimhan
Patricia Hughes (TL)
Bo Chi

OSE
Sue Kang

A planning meeting was held. The following topics were covered:

- Need for clinical audits (DSI) and sites (if needed)
- Need for consultant review input

- Determine need for Audits and sites to include
- Whether there is need for an Advisory Committee meeting and its schedule
- Plan for review time line (e.g., frequency of team meetings, review target goals)
- Periodic team progress check-ins
- Mid-cycle review meeting
- Team or sub-group interactions on particular issues
- Completion of primary reviews
- Secondary review
- Tertiary review
- Internal briefings for signatory authority
- Wrap-up (integration of review, consult and inspection input)
- Pre-approval safety conference
- Pre-approval facility inspections (BLAs)
- Labeling negotiations
- Issuance of action letter by PDUFA goal date
- Overall review schedule and assignments

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 07/20/11 ESL 07/20/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Information request; Facility Inspection Calendar

---

From: Laughner, Erik
Sent: Wednesday, July 20, 2011 10:13 AM
To: 'Carol Clark-Evans'
Subject: STN 125327; FDA information Request; PAI Eurogentec S.A.
Importance: High

Carol,

We have begun planning the pre-approval inspection of Eurogentec S.A., the drug substance manufacturing facility for the Voraxaze BLA 125327/0. The BLA states that manufacturing is scheduled to begin on 17 Oct 2011. In order to plan the exact dates of the inspection, we need additional information on the manufacturing schedule. Please submit a detailed list of activities that will occur on each date of the manufacturing run.

This information should be submitted to the BLA (also via email) as soon as possible, and no later than 7/28.

Please confirm receipt.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 05/13/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: BTG; BLA STN 125327 Voraxaze (glucarpidase) ; FDA information request

---

FDA Attendees:

Erik Laughner, RPM
Suzanne Demko, Clinical Team Leader
Patricia Dinndorf, Clinical Reviewer
Patricia Keegan, Director
Patricia Hughes, Team Leader-Facilities
Mary Farbman, Facility Reviewer
Lakshmi Narasimhan, Facility Reviewer
Emanuela Lacana, Team Leader- Product
Akhilesh Nagaich, Product Reviewer

BTG International Inc (BTG) Attendees:

Vivienne Burdge – Senior Manager, CMC

Carol Clark-Evans – Vice President, Regulatory Affairs

Russell Hagan - Senior Vice President, Head of New Business Strategy &Evaluation (Voraxaze project leader)

Chiron Howell - Technical CMC Manager, Technical Development

Sarah Howell – Vice President, CMC & Process Science

Background: BTG informed FDA in a May 10, 2011 email that they did not intend to be in production of Voraxaze during the pre-approval inspection. FDA subsequently requested a tcon to notify BTG of this possible refuse-to-file (RTF) issue.

Discussion: FDA explained that per 21 CFR 600.21, Voraxaze manufacturing must be occurring at the time of any pre-approval inspection. This was an RTF issue. BTG inquired whether they could use (b) (4) (b) (4) FDA stated this was not possible because it was not representative of the entire

manufacturing process. BTG acknowledged and noted that a (b) (4) slot was available for manufacture. The manufacturing time (b) (4)

FDA also noted that the DS manufacturing site did not appear to have an FEI number which was required for filing the BLA. BTG was asked to ensure that all appropriate sites were registered with FEI numbers. BTG acknowledged and noted that the DP site (b) (4) (b) (4) FDA acknowledged that the primary focus was with the DS site. Active manufacturing of the DP was not required and FDA would determine whether to inspect the DP site at the time of the final BLA submission to activate the PDUFA clock.

(b) (4)

Based on the above discussions regarding inspectional readiness, BTG and FDA agreed that the final piece of the rolling BLA (to activate the PDUFA clock) should be submitted 3 months prior to commencing production of the next glucarpidase drug substance batch to coincide with the agency's pre-approval inspection.

BTG inquired whether FDA had reviewed their CMC rolling unit and determined whether the previous CMC RTF issues had been resolved. FDA noted that this would require in-depth review and that there was no timeframe commitment until the rolling BLA application was considered complete. BTG acknowledged.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 03/30/10 ESL 3/30/10

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: IND 11557(Protherics; Glucarpidase [Voraxaze]) Telecon Summary; Regarding treatment protocol as well as update regarding final rolling BLA schedule. **This memo will also be filed to STN 125327; rolling BLA.**

FDA Attendees:

Jeff Summers, Deputy Director Safety/Team Leader
Suzanne Demko, Medical Team Leader
Patricia Dinndorf, Medical Reviewer
Anne Pilaro, Supervisory Toxicologist
Stacey Ricci, Toxicology Reviewer (joined late)
Erik Laughner, RPM
Emanuela Lacana, CMC Reviewer

Protherics Attendees:

Nikhil Chauhan, Senior Manager of Biostatistics
Carol Clark-Evans, VP Regulatory Affairs
Claire Daugherty, Senior Manager of Biostatistics
Russ Hagan, Voraxaze Project Leader
Chris Lewis, Manager of Regulatory Affairs
Janet Rush, MD, VP Scientific Licensing
Karen Serafini, Voraxaze Clinical Project Lead

Background:

On March 24, 2010, Carol Clark-Evans from Protherics provided an email requesting a teleconference to discuss the rolling BLA schedule, the ongoing IND treatment protocol, and FDA's 02/05/10 AI letter under STN 125327 regarding eCTD and clinical deficiencies associated with current review units of the rolling BLA. With regard to the 02/05/10 letter, Protherics would like to discuss a response to FDA's comments 17 and 18 as well as provide an update on the Integrated Summary of Safety (ISS) preparation. Protherics provided 2 attachments for FDA review in advance of the telecon (ATTACHED AT END OF THIS MEMO).

Discussion:

Protherics noted that the eCTD file problems were being corrected and that a resubmission should occur within a few weeks.

FDA stated that they had reviewed Protherics's response to FDA's comments 17 and 18 from the 02/05/10 letter and that they were acceptable.

Protherics inquired whether there are any additional concerns with the datasets as identified and FDA noted that the most problematic issue as noted in the letter was that the datasets were hard to navigate. FDA mentioned that comments should be added to the columns for easy reference so that the reviewer can identify what the variables mean (i.e., when there is a 1 vs. 2 etc.). Protherics acknowledged and agreed to address all the comments in the letter. FDA emphasized that the CRF's were just pooled together from different studies and this was unacceptable. A eCTD BLA that was not navigable was likely to get an RTF designation. Protherics acknowledged.

FDA cautioned that the issues identified were not all conclusive, but only what had been identified during the initial review. More problems could be found as the review proceeded.

With regard to the ISS, Protherics noted that they had underestimated the work needed to complete this and that there was going to be some delay. Protherics would provide a revised "final" rolling BLA schedule near the end of April.

With regard to the active Treatment Protocol with charging, Protherics inquired how the new cost-recovery regulations (21 CFR 312.8) should be applied. Protherics inquired on the timing of the cost recovery request and how much time the FDA would need to review. FDA noted as the regulations were new, consultation with the Immediate Office in OND would occur and that a response would be provided to Protherics after the telecon. FDA's review, however, should be relatively quick.

FDA informed Protherics that advice/information comments regarding the immuno assays would be provided soon in a letter (undergoing clearance at team-leader level). Protherics acknowledged and noted that patient samples had been run for binding and those samples which tested positive were archived until FDA had cleared the neutralization assay.

Laughner, Erik

From: Carol Clark-Evans [Carol.Clark-Evans@btgplc.com]
Sent: Wednesday, March 24, 2010 5:33 PM
To: Laughner, Erik
Subject: Voraxaze - Request for Teleconference
Attachments: Response to items 17 & 18 in FDA letter of 5Feb10.doc; Ceriotti age-adjusted creatinine.pdf

Dear Erik,

We would like to request a teleconference to discuss a couple of the clinical items in FDA's letter dated 5 Feb 2010 regarding STN BL 125327/0, specifically items 17 and 18, as well as a revised rolling BLA schedule and timing for submitting a new breakdown of costs for charging under the Voraxaze treatment protocol. Attached is a summary of how we intend to address items 17 and 18 as well as a supporting reference. We would like to know whether these plans are adequate to address the agency's requests. We would also be interested in any other issues the FDA medical reviewers would like us to consider as we amend the clinical sections of the BLA.

We need to revise the rolling BLA schedule to account for delaying the submission of Module 3 (CMC) until after we are able to verify that the structural eCTD problems have been fixed, a determination that will be made once Module 4 (Non-clinical) is successfully re-submitted through FDA's gateway. Another item impacting the schedule is that we have determined that preparation of an Integrated Summary of Safety (ISS) will require more work than we originally anticipated, which means the revised clinical sections will now be the final part of the BLA submission rather than CMC and we are currently targeting Dec for this submission. We are proposing to provide a revised schedule by the end of April, when timings for these activities are clearer, and would like to know if this is acceptable.

The anniversary date of the treatment protocol for Voraxaze (Study PR001-CLN-016) is 24 May and the anniversary date for the IND annual report is 21 June (due by 21 August). We would like clarification on timing for submitting a new breakdown of costs in accordance with the new regulation in 21 CFR 312.8. and obtaining FDA authorization to continue charging on a cost recovery basis.

Please let us know what dates/times are possible for a teleconference. The following individuals will be participating from BTG/Protherics:

Nikhil Chauhan, Senior Manager of Biostatistics
Carol Clark-Evans, VP Regulatory Affairs
Claire Daugherty, Senior Manager of Biostatistics
Russ Hagan, Voraxaze Project Leader
Chris Lewis, Manager of Regulatory Affairs
Janet Rush, MD, VP Scientific Licensing
Karen Serafini, Voraxaze Clinical Project Lead

I will provide a toll-free dial-in number and PIN prior to the call. Please let me know if you need any further information to schedule this teleconference.

Best wishes,
Carol

Carol Clark-Evans
VP Regulatory Affairs, Site Manager | Protherics Inc.
5214 Maryland Way, Suite #405, Brentwood, TN, 37027, USA
Main Tel: +1 615 327 1027 | (b) (4)
Email: Carol.Clark-Evans@btgplc.com | Web: www.btgplc.com

17. Analysis of renal function was evaluated based on the adult range of normal for creatinine values. Analysis of creatinine should be evaluated based on values normalized to age-adjusted limits of normal, not the absolute value of 1.5 mg/dL. Approximately 20% of subjects were children up to 12 years of age.

Safety and efficacy related analyses of renal function, as measured by serum creatinine, will be evaluated based on age-adjusted limits of normal as summarized below.

These analyses will be presented for individual studies (where appropriate) and also on data pooled over relevant studies.

1 SAFETY ANALYSES OF SERUM CREATININE

1.1 Serum Creatinine Evaluations

Summary tables of serum creatinine assessments will be produced for actual values, change from baseline, shift from baseline and time to most extreme values. Only data for subjects with a baseline assessment and at least one assessment post-glucarpidase dosing will be included in the summaries.

1.2 Actual Values and Changes from Baseline

Summary statistics (n, mean, median, SD, minimum and maximum) of actual values and change from baseline to the first assessment after glucarpidase dosing (within 3 days of first glucarpidase dose), assessments at 7, 14 and 21 days after glucarpidase dosing (+/-3 days), the most extreme and last assessment (within 30 days after the last glucarpidase dose) will be presented. Due to differences in normal reference ranges by age, summary statistics will be presented separately by age-group (<12 years, ≥12 to <18 years, ≥18 years).

Baseline will be defined as the latest non-missing assessment prior to first glucarpidase dosing. Change from baseline will be calculated as the difference between the post-glucarpidase dosing assessment and the baseline assessment. The most extreme assessment will be defined as the highest assessment after first glucarpidase dosing.

1.3 Shift Tables by Reference Range and CTCAE Grade

Laboratory evaluations were taken at multiple laboratories with multiple normal ranges. In order to create a comparable dataset, out-of-range values and CTCAE v. 3 grades will be assigned programmatically based on normal reference ranges by age-group as presented in Table 1 and Table 2.

Table 1 Lower and upper limits of normal (LLN, ULN) values for serum creatinine

Age range	Sex	LLN (mg/dL)	ULN (mg/dL)
<1 year[a]	Female, Male or sex unknown	0.16	0.39
≥1 and <3 years		0.17	0.35
≥3 and <5 years		0.26	0.42
≥5 and <7 years		0.29	0.48
≥7 and <9 years or age unknown[b]		0.34	0.55
≥9 and <11 years		0.32	0.64
≥11 and <13 years		0.42	0.71
≥13 and <15 years		0.46	0.81
≥16 years[c]	Female or sex unknown[d]	0.55	1.02
≥16 years[c]	Male	0.72	1.18

LLN and ULN values are from Ceriotti et al[1].

[a] Ceriotti et al[1] gave this LLN, ULN for an infant aged between 2 months and <1 year

[b] If the age is not known then the LLN, ULN for a child aged ≥7 and <9 years will be used.

[c] Ceriotti et al[1] gave these LLNs, ULNs for 18-74 year olds

[d] If the sex is not known for an individual ≥16 years of age the LLN, ULN for females aged ≥16 years will be used.

Table 2 CTCAE grading for serum creatinine

	Grade 1	Grade 2	Grade 3	Grade 4
Serum Creatinine	>ULN to 1.5xULN	>1.5xULN to 3.0xULN	>3.0xULN to 6.0xULN	>6.0xULN

Grade 0= Within normal limits
Grade 5= Death related to toxicity
ULN values are given in Table 1

Shift tables of the number and percentage of subjects with normal, low or high results, as defined by Table 1, will be presented from baseline to first assessment after glucarpidase dosing, assessments at 7, 14, and 21 days after glucarpidase dosing, at most extreme and last assessment after glucarpidase dosing. In addition, CTCAE grades will be summarised by shift tables from baseline to first assessment after glucarpidase dosing, assessments at 7, 14, and 21 days after glucarpidase dosing, at most extreme and last assessment after glucarpidase dosing.

1.4 Clinically Significant Values

A listing of subjects with clinically significant (CS) serum creatinine values, defined as Grade 3 CTCAE or higher, will be presented. This listing will be organized by subject, and all values including normal values, will be displayed. A summary of number and percentage of subjects with CS values will also be presented.

1.5 Time Course

In order to assess the time course of serum creatinine abnormalities, summary statistics will be produced for the following: time to most extreme value (in days after methotrexate (MTX) dosing); time to most extreme value (in days after glucarpidase dosing), time to recovery to CTCAE Grade 2 or better (in days after MTX dosing), time to recovery to CTCAE Grade 2 or better (in days after glucarpidase dosing).

2 EFFICACY ANALYSES OF SERUM CREATININE

2.1 Association between timing of glucarpidase dosing and serum creatinine CTCAE grades

The incidence of most extreme post-glucarpidase serum creatinine CTCAE grade by the interval (number of days) between MTX and first glucarpidase dose will be tabulated. The median most extreme post-glucarpidase grade will also be given by dosing interval.

The association between the most extreme post-glucarpidase grade and the dosing interval will be assessed using Pearson's correlation coefficient, Spearman's rank correlation coefficient and Kendall's tau statistic.

Stratified analyses of association between most extreme post-glucarpidase serum creatinine grade and the dosing interval, controlling for the following baseline characteristics, will be performed, using Mantel-Haenszel tests.

- Pre-glucarpidase grade
- Age group (<12 years, ≥12 to <18 years, ≥18 years)
- Sex
- Diagnosis category (Osteosarcoma, Lymphoma, Leukaemia, Other cancer, Non cancer, Unknown)

In pooled analyses across studies, Mantel-Haenszel tests will control for between-study differences in addition to the baseline characteristics listed above.

18. Analysis of risk of death compared to time to glucarpidase infusion was done based on deaths attributed to methotrexate toxicity. This analysis should also be done on any death regardless of attribution.

Analysis of risk of death compared to time of glucarpidase administration will be performed for all deaths, regardless of causality attribution as summarized below:

Summary tables of mortality will be presented overall and by the interval (number of days) between MTX and first glucarpidase dose.

The association of time of glucarpidase administration with risk of death will be assessed using Mantel-Haenszel tests controlling for the following baseline characteristics:

- Age-group (<12 years, ≥12 to <18 years, ≥18 years)
- Sex
- Diagnosis category (Osteosarcoma, Lymphoma, Leukaemia, Other cancer, Non cancer, Unknown).

A logistic regression will be conducted to estimate the odds ratio of risk of death for each 1-day increase in the interval between MTX dosing and first glucarpidase administration, together with a corresponding 95% confidence interval.

In pooled analyses across studies, Mantel-Haenszel tests will control for between-study differences in addition to the baseline characteristics listed above.

References

1. Ceriotti, F., Boyd, J. C., Klein, G., Henny, J., Queralto, J., Kairisto, V., Panteghini, M. Reference intervals for serum creatinine concentrations: assessment of available data for global application. Clin Chem Mar2008 54: 559-566

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-11557	ORIG-1	PROTHERICS INC	Glucarpidase [Carboxypeptidase G2]

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIK S LAUGHNER
03/30/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 03/30/10 3/30/10

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: STN 125327; BTG rolling BLA. Glucarpidase (Voraxaze); Advice on resubmission of eCTD files requiring corrections.

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Tuesday, March 30, 2010 9:01 AM
To: Carol Clark-Evans
Subject: FW: Deficiencies Protherics Rolling eCTD BLA 125327

Carol,

For resubmission of the eCTD files, please note the following advice from our eSUB staff:

Using "replace" instead of "new" should be used whenever possible to avoid duplicate information from being displayed to the reviewers. In some cases, the sponsor, may need to use the delete operator attribute to delete a document from a location and then add as "new" to place the document in its correct location.

Since there were a number of issues where study tagging files weren't used, but should have been used or the study tagging files were not used correctly, the sponsor should refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1[10] [PDF] (6/3/2008) which provides instructions on how to correct study tagging file issues. Whenever possible the sponsor should just create an STF (study tagging file) and reference the documents that were not previously referenced in an in that STF to ensure proper, correct display of the study information.

The sponsor should view their application in a cumulative view (new sequence and previous sequences) to ensure that the application will display correctly when we load their new submission sequence.

Please confirm receipt.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
http://www.fda.gov/cder/Offices/OODP/about.htm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 03/17/10 ESL 03/19/10

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: IND 11557(Protherics) Glucarpidase (Voraxaze); Regarding treatment protocol as well as update regarding final rolling BLA schedule. This memo will also be filed to STN 125327; Protherics rolling BLA.

Carol Clark-Evans from Protherics called to discuss the rolling BLA schedule, the ongoing IND treatment protocol, and FDA's 02/05/10 AI letter under STN 125327 regarding eCTD and clinical deficiencies associated with current review units of the rolling BLA.

With regard to the 02/05/10 letter, Protherics did not require a tcon to discuss the issues associated with eCTD content/format. Their contractor was addressing the issues and a revised eCTD structure would be sent thru the gateway soon. I requested that Protherics notify me a day or two in advance of this electronic submission so that I could alert the electronic submissions folks to help QC the fixes in a timely manner. Protherics agreed. Protherics also noted that they were working thru the clinical deficiencies identified in the letter and would likely request a telecon within the next few weeks to discuss the response/solution. Prior to this telecon, Protherics would provide a written response to facilitate the discussion. I acknowledged.

With regard to the current treatment protocol under IND 11557 w/ charging, I noted that per the recent 2009 new rules associated with charging, Protherics would need to provide a new charging justification. I explained that certain recoverable costs were now prohibited and that Protherics would have to provide a revised per vial cost. Protherics acknowledged and noted that the anniversary date for the treatment protocol was coming up and that they wanted to make sure that FDA had enough time to review the new cost analysis.

With regard to the rolling BLA schedule as originally outlined and agreed upon by FDA, Protherics noted that there would likely be some additional delays. The final CMC portion was originally due at the end of March, however, that would be slightly delayed. Protherics had also identified some clinical data analysis issues which could also cause a delay of some months. I also conceded that FDA had still not provided feedback on the neutralization assays for immunogenicity testing of samples. I agreed to once again follow-up with the review team.

I requested that when Protherics requests the informal telecon to discuss the 02/05/10 AI letter, they use that time to provide FDA an update on the rolling BLA schedule as well as their plans for seeking continued cost recovery for the treatment protocol under the new 2009 regulations. Protherics agreed to do so.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-11557	ORIG-1	PROTHERICS INC	Glucarpidase [Carboxypeptidase G2]

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIK S LAUGHNER
03/18/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125327/0

INFORMATION REQUEST
February 5, 2010

Protherics Inc.
Attention: Carol P. Clark-Evans
Vice President, Regulatory Affairs
5214 Maryland Way, Suite 405
Brentwood, TN 37027

Dear Ms. Clark-Evans:

This letter is in regard to your rolling biologics license application for Voraxaze (glucarpidase) submitted under Section 351 of the Public Health Service Act. To date, you have submitted the non-clinical and clinical portions of this application as originally outlined in your letter of November 10, 2008, submitted to your IND 11557. Although the formal review clock will not start until the date on which you submit the final Chemistry, Manufacturing, and Controls (CMC) portion and inform us that your application is complete, we do have the following preliminary comments and information requests. Please note that these issues should be rectified as soon as possible, but no later than the submission of the last portion of the application. The type and extent of the issues raised below are substantial and if these deficiencies are not remedied are likely to result in a determination that the application is not fileable.

Overall Organization of the Electronic Common Technical Document (eCTD)

The application is poorly organized and does not follow the standard eCTD format. In addition the submissions do not follow FDA eCTD specifications and guidance (see: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

Specifically:

1. Module 4 study documents are not referenced and organized in a study tagging file (STF). Instead the studies were only referenced in the index.xml. For official submissions, all files submitted in modules 4 and 5 are supposed to be referenced in an STF with the exception of literature references and 5.2 Tabular Listing of All Clinical Studies. See module 4.2.1.1 for an example where STFs were not used to reference study documentation. Additionally PDF specifications were not followed.

2. Blue text should be reserved and used for links only, but not all blue text was linked. See pg 5 of 2.7.3.1 Background and overview of clinical efficacy for an example where blue

text was not linked. There are many instances where this issue occurred in this document.

3. There should be active links from lists of references to the referenced article. Examples of missing active links for references include, but are not limited to, sections m2-5-6-ben-risk-conc, section m2-5-7-lit-refs, and section m2-7-3-1-bg-over.

4. There are instances where links were not created and instances of invalid, nonworking links. Examples are:

   a. Links to tables and figures in the text do not work, e.g., in section m2-7-3-1-bg-over.

   b. In section m2-7-3-6-i-rel-mtx-conc-tox, the link for Fouladi *et al*, 1997 does not lead to the cited abstract but to an article by Widemann in J Clin Oncol 1997.

   c. References are not linked. See page 9 of 2.7.3.1 Background and overview of clinical efficacy for an example where references were not linked.

   d. Module 5 studies appear not to have links to referenced information other than the links in the table of contents and in the text to the tables and figures. There appear to be quite a few references that are not linked. Also the links should be blue text or blue box links, but neither blue text or blue box was used to indicate what was linked (for example see pr001-cln-001 in section 5.3.5.2.1).

5. PDF documents should open to bookmarks, panel and page, but many documents did not.

6. Section 5 Clinical Study Reports should include a section 5.2 Tabular Listing of All Clinical Studies, but the document was not included in the application. The table in section 5.2 should summarize the characteristics of the studies in the application and contain links to the study reports.

7. STFs were incorrectly used in module 5. Documents were not tagged correctly. Each study should be referenced in its own STF file and all supporting documentation for that study should be referenced in the STF file and have the correct study tags applied to each file. For example:

   a. The clinical studies in module 5 were tagged as preclinical-study-report instead of legacy-clinical study report.

   b. STFs were not created for each study and did not contain the study's title and study ID.

   c. The STFs did not contain reference links to all the study's documents and include the correct file tags. Instead, some STFs were created that had references to several studies and contained incorrect file tags.

   d. An STF was created for the Literature References and then all the literature references were tagged as "protocol-deviations." No STF should have been

created for the literature references and, therefore, no file tags should be applied to literature reference documents.

e. The data definition and annotated case report form for all studies are tagged as a sample case report form instead of being tagged as **annotated-crf** or **data-tabulation-data-definition,** as applicable.

8. In section 5.3.5 Reports of Efficacy and Safety Studies [Indication], there should be a folder for the category of study 5.3.5.2 Study Reports of Uncontrolled Clinical Studies [Study ID –Title]. In this folder there should be folders for each of the individual studies submitted to support safety and efficacy. In each of these folders for the individual studies there should be a series of folders. Folder 5.3.5.2.1 should contain the study report. Folder 5.3.5.2.24 Case Report Forms [Site ID] should contain case report forms. The individual case report forms should be for the specific study in the folder and the case report forms should have unique identifiers. Folder 5.3.5.2.25 Individual Subject Data Listing should contain folders for Data Tabulation, Data Listing, Analysis Datasets, and Annotated Case Report Forms (CRFs).

9. The annotated CRFs should contain links that connect to the document that defines the variable name and lists the data sets that contain the specific item.

10. CRFs for all studies are in a heading element separate from heading element " 5 Clinical Study Reports." This separate heading element is called "Unassigned." It contains the submitted CRFs from studies. The names of the individual CRFs are not unique. For example, there are 2 documents for 2 individual subjects called "crf-001,",2 documents for 2 individual subjects called "crf-002," etc.

    The CRFs were not referenced in their corresponding study's STF and tagged as "case-report-forms." CRFs were provided under 5.3.7 and since FDA doesn't use 5.3.7, this is why the CRFs appeared under the "Unassigned" heading element instead of under their corresponding study.

11. Most literature reference documents didn't appear under 5.4 Literature References and instead appeared under the "Unassigned" heading along with most of the CRF files.

    Many module 5 literature references did not appear under the 5.4 Literature Reference Heading element because an STF was created under m5-3-7-case-report-forms-and-individual-patient-listings.

```
<title>stf-m5-4-2-lit.xml</title>
 <study-id>stf-m5-4-2-lit.xml</study-id>
</study-identifier>
<study-document>
 <doc-content xlink:href="../../../../0001/index.xml#id1738088" xlink:type="simple">
  <file-tag name="protocol-deviations" info-type="ich" />
 </doc-content>
```

<doc-content xlink:href="../../../../0001/index.xml#id1738123" xlink:type="simple">
<file-tag name="protocol-deviations" info-type="ich" />
</doc-content>
<doc-content xlink:href="../../../../0001/index.xml#id1738147" xlink:type="simple">
<file-tag name="protocol-deviations" info-type="ich" />

12. The data definition table [5.3.2.2.5 Sample Case report Form "define.pdf"] for Study 006 was analyzed. There were 61 pages. On page 1 and 2, the table had 3 columns. Only the first 3 were filled in.

Datasets	Description	Location	Purpose	Keys	Comments
ADDI	006-ADDI	addi.xpt			
AE	006-AE	ae.xpt			
etc. . . .					
VIT	006-VIT	vit.xpt			

It is unclear how this table is supposed to be helpful. There are no explanatory entries in "Purpose," "Keys," or "Comments" Please explain.

This is followed on pages 3 to 39 by separate tables for each of the datasets listed on the first table [above pages 1-2] with the following format.

ADDI addi.xpt

Variable Name	Variable Label	Variable Type	Format Name	Format Decodes	Role	Comment
PROTOCOL	PROTOCOL_NAME:Protocol Name	C				
CENTNO	CENTNO:Center Number	C				
etc . . .		C				
AENO	AE number	C				

Every entry in the Variable Type column page 3 to page 39 is designated as C. There is no definition of what C signifies. Presumably it means character, although in the actual datasets, data is both presented in character and numeric data types. There are no explanatory entries in "Format Name," "Format Decodes," "Role," or "Comments".

This was followed on pages 40 to 61 by a table labeled "All Variables in Alphabetical Order" which lists all the datasets that contain each individual variable. There were 7 columns but no explanatory entries in "Variable Origin," "Role," or "Comments".

The lack of explanation provided that would facilitate interpretation of the data presented in the datasets is also discussed below.

Evaluation of the Current BLA Application Content in Relationship to Deficiency Comments Provided to Protherics Under Withdrawn BLA STN (b) (4)

We have reviewed the current eCTD submission to determine if FDA comments provided on October 6, 2006, were incorporated into the current clinical module. Based on the review of the datasets for Study 006, we have the following comments:

13. You were instructed to identify patients in the datasets with unique patient identifiers and to use the unique identifier in the data set 013, the "meta analysis." This was not done. The patients included in the "meta analysis" from the other studies are identified with a different identifier. Individual patients are identified by more than one unique patient identifier, i.e., one id in the primary study and a different id in the "013 Meta Analysis."

14. You were instructed to provide information in the dataset comment section. Specifically: "The comment section of the column information should have adequate information to understand what type of information is contained in the column and what the entries mean. For example, from file CPG2, the variable HOURMARK has no explanatory comment and contains 75 lines that are blanks and 6 with "#" entered. A concise explanation should be included in the comment section of the column."

15. Regarding review of a subset (Study 006) of datasets included in this submission, the comment section of the column information in the data sets is inadequate. For example:

    - addi.xpt Column "POPN." The data in this column are coded 0 through 3, but the comment section in the column information does not include an explanation of what the codes mean
    - ae.xpt Column "MONITOR." The comment section does not indicate who is included in the monitored population, there is a code 1 monitored, 2 not monitored.
    - cpab.xpt Column "POSNEG." The comment section does not indicate what is positive or negative [we presume test for antibody]
    - diag.xpt .'DIAGTYPE." The data in this column are "Classification of Diagnosis" and are coded 1 through 4, but the comment section in the column information does not include an explanation of what the codes mean.
    - diag.xpt Column "METAST." The explanation of the data in this column is "Metastasis;" the data in the column are numbers 1, 2, 5, 9, 10; there is no indication as to what the numbers refer.
    - dth.xpt Column "MTXRELAT." The explanation is "Death related to methotrexate" but the data in the column are coded 0 or 1 but there is no explanation of what the code means.
    - Same comment for columns "SERIOUSI" and "PROGDISE"
    - nhlp.xpt Column "SAMPTYP." The explanation is "Sample Type" but there is no explanation of what the code contained in this column means.

- ss.xpt Columns "CPG2LOG," and " OTHLOG" include data designated "NC." There is no explanation of the meaning of NC.
- toxg.xpt Column "PARAM." The explanation is "MTX Toxicity" but there are either no data (blank) or numbers 1 to 6 with no explanation of what 1 to 6 signify. Column "OTHERGRO" with explanation of "Other MTX CTC category" contains data in numbers between 3 to 99 with no explanation.

In general, many columns in various datasets include data designated "NA." "NA" is not defined in the dataset comment section.

16. The datasets for the ISE and the ISS are incomplete. This is especially problematic as the data are not presented with unique subject identifiers across studies.

Additional Preliminary Content Issues Identified

17. Analysis of renal function was evaluated based on the adult range of normal for creatinine values. Analysis of creatinine should be evaluated based on values normalized to age-adjusted limits of normal, not the absolute value of 1.5 mg/dL. Approximately 20% of subjects were children up to 12 years of age.

18. Analysis of risk of death compared to time to glucarpidase infusion was done based on deaths attributed to methotrexate toxicity. This analysis should also be done on any death regardless of attribution.

19. We request that CRFs for all subjects enrolled on Study 006 be provided and not just those in the pivotal efficacy subset (PES).

20. In the dataset "MTXH," MTX and DAMPA levels should have units. Assuming all entries are in the same units, this should be specifically stated in the notes section of the column information in the dataset. If there are different units, there should be a separate column with the appropriate units. This information about the units should also be presented in the in the define.pdf file. This comment also applies to any other laboratory values included in datasets.

If needed, we are willing to arrange for follow-up discussion with FDA's Office of Business Process Support, Division of Regulatory Review Support (OBPS-DRRS), in CDER to assist you with the remediation of the eCTD structure problems outlined above.

If you have any questions, please contact the Senior Regulatory Health Project Manager, Erik Laughner, at (301) 796-1393.

Sincerely,

/Patricia Keegan/
Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

BLA ACKNOWLEDGEMENT

Our STN: BL 125327/0

DEC 11 2008

Protherics Inc.
Attention: Carol P. Clark-Evans
Vice President, Regulatory Affairs
5214 Maryland Way, Suite 405
Brentwood, TN 37027

Dear Ms. Clark-Evans:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following:

Name of Biological Product: Voraxaze (glucarpidase)

Date of Application: November 17, 2008

Date of Receipt: November 20, 2008

Our Submission Tracking Number (STN): BL 125327/0

Proposed Use: (b) (4) reduction of methotrexate (MTX) levels in patients who have toxic MTX levels due to impaired renal function.

We have received your application submitted under Section 506(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356) for review of an incomplete application for a Fast Track Product. We also acknowledge your schedule for submission of the remaining portions of this application, as described in our letter of November 10, 2008, regarding your IND 11557. In accordance with provision (c) of the act, our review clock will not start until the date on which you submit the final portion and inform us that your application is complete.

The BLA Submission Tracking Number (STN) provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

If you have any questions, please contact the Regulatory Project Manager, Erik Laughner, at (301) 796-1393.

Sincerely,

Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug
Administration
Rockville, MD 20857

IND 11557

Protherics, Incorporated
Attention: Suzanne E. Smith
Associate Director, Regulatory Affairs
5214 Maryland Way, Suite 405
Brentwood, TN 37027

Dear Ms. Smith:

Please refer to your IND for "Glucarpidase [Carboxypeptidase G2]." We also refer to the meeting held on June 4, 2007, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1393.

Sincerely,

{See appended electronic signature page}

Erik S. Laughner
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosures - Meeting Minutes

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Meeting Type:	C
Meeting Category:	Other
Meeting Date and Time:	June 4, 2007, 1:00 p.m. ET
Meeting Location:	Teleconference
Application Number:	IND 11557
Product Name:	Glucarpidase [Carboxypeptidase G2]
Sponsor Name:	Protherics, Incorporated
Meeting Requestor:	Protherics, Incorporated
Meeting Chair:	Patricia Keegan
Meeting Recorder:	Erik Laughner

FDA Attendees:

Division of Biologic Oncology Products
Patricia Keegan, M.D., Director
Patricia Dinndorf, M.D., Clinical Reviewer
Jeff Summers, M.D., Medical Team Leader
Erik Laughner, M.S., Regulatory Project Manager
Anne Pilaro, Ph.D., Acting Supervisory Toxicologist
Karen Jones, CPMS

Division of Monoclonal Antibodies
Daniela Verthelyi, M.D. Ph.D., Reviewer
Elizabeth Shores, Ph.D., Team Leader

Division of Clinical Pharmacology 5
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader
Leslie Kenna, Ph.D., Reviewer

Sponsor Attendees:

Protherics
Tim Auton (TRA), Head, Project Management and Biostatistics
Carol Clark-Evans (CCE), Vice President, Regulatory Affairs
James Glover (JFG), Director, Scientific Affairs - Business Development
Elizabeth Lovell (EAL), Development Project Leader
Ajaz Rosul (AR), Manager, Non-clinical and Bioanalytical contracts
Suzanne Smith (SES), Associate Director, Regulatory Affairs

(b) (4)

Background and Meeting Purpose: On April 5, 2007, Protherics, Inc., requested a formal meeting with FDA to discuss their revised plans to develop and validate analytical methods to measure anti-glucarpidase antibodies in human serum and to assess the ability of serum containing these antibodies to neutralize glucarpidase activity. FDA had previously identified deficiencies in the assay methodology and validation plan and had issued to Protherics, Inc., letters dated July 18, 2006, and December 7, 2006.

Preliminary comments were provided to Protherics, Inc., on June 1, 2007. The actual minutes are incorporated below as "***DISCUSSION DURING THE TELECONFERENCE***."

Sponsor Submitted Questions and FDA Response:

FDA Introductory Statement (Provided on June 1, 2007)

At this time, and based on the limited data and plans submitted, the assays used to monitor the presence and levels of antibodies to carboxypeptidase (screening, confirmatory and neutralizing assays) and their validation plans appear incomplete and inadequate. The absence of assays in place and meaningful data will hinder the interpretation of the clinical data as it relates to product immunogenicity and will be considered in describing uncertainties and/or limitations to safety and effective use in the product labeling.

Accurate assessments of immunogenicity are critical to the approval of biologic products. Understanding the generation of antibodies is essential for assessment of safety and efficacy as antibodies can neutralize product activity, alter biodistribution, and/or induce hypersensitivity responses. Also, since the screening assay is used to trigger the quantitative assessment and the presence of neutralizing antibodies to the product, it is essential that the assay be sensitive and specific. Antibody evaluation will used to generate the "Immunogenicity" section of the package insert so it is necessary that the

immunogenicity section be based on data from validated assays. The following are some critical precepts for the design and validation of these assays.

- *The screening and quantitative assays should detect all human immunoglobulin isotypes, particularly IgG and IgM but need not differentiate between the different isotypes. For product delivered one time, it is anticipated that IgM will be a major component of the response and the assay should be shown to be able to detect this isotype. Further, if clinical events consistent with IgE-mediated hypersensitivity reactions are observed, FDA may request that an IgE antigen specific assay be developed.*

- *Adequate positive and negative controls are needed to validate the assay. This reagent is necessary both for formal validation (sensitivity particularly) and for quality control when assessing patient sera. We highly recommend that such a reagent be developed (purified antisera, monoclonal) that is detected by the anti-human Ig detecting reagent (e.g. sera from a hyper immunized primate, human Ig transgenic mice, etc). Rabbit antisera is problematic, particularly for assessing the presence of IgM.*

- *Assay validation requires the establishment of acceptance criteria and entails demonstrating that an assay can perform within the pre-established parameters. The acceptance criteria are derived from the information gained during assay development and qualification and therefore it is recommended that the assay development and validation are not done in parallel.*

- *While the assay must be quantitatively validated for sensitivity in mass units, it is not recommended that you report human patient data in this form as it would be dependent on a specific positive control. Please consider reporting patient antibody levels as titers as these can be more meaningful to clinicians than reporting quantitative amount in terms of mass units of antibody.*

- *Establishing the cutpoint of each assay is critical to determine whether a patient is mounting a response to the product. This should be established using serum from the untreated patient population*

- *The screening, confirmatory and neutralizing assays need to be correctly qualified before use. Please bank samples until the immunogenicity assays have been developed and approved by the Agency. Full validation can be performed in parallel with the testing of initial clinical samples.*

1. **Does FDA concur that the proposed development of a screening ELISA (for detection of IgG, IgM, IgA, and IgE antibodies to glucarpidase) and its validation are acceptable for their intended purposes (see Section 9.2, Tables 1 and 2). Does FDA agree that screening for IgD is not relevant because it's main function is to act as a transmembrane receptor on B cells and because this Ig isotype does not bind to Protein A/G and will not be detected in the screening ELISA?**

PRELIMINARY COMMENTS SENT JUNE 1, 2007: The use of a qualitative assay for screening is acceptable; however, you must demonstrate that Protein A/G system will allow the detection of low levels of IgM, IgE, IgA as well as IgG antibodies. It is critical that the detection system of your screening assay capture all of these immunoglobulin isotypes. It is not necessary for the screening assay to include IgD.

Regarding the development of the screening assay and its validation, the proposed studies are not acceptable. Before proceeding with testing of patient samples, please address and submit for FDA review the items listed below:

DISCUSSION DURING THE TELECONFERENCE: *Protherics acknowledged FDA's comments and noted that their Development Table in the briefing document included information regarding the detection of IgG, IgM, IgA, and IgE as positive controls to show that protein A/G did allow their detection. FDA noted that the data provided was incomplete and it could not be fully evaluated.*

FDA restated that the objective of the screening test is that it should detect antigen-specific IgG, IgE, IgA, or IgM antibodies produced. FDA noted their concern that the assay may not be sensitive to IgM antibodies under the specific conditions of this anti-glucarpidase assay due to the low affinity of Protein A/G for IgM. FDA stated that for the screening assay, sensitivity will need to be established for each individual antibody isotype, particularly IgG and IgM. FDA noted that while it is not currently critical to have a quasi-quantitative assay for IgE, one may be needed later if the hypersensitivity reactions in patients receiving Voraxaze becomes a concern.

Protherics proposed that a quantitative assay not be used for IgM since IgM antibodies were not generated in the rabbits exposed to glucarpidase. If IgM levels need to be quantitated, Protherics stated that they propose to use a commercial human total IgM to quantitate the antibodies present, because they did not possess affinity purified anti-glucarpidase IgM antibodies, and because the treated rabbits did not produce detectable anti-glucarpidase IgM antibody levels. FDA stated that rabbit may not be the best model to evaluate whether human patients would make an IgM antibody response. In addition, rabbits are a poor source of a positive control antisera as they are low producers of IgM. FDA proposed other approaches be considered such as hyperimmunization of

transgenic mice, primates, or an alternative species. Protherics responded that primates, like the rabbit, are not human, and that using affinity-purified rabbit or monkey anti-sera will not provide the exact sensitivity of the assay either.

FDA reiterated their concern regarding the screening assay to detect antigen-specific IgM antibodies and remarked that using total human IgM may not render a good measure of the sensitivity of the specific anti-glucarpidase assay. FDA suggested several approaches by which Protherics could evaluate the sensitivity of the assay for IgM under the condition of the anti-glucarpidase assay including a co-coating approach. Protherics suggested other approaches and will submit for review the concept of an alternative assay. Protherics agreed to provide this submission within the next several weeks.

Regarding the quantitation of the assay, FDA suggested that a dilution titer assay be developed and validated to quantitate IgG and IgM isotypes. This approach will allow Protherics to relate the antibody titer to clinicians, a solution that was preferable to that of arbitrary "units". After a short discussion of the potential advantages of each method Protherics agreed to develop a titer-based semi-quanitative assay for IgM and IgG antibodies to the product.

a. Assay Controls: Please set specifications for antibodies that will be used as controls/standards in your assays.

DISCUSSION DURING THE TELECONFERENCE: *Protherics acknowledged and noted that for the affinity-purified antibodies, ELISAs and Western blots will be performed and a certificate of analysis (COA) would be provided to assure purity of these antibodies. For the commercial human \antibodies, COAs from the manufacturer will be provided.*

b. Serum dilutions: Please establish the optimal serum dilution for the screening assay. The optimal dilution should minimize background while ensuring assay sensitivity. Importantly, the validation of the assay must be performed at the optimal serum dilution.

DISCUSSION DURING THE TELECONFERENCE: *Protherics acknowledged FDA's comments, but noted that a plan for determining the optimal dilution was included in the briefing document. FDA noted that the document stated a single serum dilution that would be used and made no reference to any studies to determine the optimal serum dilution.*

c. Assay cut point:

1) Please note that the assay cut point and limit of detection are two distinct parameters. Please submit to the Agency a plan summarizing how the cutoff point will be statistically derived.

DISCUSSION DURING THE TELECONFERENCE: *Protherics acknowledged that the assay cutpoint and limit of detection are two separate parameters and noted that they were sometimes inappropriately used interchangeably in the information package. Protherics stated that the cutpoint for the screening assay was presented on page 10 of the briefing document. Protherics noted that they planned to derive the cutpoint from the sera from 50 healthy patient samples. FDA inquired whether these patients would be healthy volunteers and Protherics confirmed that healthy subjects would be used to derive the cutpoint during qualification. Protherics agreed to then redefine the cutpoint during validation using patient samples from clinical studies. The sensitivity for the screening assay would be determined by diluting the reference standard until no antibody was detected. The cutpoint is then defined as that absorbance above which the assay is positive and below which the assay is negative.*

2) Please use sera from an untreated patient population to confirm the cutoff for the screening assay.

DISCUSSION DURING THE TELECONFERENCE: *See 1e. 1), above.*

d. Assay Normalization: Please clarify how the normalization factor will be derived and used. If the normalization factor will be used to set the plate-specific cut point, please ensure that low (scarcely above the cut point), medium and high positive controls are included on every plate to ensure the sensitivity and range of the assay.

DISCUSSION DURING THE TELECONFERENCE: *Protherics noted that the normalization factor derivation and intended use was defined on pages 10 and 11 of the briefing document. FDA stated that the terms used were confusing and the information incomplete.*

e. Assay Validation: Validation of the sensitivity, specificity, precision, reproducibility and robustness are critical to the validation of the screening assay.

1) It is critical to determine the sensitivity of the assay in order to have confidence when reporting immunogenicity rates. Please

use human antigen-specific antibodies to determine the sensitivity of the assay by spiking known amounts of antibody into the assay.

DISCUSSION DURING THE TELECONFERENCE:
Protherics acknowledged and agreed with FDA's comments.

2) Non-specific binding studies and competition by unbound product can be used to demonstrate the specificity of the assay. When performing a competition study, the inclusion of an irrelevant protein of similar charge and size as control is recommended.

DISCUSSION DURING THE TELECONFERENCE:
Protherics acknowledged and agreed with FDA's comments

3) Please establish the robustness of the assay. The evaluation of robustness provides an indication of your assay's reliability during normal usage and should be assessed by examining the impact of small but deliberate variations in method parameters (critical parameters include serum storage conditions, the presence of hemolized red blood cells or higher lipid content in sera).

DISCUSSION DURING THE TELECONFERENCE:
Protherics acknowledged and agreed with FDA's comments

4) Please establish the reproducibility of the assay :

a) It is recommended that intra-assay precision be evaluated on a minimum of 3 different days with a minimum of two to three replicates of the same sample in each assay. Samples should include negative controls and positive samples whose testing yields values in the low, medium and high levels of the assay dynamic range. To assess inter-assay variability please ensure that the assays are performed by at least 2 technicians on different days.

DISCUSSION DURING THE TELECONFERENCE:
Protherics acknowledged and agreed with FDA's comments.

b) Please establish acceptance criteria for the ranges of the negative, low, medium and high positive controls that will be used to ensure reproducibility of the test's range when testing patient data. The inter-assay coefficient of variation for your positive controls should be under 20%. This will ensure that the assay not only has a reproducible cutoff, but also a reproducible range.

DISCUSSION DURING THE TELECONFERENCE:
Protherics acknowledged and agreed with FDA's comments.

c) Please confirm that the screening assay is to be performed at a single centralized location, otherwise please provide data demonstrating that the laboratories involved produce comparable data.

DISCUSSION DURING THE TELECONFERENCE:
Protherics acknowledged and confirmed that screening will be performed at a single centralized location.

5) Please include in the validation of your assay tests to establish the impact of onboard product or likely concomitant medications (e.g. Leucovorin) could interfere with the assay at the time when samples will be tested.

DISCUSSION DURING THE TELECONFERENCE:
Protherics acknowledged and agreed this information would be provided in the validation protocol.

f. Regarding the confirmatory assay,

1) The comments pertaining to assay development and validation of the screening assay to this assay as well.

DISCUSSION DURING THE TELECONFERENCE:
Protherics acknowledged and noted that there was a mistake in one of the diagrams of the briefing package, and that the IgM ELISA study design does not utilize a Voraxaze-IgM construct. In response to Protherics' request for clarification regarding a recommendation to quantitate antibody by titering patient samples in an appropriate matrix, FDA noted that the proposed assay lacks a good positive control. FDA noted that it will be difficult for clinicians to understand Protherics' proposed relevant mass units readout for the assays. Titers would be better and would be not as dependent upon specific positive controls. After some discussion Protherics acknowledged and agreed that titers would be more appropriate. Protherics stated that a cutpoint must be established which requires diluting the samples (titering) using a relative positive control. Protherics asked if both titers and mass units of antibody were required. FDA stated that a standard reference curve should be established during validation to assign mass units of antibody for the sensitivity of the assay. Protherics

acknowledged and stated that they would incorporate the use of a cutpoint and titers into the alternative assay that had been proposed. Patient samples will be serially diluted in a single assay to quantitate IgG and IgM.

2) Please establish a statistically-based cut point for this assay.

DISCUSSION DURING THE TELECONFERENCE: *See discussion in 1.f.1), above.*

2. Does FDA agree that (b) (4) (b) (4)

PRELIMINARY COMMENTS SENT JUNE 1, 2007: No, the Agency does not agree because the procedure is not clear. Please clarify what are the critical reagents that will be used for each of the assays including what will be the positive controls used. Your diagram on page 17 implies that an IgM-Voraxaze will be used to coat plates. Please clarify if a construct of Voraxaze-IgM will be used to quantify the amount of antigen-specific IgM in patient's sera. Please apply the comments regarding assay development and validation (question 1) as well as the relevant comments from prior letter from the Agency to the validation of this assay. Additional information on the validation of analytical procedures can be found in ICH Q2b"Validation of Analytical Procedures: Methodology".

a. What concentration range of anti-glucarpidase IgM should be used for the positive coating control during methods development (we are using an IgG range of 250-500 ng/mL)?

PRELIMINARY COMMENTS SENT JUNE 1, 2007: FDA cannot provide an answer to this question as it is unclear. However, be advised that binding known amounts of anti-glucarpidase IgM antibodies to the plate will not define the sensitivity of the assay, it will only help define the sensitivity of the secondary testing reagent.

DISCUSSION DURING THE TELECONFERENCE: *Protherics acknowledged FDA's comments 2. a-c., and agreed that discussion will be deferred until more information is provided.*

b. Does FDA concur that it is acceptable to use the acceptance criteria of ≤25% C.V. for precision, and ±25% for specificity, stability, and accuracy during development and validation (see Sections 9.5, 9.6,

and Tables 2 and 3) as per Findlay JWA et al, 2000 (reference number 6).?

PRELIMINARY COMMENTS SENT JUNE 1, 2007: FDA cannot provide an answer to this question as it is unclear. Acceptance criteria are usually different for development and assay validation. During validation, 25% CV may be acceptable for absorbencies close to the detection level like the negative control but would probably be unacceptable for higher absorbencies like a robust positive control. The CV set for validation assay should be derived from the experience during assay development, but it should not unreasonable large.

c. **Does FDA concur that a change in OD values >50% between reference standard in buffer versus reference standard in buffer + glucarpidase is indicative of a positive immunodepletion assay (that antibody is specific for glucarpidase) (see Sections 9.2.3, 9.5.1, and Tables 1 and 3)?**

PRELIMINARY COMMENTS SENT JUNE 1, 2007: The Agency agrees that a 50% reduction in absorbance of low and high positive samples when adding soluble protein to the assay to confirm the specificity of the screening assay would be adequate provided a validated assay with acceptable accuracy, sensitivity, specificity and reproducibility were used. Please note that this is different from establishing the cut point for the confirmatory assay at 50% reduction.

3. **Does FDA concur that our proposed validation plans for the quasi-quantitative ELISAs include all essential validation parameters, as discussed in the publication by Mire-Sluis, et al, 2004, the Guidance for Industry entitled "Analytical Procedures and Methods Validation," and the ICH guideline entitled "Validation of Analytical Procedures: Text and Methodology (Q2(R1))" (see Section 9.6 and Table 2)?**

PRELIMINARY COMMENTS SENT JUNE 1, 2007: No, the proposed validation plan for the semi-quantitative ELISA is not complete. Please refer to the comments for the validation of the screening assay and previous FDA letters. Please ensure that the assays protocols include high, medium and low binding controls with pre-defined specifications to ensure the sensitivity and range of the assay. However, antibody quantitation may also be accomplished by titering the patient samples diluted in an appropriate matrix using the same format as the screening assay.

a. **Does FDA concur that the limited robustness validation that is proposed is acceptable because robustness parameters have been optimized during development and are not thought to be affected when a single laboratory is used for development and validation of the**

assay (Geng, et al, 2005 – reference number 7) (see Section 9.6 and Table 2)?

PRELIMINARY COMMENTS SENT JUNE 1, 2007: No, the Agency does not concur with a limited robustness validation study, and the data supplied does not support this.

DISCUSSION DURING THE TELECONFERENCE: *Protherics acknowledged FDA's comments 3. a-b., and agreed that discussion will be deferred until more information is provided.*

b. **Does FDA concur that validation of specificity using leucovorin interference and the human carboxypeptidases is sufficient for the screening and IgG and IgM quasi-quantitative ELISAs (see Sections 9.2.4, 9.6, and Table 2)?**

PRELIMINARY COMMENTS SENT JUNE 1, 2007: The approach seems appropriate. Coating the plates with human carboxypeptidases or introducing soluble carboxypeptidases to compete for binding can be used to establish assay specificity. However, as stated in previous letters, unexpected results were observed in the data submitted when plates were coated with human carboxypeptidases. As per our response 1e,5), the impact of likely concomitant medications such as Leucovorin on the sensitivity of the assay needs to be established during assay validation.

4. **Does FDA concur that our stability program (room temperature and freeze-thaw stability) for reference rabbit anti-glucarpidase antibody, that will be undertaken during assay validation, is acceptable (see Sections 9.2.4, 9.6, and Table 2)?**

PRELIMINARY COMMENTS SENT JUNE 1, 2007: Assessing the impact of changes in serum storage conditions on the rabbit sera may be acceptable. Specifications and a plan for periodic qualification for antibodies should be established. Please be aware that establishing the impact of storage conditions on the patient samples to be tested is only part of the studies that are needed to validate the robustness of the assays. Please refer to question 1 and ICH Q2b"Validation of Analytical Procedures: Methodology.

DISCUSSION DURING THE TELECONFERENCE: *Protherics acknowledged FDA's comments. There was no further discussion.*

5. **Does FDA agree that if there is no production of IgM anti-glucarpidase antibody in rabbits, that Protherics need only monitor for IgM in the ELISA screening assay (which does not distinguish between different immunoglobulin types)?**

PRELIMINARY COMMENTS SENT JUNE 1, 2007: No, it is essential that you measure IgM antibodies. If the rabbit sera is inadequate, please generate an appropriate reagent. As mentioned above, assays to quantify the anti-glucarpidase antibody titers in sera needs to capture low levels of both the IgG and IgM isotypes, although it may not be necessary to identify each isotype.

DISCUSSION DURING THE TELECONFERENCE: *Protherics acknowledged FDA's comments. There was no further discussion.*

6. **Does FDA concur that quasi-quantitative ELISA (or other) assays to quantify IgA and IgE anti-glucarpidase antibodies will not be required for Voraxaze?**

PRELIMINARY COMMENTS SENT JUNE 1, 2007: The need to develop and IgE specific test will depend on the clinical events and there possible relationship to IgE related hypersensitivity events. Should such events be apparent, there will be a need to develop an assay to screen for the presence of IgE. At this time, there is no need to develop an IgA specific assay.

DISCUSSION DURING THE TELECONFERENCE: *Protherics acknowledged FDA's comments. There was no further discussion.*

7. **Does FDA agree that the modifications to the neutralizing (enzyme inhibition) assay, using quantified rabbit anti-glucarpidase antibody for detecting the presence of neutralizing antibodies, and its planned re-validation, are acceptable to the agency (see Section 9.7 and Table 2)?**

PRELIMINARY COMMENTS SENT JUNE 1, 2007: There is not adequate information or data to comment; however we have the following comments and requests for additional information:

a. Please state the source of the purified and quantified rabbit anti-glucarpidase that will be utilized in the assay.

DISCUSSION DURING THE TELECONFERENCE: *Protherics acknowledged and agreed to provide the requested information.*

b. Please validate and provide data addressing the specificity of the assay.

DISCUSSION DURING THE TELECONFERENCE: *Protherics acknowledged and agreed to provide the requested information.*

c. Please validate and provide data as to the sensitivity and range of the assay. Ideally, validation of the assay sensitivity would involve the use of

appropriately diluted plasma from an unexposed patient population spiked with known concentrations of positive control antibody.

DISCUSSION DURING THE TELECONFERENCE: *Protherics acknowledged and agreed to provide the requested information.*

d. Please assess the robustness of the assay (e.g. using hyperlipemic plasma), and test the effect of onboard product or likely concomitant medications on the neutralization assay.

DISCUSSION DURING THE TELECONFERENCE: *In response to FDA clarifying that that lipids can interfere with binding, Protherics agreed to test for these interferences by spiking samples and defining a range of variability for which the assay is valid. Protherics also noted that they would perform stability studies on the positive controls to ensure that they are stable for the duration of the testing.*

e. Please specify how the cut off for each assay will be calculated. Ideally, the assay cut off would be calculated using appropriately diluted plasma from an unexposed patient population (20-40 blank donors/ untreated patients).

DISCUSSION DURING THE TELECONFERENCE: *Protherics acknowledged and agreed to provide the requested information.*

f. Please submit representative data for the samples as well as for the standard curve.

DISCUSSION DURING THE TELECONFERENCE: *Protherics acknowledged and agreed to provide representative calculations and raw data (titers, O.D readings, etc) in tabular format.*

g. Additional guidance on qualification of a neutralizing assay can be found in Gupta et al, 2007.

DISCUSSION DURING THE TELECONFERENCE: *Protherics acknowledged the guidance source provided by FDA.*

8. **Does FDA agree that the methods for collection and storage of patients' samples prior to testing are satisfactory (see Section 10)? At FDA's request, we have been asked to include anti-glucarpidase antibody collection at baseline, 7 – 10 days, and 4 – 6 weeks post-dosing for the treatment protocol. Is this sampling schema sufficient for testing our 100 patients for the post-approval commitment (ie, no 3 or 6 month followup)?**

PRELIMINARY COMMENTS SENT JUNE 1, 2007: No, patients that develop IgG or IgE antibodies to glucarpidase should have serum collected at 3 and 6 months post treatment to determine whether the titers go down.

DISCUSSION DURING THE TELECONFERENCE: *Protherics asked for clarification as the proposed antibody collection was different than what was asked for in the Treatment Protocol. FDA replied that it was in the best interest of patients to totally characterize the antibody response to the product, and to use the data for labeling statements that would apply to retreated patients. FDA noted that for single use treatment, immunogencity was not a major issue, but that there was a concern that patients will be re-treated off-label. FDA noted that if this information is not collected, it will impact requests for re-treatment on the treatment protocol and the product labeling will indicate the lack of data. FDA recommended 3 and 6 month antibody monitoring apply to the treatment protocol.*

Additional Comments:

As you progress in the validation of your assays please address the following issues. These will need to be included in the BLA validation package:

9. Please provide specifications for critical reagents utilized. It is recommended that several lots of all your critical reagents are tested to ensure the continued reliability of the assay and that you establish an SOP to enable the use of a new lot of critical reagents when needed. This approach will ensure the continuous reliability of your assays.

10. We recommend you perform additional tests to assess the robustness of the assays such as, but are not limited to, changes in temperature, pH, buffer, incubation times, reagent storage conditions, serum storage conditions or the presence of hemolized red blood cells or higher lipid content in sera.

11. Please set specifications and a plan for periodic qualification for antibodies that will be used as controls/standards in your assays. Please provide assurance that you have adequate data to support the ongoing use of this antibody (characterization data, certificate of analysis and stability data).

12. Additional information on the validation of analytical procedures can be found in ICH Q2b"Validation of Analytical Procedures: Methodology".

Action Items:

Protherics agreed to submit a proposal for alternate IgG and IgM assays within several weeks of the teleconference. Protherics also agreed to consider incorporation of the FDA-suggested 3 and 6 month sampling timepoints in the treatment protocol.

Linked Applications	Sponsor Name	Drug Name
IND 11557	PROTHERICS INC	Glucarpidase [Carboxypeptidase G2]

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/s/

ERIK LAUGHNER
07/03/2007

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug
Administration
Rockville, MD 20857

IND 11557

Protherics, Incorporated
Attention: Carol Clark-Evans
Vice President, Regulatory and Clinical Affairs
5214 Maryland Way, Suite 405
Brentwood, TN 37027

Dear Ms. Clark-Evans:

Please refer to your IND for "Glucarpidase [Carboxypeptidase G2]." We also refer to the meeting held on April 28, 2006, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1393.

Sincerely,

{See appended electronic signature page}

Erik S. Laughner
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosures - Meeting Minutes
Attendance Sheet

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	April 28, 2006
TIME:	3:00 PM EST
LOCATION:	WO, Room 1313
APPLICATION:	11557
DRUG NAME:	Glucarpidase [Carboxypeptidase G2]
TYPE OF MEETING:	Pre-BLA
MEETING CHAIR:	Dr. Patricia Keegan
MEETING RECORDER:	Erik Laughner

FDA ATTENDEES:

Patricia Keegan, Director, DBOP/OODP
Erik Laughner, RPM, DBOP/OODP
Hong Zhao, Team Leader, Clinical Pharmacology/DCP5
Karen, Jones, CPMS, DBOP/OODP
Joseph Gootenberg, Medical Team Leader, DBOP/OODP
Patricia Dinndorf, Medical Reviewer, DBOP/OODP
Karen Weiss, Deputy Director, OODP
Richard Pazdur, Director, OODP
Emanuela Lacana, Product Reviewer, DTP/OBP
Henry Startzman, Orphan Products, OOPD
Yuan-Li Shen, Statistical Reivewer, OPSS/OB

PROTHERICS ATTENDEES:

Elizabeth Lovell
Sally Waterman
Peter Adamson
Carol Clark-Evans
Brigitte Wideman
Matt Boron
Nalini Jayaprakash
Jan Casadei
Tim Auton
John Constant
S. Percy Ivy

BACKGROUND: On February 17, 2006, Protherics, Inc., requested a formal meeting to seek clarification on FDA's December 5, 2005, Advice and Information letter and to reach agreement on unresolved issues which are critical to the content of a planned BLA submission. In addition, Protherics, Inc., would like to discuss a prospective statistical analysis plan for Study PR001~CLN-rpt006 which would serve as the primary efficacy and safety dataset. FDA determined that the meeting would be conducted as a PDUFA type "B" meeting. The meeting briefing packages were received on March 21, 2006.

DISCUSSION POINTS:

Sponsor Submitted Questions:

1. In a letter dated 5 December 2005, the FDA stated that the two studies previously proposed by Protherics as pivotal (NCI and Berlin studies, PR001-CLN-rpt002 & PR001-CLN-rpt001) were not considered adequate to serve as the primary data in support of the efficacy and safety of Voraxaze. FDA indicated that 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 (b) (4) This study, which began enrollment in July 2004, has a cut-off date of 4 November 2005, at which time the NCI simplified the protocol to remove collection of patient samples. Data on 8 patients has previously been reported (IND Amendment 018 dated 16 August 2005). As requested by the FDA in the 5 December 2005 letter, the BLA will include all available data on patients enrolled in this study, which consists of the following:

   N = 68
   N enrolled but untreated = 0
   N with HPLC MTX data = 27 (minimum)
   N with anti-glucarpidase antibody data = 27 (13 complete; 14 incomplete)

   FDA indicated in its letter of 5 December 2005 that Study PR001-CLN-rpt006 was not acceptable to support licensure because the statistical analysis plan had not been revised as previously requested. Protherics has therefore prepared a revised prospective statistical analysis plan (SAP) for this study that incorporates FDA's guidance in a letter dated 31 March 2004 and at meetings on 13 April and 9 November 2004 and wishes to have FDA's agreement to this plan prior to analyzing the full dataset. **Is this plan (Appendix 2) acceptable for analysis of the primary efficacy and safety data in support of a request for regular approval of Voraxaze? If not, how does the FDA recommend the plan be modified to meet this objective?**

FDA Comments Faxed on April 27, 2006: The statistical analysis plan is not acceptable. The analysis should include all eligible patients, that is patients with impaired methotrexate clearance with methotrexate levels > 1 μmol/L prior to treatment with glucarpidase. The analysis should be to determine the point estimate of response rate and determination of the confidence intervals around the observed proportion of eligible patients with sustained post glucarpidase methotrexate levels ≤ 1 μmol/L measured by HPLC. A subgroup analysis should be conducted on groups based on baseline methotrexate levels. (such as patients with > 1, >10, or > 100 μmol/L immediately prior to treatment; you may also conduct analyses in other subgroups with justification for the subgroup selection). Given that eligibility criteria were different for patients with osteosarcoma as compared to patients with other diagnoses, please perform subset analysis in patients with osteosarcoma and in those with other cancer subtypes.

***Discussion During Meeting**: Protherics, Inc., acknowledged the FDA's responses to question 1, including parts a-f (below), and noted that the responder analysis would be performed and that subgroup analysis could also be analyzed, albeit with a small N. Protherics, Inc., agreed to revise the SAP to address FDA comments and submit this under the IND for review prior to the BLA submission.*

Sponsor Questions: Specifically, we would appreciate comments on the acceptability of the following to support registration:

a. The primary objective: Estimate the proportion of patients who achieve 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 Comments Faxed on April 27, 2006: This is acceptable.

b. The primary endpoint: Maximum pMTX determined by HPLC analysis in any post-glucarpidase sample.

FDA Comments Faxed on April 27, 2006: This is acceptable.

c. The primary hypothesis: The proportion of patients achieving CIR is at least 35%, based on a one-sided statistical test with P = 0.025. This is equivalent to showing that the symmetric 95% confidence interval as calculated above is entirely above 0.35.

FDA Comments Faxed on April 27, 2006: A hypothesis should be developed prior to study data availability. A primary hypothesis proposed after the results of the trial are already available is neither relevant nor necessary.

d. The primary analysis method: The analysis method is described in detail in the SAP (provided in Appendix 2). In essence, linear regression modeling will be used to analyze the statistical distribution of the maximum post-glucarpidase concentration after adjustment for the estimate.

FDA Comments Faxed on April 27, 2006: This is not acceptable, as discussed above. The primary analysis should be a point estimate of the CIR rate with a corresponding confidence interval for those patients in the analysis set, not for some target population.

e. The primary analysis population: Patients with pMTX determined by HPLC (alternative assays are known to be affected by cross-reactivity with DAMPA and other metabolites of MTX) and pMTX >1 umol/L in their last sample before receiving glucarpidase (threshold associated with higher incidence of severe MTX toxicity).

FDA Comments Faxed on April 27, 2006: This is acceptable.

f. The power calculation: A study with evaluable samples from at least 20 patients will have more than 90% power to show that, with 97.5%confidence, the predicted proportion of CIRs in the target population exceeds 35%.

FDA Comments Faxed on April 27, 2006: No. A power calculation is neither relevant nor necessary at this stage of the protocol.

2. The agency's letter of 5 December 2005 also notes deficiencies in the design of Study PR001-CLN-rpt006, specifically with regard to collection of immunogenicity and pharmacokinetic data. The rationale for the study design in the setting of emergency compassionate use treatment has previously been presented by Protherics and the NCI at meetings on 13 April 2004, 9 November 2004 and 21 July 2005. Sections 9.1 and 9.2 of this submission contain proposed post approval commitments for collecting glucarpidase pharmacokinetic data in patients (as requested in point 3.c of the 5 December 2005 letter) and additional immunogenicity data to supplement the results from 'the studies to be included in the BLA. **Does the Agency have any comments on these proposed plans?**

FDA Comments Faxed on April 27, 2006: This is not acceptable. The proposed plan to collect immunogenicity data will be inadequate to characterize the potential risk. As you were informed during the November 9, 2004, meeting with us, and as reflected in the meeting minutes issued, you were informed that "You 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." Furthermore, you stated in question 1 above that the NCI simplified the protocol to remove collection of patient samples. It has come to our attention that the protocol amendment of October 31, 2005, was not submitted as a protocol amendment to BB-IND (b) (4) Although we have not received the amendment, we wish to inform you that this revision is not acceptable because such data are necessary to characterize the toxicity of your product and provide adequate directions for use.

Study PR001-CLN-rpt006, which was amended to stop collecting samples in November 2005 [as stated in the background of your first question], should be amended as soon as practical to resume collection of patient samples for immunogenicity testing on days 14, 21, and 28. All available immunogenicity data from patients enrolled in Study PR001-CLN-rpt006 should be submitted in the original BLA; additional immunogenicity testing data obtained after submission of the BLA should be included in the day 120 safety update of the BLA.

In order for pharmacokinetic (PK) information obtained from patients with circulating methotrexate to be included in the product label, preliminary PK data from the PR001-CLN-rpt011 trial should be submitted in the original BLA and additional data obtained after the submission of the BLA should be submitted with the day 120 safety update to the BLA.

Discussion During Meeting: *Protherics, Inc., stated that is was not possible to obtain samples from the ongoing NCI study due to their inability to ensure sample collection under this protocol; instead, Protherics Inc., proposed to revise the proposed post-marketing commitment by expanding the sample size to 100 patients, who would be assessed at 28 days post-Glucarpidase with additional samples to be obtained in those patients who were seropositive at day 28. FDA noted that generally a minimum of 300 patients was useful immunogenicity experience and this was a safety issue in a pre-approval setting. FDA stated that all available data should be submitted at the time of the BLA, but agreed to the concept of a PMC to collect additional safety information and inquired what studies Protherics, Inc., could perform to collect and provide this data in the original BLA.*

Protherics, Inc., noted that they submitted an amendment to IND 11557 regarding prospectively specified antibody sample collection and processing from approximately 40 subjects participating in trials at a single site at MD Anderson Cancer Center. Protherics, Inc., anticipated that at least some of the MD Anderson data would be available for inclusion in the original BLA submission and additional data provided at a later timepoint (same time as the 120-day safety update). FDA cautioned that limited patient data could result in label restriction to a single dose. Protherics, Inc., acknowledged and noted that based on the above discussion, the NCI protocol would not be amended.

Protherics, Inc. agreed to provide the PK data and all safety information at original submission and supplement with additional data later in the review, in conjunction with the 120 day safety update. In response to an FDA inquiry on the immunogenicity assay methodology, Protherics, Inc., noted that a previously submitted, June 17, 2005, amendment to the IND contained validation on the ELISA (binding) assay. A detailed description of the neutralization assay method and validation has not yet been submitted to the IND. FDA asked that the neutralization assay be submitted to the IND for Agency review and comment prior to BLA submission and prior to analysis of patient samples for ongoing studies. Protherics, Inc., acknowledged, and noted that samples were being batched for future analysis. For reviewer convenience, Protherics, Inc., agreed to provide all the assay (ELISA and neutralization) information in one future IND amendment.

3. In points 5.a.4, 5.b.4 and 5.c.5 of the 5 December 2005 letter, the FDA indicates that patient narratives and case report forms (CRFs) are to be provided for any patient who experienced a serious adverse event (SAE), death within 30 days of last receipt of study drug, or who withdrew consent (dropped out). Protherics will include this information in the BLA with one proposed modification. Narratives and CRFs will be provided only for SAEs that were not considered MTX-related, rather than all SAEs, on the basis that protocol inclusion criteria required every patient enrolled in the studies to be at risk of MTX toxicity which would qualify as a SAE and in practice every patient enrolled was experiencing MTX toxicity. Full details of the MTX toxicities experienced and their resolution, or otherwise, are include in the clinical study reports. **Is this proposal acceptable to the agency?**

FDA Comments Faxed on April 27, 2006: No. Because we do not believe you can reliably assess attribution of toxicity for an investigational agent, you should provide narratives for all SAEs.

***Discussion During Meeting**: Protherics, Inc., acknowledged the FDA's comment and agreed to provide narratives for all SAEs.*

Pharmacology and Toxicology

4. In point 2.b of the 5 December 2005 letter, the FDA requested that all programs used in the analysis of the non-clinical studies be provided in the BLA. Analysis of the rat and dog toxicology studies (listed in point 2.a of the letter) was limited to descriptive statistics, so no programs will be provided in the BLA. **Is this acceptable?**

   FDA Comments Faxed on April 27, 2006: This is acceptable if you provide a citation to the program or procedure used to analyze the data.

   Discussion During Meeting: *Protherics, Inc., acknowleged the FDA's comment and agreed to provide the requested information.*

Regulatory

5. Voraxaze is intended for use in patients at risk of MTX toxicity that are not adequately treated with existing therapies. Protherics intends to request priority review of the BLA on the basis that the product addresses an unmet medical need in the indicated patient population (Appendix 3). **Does the agency agree that this product would qualify for priority review?**

   FDA Comments Faxed on April 27, 2006: The BLA may be considered for priority review. However, the final determination of designation will be made when the BLA is submitted.

   Discussion During Meeting: *Protherics, Inc., acknowleged FDA's comment.*

6. To expedite review of this product that addresses an unmet medical need in a potentially life-threatening condition, Protherics would like to submit non-clinical sections of the BLA as IND amendments. We recognize that commencement of the review would depend on FDA workload and priorities. **Would this be acceptable to the agency?**

   FDA Comments Faxed on April 27, 2006: Filing of reports to the IND would not necessarily expedite the review. If you wish FDA to initiate an earlier review of certain complete sections (such as the toxicology section) of the BLA, we recommend that you submit a request for Fast Track designation. If granted, you can request a "Rolling BLA" which would allow for the submission of separate reviewable units [Guidance information: see http://www.fda.gov/cder/guidance/].

   Discussion During Meeting: *Protherics, Inc., acknowleged FDA's comments.*

Additional Comments:

7. In your BLA submission, please provide information on any endogenous and exogenous compounds that may be substrates of carboxypeptidase to explore the possibility of drug interactions.

   Discussion During Meeting: *FDA clarified that a literature search could be performed for proposed substrates of carboxypeptidases G and if a relevant compound is discovered, in vitro studies should be performed to assess for possible drug-drug interactions as the first step. Protherics, Inc., should provide justification/rationale that drug-drug interactions are not likely to occur or to affect Glucarpidase or other drug activity.*

8. Please confirm that the datasets will contain all primary data required to be collected per-protocol and as requested in previous meetings, telecons, and letters.

   Discussion During Meeting: *Protherics, Inc., acknowleged the FDA's comment and noted that the datasets would be complete.*

9. Please clarify the manner in which acquisition time for time-dependent data will be displayed in the datasets.

   Discussion During Meeting: *Protherics, Inc., clarified that the time recorded was the actual time of sample acquisition. Protherics, Inc., agreed to provide a derived value based on time relative to dosing in the datasets.*

10. Please submit a detailed description of the immunogenicity assays pertaining to the measurement of anti-glucarpidase antibody and assessment of their neutralization potential, as requested on April 13, 2004, and July 20, 2004. The description should address reproducibility, sensitivity, specificity, accuracy and precision of the assays. Please be aware that these assay(s) need to be validated at the time the BLA is submitted. If you do not provide results using a validated assay(s) in the BLA, determination of a risk:benefit assessment in patients will be impacted.

    Discussion During Meeting: *As noted in the discussion of question 2 above, Protherics, Inc., agreed to submit the neutralization and ELISA assay methodology and validation data together for Agency review prior to further sample analysis.*

Additional Discussion:

Protherics, Inc., noted that they did not intend to seek Fast Track designation and anticipated that their BLA would be submitted in August of 2006. Protherics, Inc., also stated that they had recently submitted a request for tradename review under IND 11557.

MEETING ATTENDANCE LIST

Meeting between Protherics and the Center for Drug Evaluation and Research.

DATE: 04/28/06 TIME: 3:00 PM ROOM: WO22, Room 1313

NAME - Please print	AFFILIATION
Erik Laughner	DBOP/CDER
Elizabeth Lovell	Protherics
Sally Waterman	Protherics
(b) (4)	
Carol Clark-Evans	Protherics Inc.
Brigitte Widemann	NCI/POB
Matt Boron	NCI
NALINI JAYAPRAKASH	NCI, POB
Jan Casadei	NCI
TIM AUTON	Protherics
(b) (4)	
Peraylu	NCI, CTEP, IDB
HONG ZHAO	FDA/CDER/OCP
Yuan-Li Shen	FDA/CDER/OB
Patricia Dinndorf	DBOP/OODP/CDER
Patricia Keegan	DBOP/OODP/CDER
Richard Pazdur	FDA/CDER
Joe Gootenberg	FDA/DBOP/OODP/CDER
Karen Weiss	FDA/OODP/CDER
Emanuela Lacana	FDA/OBP/DTP/CDER
Karen Jones	FDA/OWP/OODP/DBOP
Henry Starteman	FDA/OODP

Linked Applications	Sponsor Name	Drug Name
IND 11557	PROTHERICS	Glucarpidase [Carboxypeptidase G2]

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/s/

ERIK LAUGHNER
05/24/2006