CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125327Orig1s000

OTHER REVIEW(S)

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

Memorandum

Date: 1/13/12 ESL 01/13/12

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

Subject: BTG International Inc.; BLA STN 125327; TB-EER completed

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From: Ramanadham, Mahesh
Sent: Friday, January 13, 2012 8:58 AM
To: Laughner, Erik; CDER-TB-EER
Subject: RE: Request for EER (compliance check); Pending BLA STN 125327 (BTG International); Voraxaze

Dear Erik,

Please find the completed TB-EER below, there are no pending or ongoing compliance actions that prevent approval of this BLA.

TB-EER response
STN 125327 (gl...

Sincerely,

Mahesh Ramanadham, PharmD/M.B.A.
LT., USPHS
Regulatory Compliance Officer
CDER, Office of Compliance
Office of Manufacturing and Product Quality,
Division of Good Manufacturing Practice Assessment
New Drug Manufacturing Assessment Branch
(301)796-3272

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:
The review team should email this form to the email account "CDER-TB-EER" to submit:

1) an initial TB-EER within 10 business days of the application filing date
2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing[1] locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: Jan 17, 2012

Applicant Name: BTG International
U.S. License #: [not assigned]
STN(s): 125327/0
Product(s): glucarpidase (Voraxaze®)
Short summary of application: new BLA

FACILITY INFORMATION

Manufacturing Location:
Firm Name: Eurogentec S.A.
Address: Liege Science Park, Rue du Bois Sant Jean 14; 4102 Seraing, Belgium
FEI: 3003323169 (b) (4)
Short summary of manufacturing activities performed: drug substance manufacturing.

This site has been inspected in support of this BLA by CDER/OMPQ and classified VAI. The inspection took place from 10/17/11-10/28/11 and was found acceptable by DIDQ.

Manufacturing Location:
Firm Name: (b) (4)
Address: (b) (4)

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[1]The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

(b) (4)
Short summary of manufacturing activities performed: (b) (4) of in-process and DS samples

(b) (4) and classified VAI. The inspection covered control testing laboratory operations for the glucarpidase BLA. This site is acceptable for this supplement.

Manufacturing Location:
Firm Name: (b) (4)
Address: (b) (4)
(b) (4)
Short summary of manufacturing activities performed: release and stability testing for drug substance and drug product with the exception of sterility and endotoxin.

Inspected by (b) (4) and classified NAI. The CTL profile was updated and is acceptable.

Manufacturing Location:
Firm Name: Cangene bioPharma Inc.
Address: 1111 South Paca St., Baltimore, MD 21230-2591
FEI: 1000512361
Short summary of manufacturing activities performed: drug product manufacturing; sterility and endotoxin testing for release and stability study of the drug product.

Inspected by BLT-DO from July 18-22, 2011 and classified VAI. This was a pre-approval inspection as well as a general cGMP surveillance inspection. The SVS, SVL, and TRP profiles were updated and are acceptable.

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

PMC #16 Description: BTG commits to develop and implement a more sensitive assay for the measurement of (b) (4) in drug substance. The results of the assay development and validation, and proposed specifications along with a justification based on appropriate non-clinical data, will be submitted to the Agency.

PMC Schedule Milestones:

Final protocol Submission Date:	MM/YYYY
Study Completion Date:	MM/YYYY
Final Report Submission Date:	MM/YYYY
Other: _____	MM/YYYY

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- X☐ Improvements to methods
- ☐ Theoretical concern
- X Manufacturing process analysis
- ☐ Other

The sponsor currently has an assay that measures (b) (4) content in the drug substance at release. The limit of quantitation is (b) (4) and the limit of detection of the assay is (b) (4). The acceptance criteria proposed by the sponsor is (b) (4) the same as observed for the material used in the clinical studies. However, several lots have (b) (4) of this impurity and would fail the release specification. Product specific toxicology data supporting the LOQ or LOD are unavailable. The LOD is monitored in every assay. The review team felt that the risk to product safety at levels below the LOD was small given the nature of the impurity and the existing clinical data. Revising the assay and increasing the acceptance criteria will require additional assay development and may require supporting non clinical data. These activities could not be completed within the review cycle.

2. Describe the particular review issue and the goal of the study.

At the current limit, the method is (b) (4) introducing additional variability. Additionally, multiple lots will fail specification. In order to better ensure assay precision, product quality and product availability, the results should be (b) (4) increase in the allowable content supported with appropriate non clinical data. The applicant needs to revise the assay by improving the limit of quantitation and detection of the assay, to revise the acceptance criteria and perhaps to perform an additional non-clinical study to support any proposed increase in the upper limit of acceptance.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- X☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- X☐ Impurity characterization
- ☐ Reformulation
- X Manufacturing process issues
- ☐ Other

Describe the Agreed upon study:

BTG need to improve the sensitivity of the assay by lowering the limit of quantitation and detection and revise specification. The proposed specification should be supported by non-clinical toxicology study, as discussed by the pharm-tox reviewer

5. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

1/10/12

(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

PMC #15 Description: BTG commits to develop a primary reference standard that will be used to qualify future working standard. BTG also commits to revise the reference standard qualification protocol. The revised protocol will be submitted to the Agency before future reference standards, with the esclusion of the current M-CG2-P011 reference standard, are qualified.

PMC Schedule Milestones:

Final protocol Submission Date:	MM/YYYY
Study Completion Date:	MM/YYYY
Final Report Submission Date:	MM/YYYY
Other: _____	MM/YYYY

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- X Manufacturing process analysis
- ☐ Other

Lot M-CG2-P11 is going to be used for the reference standard when this application is approved. This lot was used for process validation (b) (4) Product attributes have been reviewed and support use of this lot as the new reference standard. BTG will require additional time to update their reference standard qualification protocol, and will thus not be able to update this program before a regulatory action is taken on this application.

2. Describe the particular review issue and the goal of the study.

The improvement in the qualification protocol include the following;

1. A primary reference standard will be established that will be used to qualify future reference standards.
2. Acceptance criteria for future reference standards should be established to ensure that material is comparable to the phase III clinical lots.
3. Acceptance criteria for qualification of reference standards should be tighter for product attributes, compared to routine lot release and stability evaluation. This will prevent drift in product attributes as future standards are qualified.
4. The number of samples used in analytical testing for qualification of reference standards 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.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- X Manufacturing process issues
- ☐ Other

Describe the Agreed upon study:

Please see number 2 for items to be included in the new reference standard qualification protocol.

5. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

1/12/12

(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

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PMC #14 Description: BTG commits to establish a robust testing protocol for the qualification of incoming Host Cell Protein assay kits. The qualification protocol will be submitted to the Agency.

PMC Schedule Milestones:

Final protocol Submission Date:	MM/YYYY
Study Completion Date:	MM/YYYY
Final Report Submission Date:	MM/YYYY
Other: _____	MM/YYYY

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- X☐ Other

The sponsor is using a commercial kit to quantify residual host cell proteins (b) (4) The kit is a critical incoming material and should be appropriately qualified to ensure that the quantification of the host cell proteins is accurate and reproducible. The major concern with HCP is the potential to act as adjuvant in an immune response against the product. Since the product is administered only once, there is a low level of risk that contaminating HCP would function as adjuvant in mounting an immune response to the product.

2. Describe the particular review issue and the goal of the study.

BTG utilizes a commercial kit for the detection of Host Cell Proteins. The kit is an immunoassay that uses antibodies generated against E. Coli proteins. There is a concern that the antibody used in the kit may not be manufactured reproducibly and therefore impact the reproducibility and accuracy of detection of the HCP in the glucarpidase drug substance. Adequate procedure should be in place to ensure consistency of this critical material.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- X☐ Other

Describe the Agreed upon study:

BTG should provide a protocol describing the procedure, tests and control to be implemented to ensure the consistency of the HCP detecting kit.

5. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

1/12/12

(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

PMC #13 Description: BTG commits to reevaluate the specificity of the Host Cell Protein method by qualifying the anti-HCP antibody by two-dimensional electrophoresis. The study report will be submitted to the Agency.

PMC Schedule Milestones:

Final protocol Submission Date:	MM/YYYY
Study Completion Date:	MM/YYYY
Final Report Submission Date:	MM/YYYY
Other: _____	MM/YYYY

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- X☐ Improvements to methods
- X☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

The Host Cell Protein detection method uses a commercial kit. The method is adequate to detect E. coli proteins, but BTG has not provided sufficient evidence that the method is specific to detect the majority of proteins from the E. coli host cell line. The method detects HCP as reported by BTG in their release testing results and since the product is administered only once, there is a low level of risk that contaminating HCP would function as adjuvant in mounting an immune response to the product. Also high levels of an HCP impurity would be detected in other release tests.

2. Describe the particular review issue and the goal of the study.

BTG utilizes a commercial kit for the detection of Host Cell Proteins. The kit is an immunoassay that uses antibodies generated against E. Coli proteins. Since the strain of E. coli used to generate the antibody is different than the strain used by BTG, and the HCP that are present in the in process material may be different, the sponsor should demonstrate that the antibody used in the kit can detect the majority of the HCP proteins that are present in the process stream that produces glucarpidase.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- X☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the Agreed upon study:

BTG should conduct a study to demonstrate that the antibody form the commercial kit can detect the majority of the proteins that are present in the process stream that produces glucarpidase. The host strain proteins should be separated by two-dimensional gel electrophoresis and either stained with Silver stained or analyzed by Western blot using the kit's antibody. A similar pattern of proteins should be identified by the two detection system, in support of the idea that the kit's antibody adequately recognizes the majority of the E. coli host strain proteins.

5. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

11/4/12

(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

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PMC #12 Description: BTG commits to evaluate recovery of the protein loaded onto RP-HPLC and SEC-HPLC column. The study report will be submitted to the Agency.

PMC Schedule Milestones:

Final protocol Submission Date:	MM/YYYY
Study Completion Date:	MM/YYYY
Final Report Submission Date:	MM/YYYY
Other: _____	MM/YYYY

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- X☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

The RP-HPLC and SEC-HPLC methods have been validated to measure purity of the drug substance and drug product as a percentage of the total peak area. However, BTG did not evaluate the recovery of the proteins loaded on the RP-HPLC and SEC-HPLC columns.

2. Describe the particular review issue and the goal of the study.

In the assay validation of RP-HPLC and SEC-HPLC, the sponsor has not demonstrated that all the material loaded on the column is recovered. If the product it retained on the column, determination of the purity as a percent of total peak area would not be accurate, for example if a specific impurity is retained and not eluted from the column. Therefore, the sponsor should measure the mass balance of the separated product variants and impurities and compare it to the mass loaded onto the column.

3. [OMIT — for PMRs only

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4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- X☐ Other

Describe the Agreed upon study:

BTG should determine the mass balance for both RP-HPLC and SEC-HPLC peaks as % of the loaded material.

5. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

1/10/12

(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

PMC #11 Description: BTG commits to develop and implement an enzyme activity potency assay that measures the generation of the product of the enzyme reaction in the drug substance and drug product release and stability programs, if feasible. The results of the assay development and validation, and proposed specifications will be submitted to the Agency.

PMC Schedule Milestones:

Final protocol Submission Date:	MM/YYYY
Study Completion Date:	MM/YYYY
Final Report Submission Date:	MM/YYYY
Other: _____	MM/YYYY

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☒ Other

The current potency assay is adequate for the approval of the product; however, the assay is not optimal. The assay monitors the loss of substrate and this type of assay has a narrower dynamic range compared to assays that measure product generation. Developing a new assay requires considerable effort and could not be accomplished within the review cycle.

2. Describe the particular review issue and the goal of the study.

BTG has used a potency assay that monitors the loss of substrate (methotrexate) instead of accumulation of product. The enzyme activity assay is not optimal, since loss of substrate is a less sensitive readout than generation of product and the assay also has a narrower dynamic range. For these reasons BTG should develop and implement an assay that measures the accumulation of the reaction product. This assay should also be used to derive the kinetic parameters for glucarpidase. This would also result in tightening of the specifications for Km and Kcat for both drug substance and drug product.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- X☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the Agreed upon study:

BTG should develop and implement an enzyme activity potency assay that measures the generation of the reaction product (DAMPA or glutamic acid) in both drug substance and drug product release and stability programs.

5. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

1/10/12

(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

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PMC #10 Description: BTG commits to include in the SDS-PAGE method, a reference standard loaded in amounts near the limit of detection of the assay. The revised specifications will be submitted to the Agency.

PMC Schedule Milestones:

Final protocol Submission Date:	MM/YYYY
Study Completion Date:	MM/YYYY
Final Report Submission Date:	MM/YYYY
Other: _____	MM/YYYY

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☒ Other

The current SDS-PAGE method for purity analysis of Glucarpidase is adequate. However, BTG did not include an internal control in the test method to ensure reproducible sensitivity of the test method. The results provide to date are adequate, but an internal control would ensure that the product would not drift from its current quality standard. The risk to product quality is relatively low; therefore this issue can be addressed post-approval.

2. Describe the particular review issue and the goal of the study.

BTG has used reducing SDS-PAGE followed by colloidal blue staining for purity determination of Glucarpidase. The specifications on glucarpidase monomer and impurities were set using the SDS-PAGE data. However, the sponsor did not include an internal control to monitor for gel de-staining. While the sponsor has set specific destaining time, loading an internal control, such as the reference standard, near the limit of detection of the assays, will ensure that the destaining procedure is consistent.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- X☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the Agreed upon study:

This is not a study as the sponsor will only need to add an additional control to the SDS-PAGE method.

5. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

1/12/12

(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

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PMC #9 Description: BTG commits to reevaluate the specificity of the SEC-HPLC method to detect aggregates using an orthogonal method and to include an aggregate control as assay suitability. The study report and revised specifications will be submitted to the Agency.

PMC Schedule Milestones:

Final protocol Submission Date:	MM/YYYY
Study Completion Date:	MM/YYYY
Final Report Submission Date:	MM/YYYY
Other: _____	MM/YYYY

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- X☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

The SEC-HPLC method is used for the detection of aggregates. However, the specificity of this assay has not been evaluated with an orthogonal test method to detect protein aggregates. Additionally, BTG did not include an aggregated control in the system suitability to ensure that the method reproducibly detects protein aggregate. Aggregated product is a concern because aggregates could enhance immunogenicity of the product. In this case, there is a low level of risk because the product is administered only once under acute methotrexate toxicity conditions. The use of an orthogonal method to evaluate the sensitivity of the method could not be accomplished within the time frame of the review cycle.

2. Describe the particular review issue and the goal of the study.

BTG did not evaluate aggregates in forced degradation studies using both SEC-HPLC and an orthogonal method, such as analytical ultracentrifugation, to ensure that SEC-HPLC is sensitive to detect all types of impurities (i.e., aggregates) in the product as recommended in ICH Q2A. Furthermore, the test system suitability does not include an aggregated sample. Running this sample would ensure that the test method reproducibly detects aggregates.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- X☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the Agreed upon study:

Because an appropriate protein aggregate standard is unavailable, BTG should evaluate aggregates level in forced degradation samples using SEC-HPLC and an orthogonal analytical technique, such as analytical ultracentrifugation.

5. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

PMC #4 Description: BTG commits to reevaluate CEX-HPLC and iCE specifications to establish acceptance criteria for all major peaks. The revised specifications will be submitted to the Agency.

PMC Schedule Milestones:

Final protocol Submission Date:	MM/YYYY
Study Completion Date:	MM/YYYY
Final Report Submission Date:	MM/YYYY
Other:	MM/YYYY

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- X☐ **Improvements to methods**
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- Other

The current assays are adequate taking into considering the clinical profile, the need for available product and the adequate but not robust control of the product related species. Establishment of appropriate acceptance criteria for these variants will require development of a better test method and results from multiple lots to establish acceptable limits. This task could not be accomplished within the time frame of the review cycle. As more manufacturing experience is gained, acceptance criteria for all individual peaks and impurities should be established and the acceptance criteria for these quality attributes be revised appropriately.

2. Describe the particular review issue and the goal of the study.

BTG plans to improve their CEX-HPLC and iCE methods and use the revised validated assays to set the specification limits for individual peaks (b) (4) The current separation methods do not give baseline resolution peaks and therefore are unsuitable for quantitative measurement (b) (4). BTG uses integrated area (b) (4) to set the specification criteria. (b) (4) This issue can be addressed as post manufacturing commitment.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☒ Other

Describe the Agreed upon study:

BTG will improve the baseline resolution of the CEX-HPLC and iCE assay and evaluates the results of the test methods on several lots of drug substance and drug product. Once sufficient data and manufacturing experience are gained, appropriate specifications can be established for both assays.

5. To be completed by ONDQA/OBP Manager:

- ☒ Does the study meet criteria for PMCs?
- ☒ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

PMC #3 Description: BTG commits to update the tryptic and Glu-C peptide mapping specification using new acceptance criteria to reflect control of impurities. 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.

PMC Schedule Milestones:

Final protocol Submission Date:	MM/YYYY
Study Completion Date:	MM/YYYY
Final Report Submission Date:	MM/YYYY
Other: _____	MM/YYYY

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

☐ Need for drug (Unmet need/ Life-threatening condition)
☐ Long-term data needed (e.g., stability data)
☐ Only feasible to conduct post-approval
☐ Improvements to methods
☐ Theoretical concern
☐ Manufacturing process analysis
X☐ Other

BTG already uses the peptide mapping assays in place to evaluate drug substance identity. This assay is multifunctional and is useful to assess product purity as well. BTG is monitoring purity using SEC-HPLC and RP-HPLC, but the peptide mapping assays will provide additional assurance that the product quality characteristics are well controlled. Establishment of appropriate acceptance criteria requires evaluation of the historical data and accumulation of additional data and could not be accomplished during the review cycle.

2. Describe the particular review issue and the goal of the study.

3. BTG is using tryptic and Glu-C peptide mapping methods mostly to determine identity. Peptide mapping is a relevant assay to assess purity as well as identity, and the information gained through these assays should be incorporated in the release and stability programs for drug substance and drug product.

4. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- X☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the Agreed upon study:

BTG should reevaluate the current peptide mapping assays and use them for determination of purity as well as identity.

5. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

PMC #2 Description: BTG commits to evaluate and monitor sub visible particulates in the range of (b) (4) for lots of drug product at release and onreal time and under stressed stability conditions. The results of the evaluation, a risk assessment and a proposed control strategy will be submitted to the Agency.

PMC Schedule Milestones:

Final protocol Submission Date:	MM/YYYY
Study Completion Date:	MM/YYYY
Final Report Submission Date:	MM/YYYY
Other: _____	MM/YYYY

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- X☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

Subvisible particles represent a potential product related impurity. They can increase the immunogenicity of protein therapies. This may not be as critical of an issue with this product since most patients will only use the therapy one time in their lives. The particulates testing used in the license application does not monitor for particles in the range of (b) (4) The sponsor will need time to develop this assay and acquire manufacturing experience to justify and to establish a suitable control strategy. Therefore this issue will be addressed as a PMC.

2. Describe the particular review issue and the goal of the study.

As stated in number 1, an assay to monitor subvisible particles should be developed for use in a risk assessment and development of a suitable control strategy, possibly for release and stability testing of the product. Methods are currently available but the sponsor will require time for method development. A method will be developed and validated, and used to monitor for subvisible particles. Once sufficient data is accumulated, based on the results and a risk assessment evaluation, if warranted the sponsor will establish a specification for this product related impurity.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- X☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the Agreed upon study:

The USP particulate method could be modified to monitory for particles in the range of (b) (4) (b) (4) Other methods are available that can be used for the same purpose and the sponsor will have to choose the method most suitable with the technology at their disposal. The method will be validated and particles will be monitored, to establish a normal range for this impurity for product release and stability.

5. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☑ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

1/12/12

(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

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PMC #1 Description: BTG commits to reevaluate the mixing step for the thawed formulated drug substance [redacted] (b) (4) to include an upper limit for the mixing time based on historical experience. The revised range for the mixing time of the formulated drug substance will be submitted to the Agency.

PMC Schedule Milestones:

Final protocol Submission Date:	MM/YYYY
Study Completion Date:	MM/YYYY
Final Report Submission Date:	MM/YYYY
Other: _____	MM/YYYY

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- X☐ Other

The drug product is mixed [redacted] (b) (4) when it is manufactured. The sponsor has not specified a maximum time for the duration of this step. Validation studies have been performed and they support a [redacted] (b) (4) time limit. This deficiency did not preclude a recommendation of approval since they is very little risk that it may impact product quality. Data provided in the application indicate that the product is stable and not likely to be impacted by extended mixing. [redacted] (b) (4) Nevertheless to be cGMP compliant an upper time limit should be established for this step.

2. Describe the particular review issue and the goal of the study.

To be compliant with cGMP an upper limit time limit should be specified for the mixing step when the drug product is produced. A study is not required. They sponsor will need to review historical manufacturing information and specify a time limit. This could not be completed during the review cycle so it is being addressed as a PMC.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the Agreed upon study:

NA

5. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has ~~been~~ reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

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PMC #17 Description: BTG commits to increase the number of vials sampled for the cake appearance testing. The revised sampling testing strategy will be submitted to the Agency.

PMC Schedule Milestones:

Final protocol Submission Date:	MM/YYYY
Study Completion Date:	MM/YYYY
Final Report Submission Date:	MM/YYYY
Other: _____	MM/YYYY

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- X☐ Improvements to methods
- ☐ Theoretical concern
- X Manufacturing process analysis
- ☐ Other

The number of vials currently evaluated in the appearance tests is small and assures an adequate but not robust control of product quality. In order to ensure product availability and to improve assurance of product quality, the Division of Therapeutic Proteins proposed updating the sampling procedure for appearance post-approval.

2. Describe the particular review issue and the goal of the study.

The number of vials the sponsor is using to evaluate appearance is not commensurate to the size of the lots produced. The test is adequate but not robust to assure product quality. Since appearance is a non-destructive method and vials can be evaluated for appearance prior to being used for other tests, BTG should propose an updated sampling plan that increases the number of vials evaluated for appearance.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- X Manufacturing process issues
- ☐ Other

Describe the Agreed upon study:

BTG should provide a revised testing sampling plan.

5. To be completed by ONDQA/OBP Manager:

   - ☐ Does the study meet criteria for PMCs?
   - ☐ Are the objectives clear from the description of the PMC?
   - ☐ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

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PMC #5 Description: BTG commits 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.

PMC Schedule Milestones:

Final protocol Submission Date:	MM/YYYY
Study Completion Date:	MM/YYYY
Final Report Submission Date:	MM/YYYY
Other: _____	MM/YYYY

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☒ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

The current specifications and acceptance criteria for the Km value are not optimal (b) (4) However, BTG has very limited understanding of process capability because the assay has been introduced very recently. In order to ensure product availability and improve the assurance of product quality, once more manufacturing experience is gained on this product, specifications for Km could be (b) (4) and revised appropriately. Considering that several lots of product need to be manufactured to accumulate sufficient data, this issue could not be addressed within the review cycle.

2. Describe the particular review issue and the goal of the study.

BTG uses a potency that has limited dilutional linearity, and the determination of Km values requires large extrapolations, which increase the variability of the Km calculation. BTG will have to manufacture several lots and re-evaluate the lower limit of the acceptance range once sufficient data becomes available. The specifications of the Km values for both drug substance and drug product will be (b) (4)

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- X☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the Agreed upon study:

The sponsor will calculate Km in several lots and once sufficient lots are manufactured, will propose a revised lower limit for the Km acceptance range and (b) (4) the specification.

5. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

1/12/12

(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

PMC #6 Description: BTG commits to reevaluate specification 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 the Agency

PMC Schedule Milestones:

Final protocol Submission Date:	MM/YYYY
Study Completion Date:	MM/YYYY
Final Report Submission Date:	MM/YYYY
Other: _____	MM/YYYY

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☒ Other

The current release and stability specifications for the drug substance and drug product are adequate to adequately ensure product quality and stability, but more robust programs should be developed to provide a better assurance of product quality. The acceptance criteria for many assays are wider then the current history to ensure product availability. While the lots produced so far have shown acceptable results that are on line with the manufacturing history and clinical experience, there is a risk that maintaining the current acceptance criteria could potentially result in lots that are within specification but out of trend with lots used in the clinical trials. To established process capability and reduce the risk to product quality, a larger number of product lots are necessary and manufacturing an adequate number of lots could not be accomplished during the review cycle.

2. Describe the particular review issue and the goal of the study.

Assays used for characterization and stability testing of Glucarpidase in general are adequate for approval. However, certain assays are still under development to improve baseline resolution of the separated peaks. Additionally, BTG proposed acceptance criteria for the drug substance and drug product release and stability specifications based on a calculation establishing ranges using 3 standard deviations. The acceptance criteria proposed by BTG are too wide and do not reflect manufacturing history or clinical experience.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- X☐ Other

Describe the Agreed upon study:

BTG should re-evaluate the release and stability control strategies and (b) (4) acceptance criteria based on results of lots manufactured with the commercial process and lots used in the clinical trials.

5. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

1/12/12

(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

PMC #7 Description: BTG commits 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.

PMC Schedule Milestones:
Final protocol Submission Date: _____
Study Completion Date: _____
Final Report Submission Date: _____
Other: _____ _____

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

☐ Need for drug (Unmet need/ Life-threatening condition)
☐ Long-term data needed (e.g., stability data)
☐ Only feasible to conduct post-approval
X Improvements to methods
☐ Theoretical concern
☐ Manufacturing process analysis
☐ Other

Development and implementation of new quantitative test method for qualification of complex raw materials of biological origin for glucarpidase manufacturing process can not be accomplished within the review cycle for the BLA and will require additional time.

2. Describe the particular review issue and the goal of the study.

Different batches of complex raw materials of biological origin are variable with respect to the ability to support cell growth. The company does not use quantitative functional tests for qualification of major components of the production medium (b) (4) for the fermentation process. The goal of this study is to develop and implement a quantitative functional test for evaluation of the growth promoting properties of critical complex raw materials. The test will be used for qualification of new batches of complex raw materials for the manufacturing process.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- X Manufacturing process issues
- ☐ Other

Describe the Agreed upon study:

The company will develop quantitative growth promotion tests that will be included as part of the release monographs for complex raw materials of biological origin (b) (4) (b) (4) The proposal will also be extended to (b) (4) The company will qualify three batches of each complex raw material (b) (4) (b) (4) for their ability to consistently support quantitative growth of the glucarpidase-expressing recombinant strain. This qualification stage will be used to support the setting of new acceptance criteria for release of these raw materials.

5. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

1/12/12

(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

PMC #8 Description: BTG commits to provide the results of the shipping validation study for the drug substance bulk and QC samples. The study report will be submitted to the Agency.

PMC Schedule Milestones:

Final protocol Submission Date:	(b) (4)
Study Completion Date:	
Final Report Submission Date:	
Other:	

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- X Other

Shipping validation study for the drug substance bulk and QC samples was initiated by the company and the initial results have been submitted for review. However, the study has not been completed yet. Taking into account that anticipated completion date for the study is close to the action date, which will not allow evaluation of the data within the review cycle, and that the sponsor has already shipped drug substance to the filling site without negative impact on product quality, results of the shipping validation study may be submitted as a PMC.

2. Describe the particular review issue and the goal of the study.

The goal of the study is validation of transportation of frozen glucarpidase drug substance and QC samples from Eurogentec S.A. (EGT) manufacturing site in Liege Science Park, Seraign, Belgium to Cangene Biopharma Inc (CBI) drug product manufacturing site in Baltimore, MD, USA.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- X Other

Describe the Agreed upon study:

To complete the validation of the shipment of the drug substance bulk and QC samples between EGT and CBI, the company will perform an additional validation study under two validation protocols (VOR/SVP/077.03 and GEN/SESP/348) This study will validate the use of the [redacted] (b) (4) container with minimum and maximum loads under different temperature profiles, including the worst case temperature conditions.

5. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

Sumnu

(signature line for BLAs only) 1/12/12

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

PMC #1 Description: 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.

PMC Schedule Milestones:		
	Final protocol Submission Date:	06/2013
	Study Completion Date:	06/2013
	Final Report Submission Date:	06/2013
	Other:	06/2013

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.* USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☒ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

This is not a pre-approval requirement because the applicant has qualified the assay with a single batch of drug substance. The applicant is being requested to complete the qualification using additional drug substance batches.

2. Describe the particular review issue and the goal of the study.

The bioburden assay is a compendial assay and has been qualified using one batch of drug substance. Confirmation using two additional batches should be completed.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☒ Other

Describe the Agreed upon study:

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.

5. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

Emmer 1/3/12

(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

---

PMC #1 Description:

1. 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.

PMC Schedule Milestones:		
	Final protocol Submission Date:	06/2012
	Study Completion Date:	09/2012
	Final Report Submission Date:	01/2013
	Other:	MM/YYYY

PMC #2 Description:

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

PMC Schedule Milestones:		
	Final protocol Submission Date:	06/2012
	Study Completion Date:	09/2012
	Final Report Submission Date:	01/2013
	Other:	MM/YYYY

PMC #3 Description:

3. Provide information and data for low temperature worst case shipping validation study for finished drug product in a CBE-30 by June 2012.

PMC Schedule Milestones:		
	Final protocol Submission Date:	
	Study Completion Date:	02/2012
	Final Report Submission Date:	06/2012
	Other:	MM/YYYY

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.* USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☒ Other

Container Closure Integrity of the Voraxaze drug product was qualified using nominal crimping parameters (b) (4) for the capper. Additional information requested using the worst case crimping parameters.

2. Describe the particular review issue and the goal of the study.

This study will provide qualification data of the container closure integrity of the Voraxaze drug product performed using worst case crimping parameters,

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☒ Other

Describe the Agreed upon study:

5. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

Summer 1/3/12

(signature line for BLAs only)

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☒ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

In the current post approval stability plan sterility is tested (b) (4) The sterility testing should be performed (b) (4). Performance of the container closure integrity (CCI) test in lieu of the sterility test for drug product stability samples is recommended.

2. Describe the particular review issue and the goal of the study.

The revised post approval stability plan will provide annual CCI data of the finished product vial in lieu of sterility testing.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☒ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the Agreed upon study:

6. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☒ Other

Firm stated that the low temperature worst case shipping validation study for finished drug product will be completed in (b) (4)

2. Describe the particular review issue and the goal of the study.

This study will provide low temperature worst case shipping validation data.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☒ Other

Describe the Agreed upon study:

7. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

Summer 1/3/12

(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for ***each*** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

PMC #1 Description: To analyze patient serum samples from the Voraxaze pivotal studies for the presence of anti-glucarpidase antibodies with neutralizing activity using a validated assay.

PMC Schedule Milestones:

Final protocol Submission Date:	MM/YYYY
Study Completion Date:	MM/YYYY
Final Report Submission Date:	MM/YYYY
Other: _____	MM/YYYY

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- ☐ Need for drug (Unmet need/ Life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- X Other

This drug is indicated for a single administration. The development of neutralizing antibodies would only be expected to impact efficacy if the drug were given more than once. The Sponsor has adequate screening and confirmatory assays for assessing anti-drug antibodies. These assays are adequate to assess for immunogenicity related safety concerns. Therefore assessing neutralizing antibodies addresses a potential efficacy question not a safety concern.

2. Describe the particular review issue and the goal of the study.

The Sponsor has started the validation of a LC-MS/MS method for the determination of anti-glucarpidase antibodies with neutralizing activity. The principle of this method will be to measure inhibition of MTX hydrolysis. Once the assay is validated, the presence of anti-glucarpidase antibodies with neutralizing capacity will be tested in banked serum samples from patients enrolled in the clinical trial that showed detectable amounts of binding antibodies.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- X Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

The study will be laboratory analysis of existing samples.

Describe the Agreed upon study:

5. To be completed by ONDQA/OBP Manager:

X Does the study meet criteria for PMCs? Yes the proposed study does not address a safety concern. Therefore it is appropriate for a PMC.

X Are the objectives clear from the description of the PMC? Yes

X Has the applicant adequately justified the choice of schedule milestone dates? We are still waiting for the Sponsor to provide dates.

X Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process? The Sponsor is already developing the assay. The Agency discussed this assay with the Sponsor during the review cycle.

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

SUMMEC 1/3/12

(signature line for BLAs only)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: BLA STN 125327

PMR Description: Modeling VORAXAZE rescue of intrathecal methotrexate overdose (b) (4) under the Animal Rule (21 CFR 601.90)

PMR Schedule Milestones:		
	Final Protocol Submission:	12/31/2015
	Study/Trial Completion:	not specified
	Final Report Submission:	01/31/2015
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

FDA is asking BTG International to conduct an animal study as a post-marketing requirement (PMR) to establish the safety and efficacy of Voraxaze™ (glucarpidase) administered by the intrathecal route under the "Animal Rule" (21 CFR 610.90), based on its expected use to treat accidental intrathecal methotrexate (IT MTX) overdose. The occurrence of accidental IT MTX overdose is infrequent; however, the consequences can be fatal and there are no approved intrathecal rescue agents for IT MTX overdose. The safety and efficacy of intravenous Voraxaze as a rescue agent for toxic plasma MTX concentrations have been established with the present approval of this BLA submission. Intrathecal use of Voraxaze is expected to provide additional therapeutic benefit to the existing standard of care for IT MTX overdose.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

There is a reasonable likelihood that once approved for the reduction of systemic, toxic methotrexate concentrations, commercially available Voraxaze will be administered intrathecally if and when IT MTX overdose occurs. BTG International provided anecdotal information from 9 subjects who received investigational glucarpidase to reduce methotrexate levels in cerebrospinal fluid following IT MTX overdose. This animal study is being asked for as a PMR because the number of accidental IT MTX overdose cases constitutes a small subset of patients that experience methotrexate overdose, and because it would be unethical to conduct a placebo-controlled clinical trial to establish the safety and efficacy of intrathecal Voraxaze in this setting. Therefore, BTG International must evaluate intrathecal administration of Voraxaze under conditions of the "Animal Rule" (21 CFR 601.90 for biological products) in order to assess the risks and benefits of its use to treat IT MTX overdose. Safety and efficacy data derived from the evaluation of intrathecal Voraxaze (b) (4) will be included in future product labeling and will inform clinical decisions about the timing and dosage of intrathecal Voraxaze following accidental IT MTX overdose.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☒ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

FDA is requiring and the applicant has agreed to conduct an animal safety and efficacy study to evaluate Voraxaze treatment of IT MTX overdose under the conditions of the "Animal Rule" (21 CFR 601.90 for biological products). BTG International proposes (b) (4) for IT MTX overdose and Voraxaze treatment. The animal safety and efficacy study conducted under 21 CFR 601.90 is expected to provide data that will establish a dosing regimen of Voraxaze that will provide clinically meaningful benefit to patients with IT MTX overdose.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

_____

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

1/12/12

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: BLA STN 125327

PMC Description: Safety testing of intravenous administration of [redacted] (b) (4)

PMC Schedule Milestones:

Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	MM/DD/YYYY
Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The safety of the intravenous administration of the [redacted] (b) (4) and any carryover into the final drug substance/product, has not been adequately addressed. The issue was identified late in the review cycle. The analytical assay used to detect [redacted] (b) (4) was implemented after the expiration date of the glucarpidase lots used for the toxicology studies and therefore, the [redacted] (b) (4) levels in the toxicology lots are unknowable. The manufacturing process remained unchanged during development of the glucarpidase lots used for toxicology studies and clinically. [redacted] (b) (4) was detectable at levels below the limit of quantification of the assay in one glucarpidase lot that has been used clinically.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The applicant must provide data to appropriately qualify the safety of [redacted] (b) (4) at the proposed specification for lot release. To obtain these data, a single dose toxicology study will need to be conducted in which animals are dosed intravenously with [redacted] (b) (4) alone and in the presence of Voraxaze, at the lot release specification limit set for [redacted] (b) (4)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

FDA recommends that BTG conduct a single dose, general toxicology study with a 14 day follow-up observation period including dose groups that receive (b) (4) alone and with Voraxaze. FDA also recommends the following: (1) that BTG test multiple dose levels of (b) (4) in order to identify a tolerable level that would qualify the safety of this agent for intravenous use; (2) that BTG test one dose level at the amount of (b) (4) (b) (4) that would be expected in a dose of Voraxaze if it contains the upper acceptance limit, plus at least one dose lower and potentially one dose higher than this amount; (3) that BTG include dose groups that receive Voraxaze plus additional (b) (4) equal to the amounts used in the (b) (4) arms alone to evaluate whether the presence of glucarpidase alters the safety of (b) (4), (4) that the study endpoints include clinical observations, clinical chemistry parameters and histopathology; (5) that necropsies be performed at the end of the 14 day observation period, and potentially within 24 to 72 hours after dosing if clinical observations indicate that the dosing is not tolerated.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☑ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

11/9/12

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: BLA STN 125327

PMR Description: PILOT STUDY for Modeling VORAXAZE rescue of intrathecal methotrexate overdose [redacted] (b) (4) under the Animal Rule (21 CFR 601.90)

PMR Schedule Milestones:

Final Protocol Submission:	Not needed
Study/Trial Completion:	Not needed
Final Report Submission:	01/31/2015
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

FDA is asking BTG International to conduct an animal study as a post-marketing requirement (PMR) to establish the safety and efficacy of Voraxaze™ (glucarpidase) administered by the intrathecal route under the Animal Rule (21 CFR 601.90), based on its expected use to treat accidental intrathecal methotrexate (IT MTX) overdose. The occurrence of accidental IT MTX overdose is infrequent; however, the consequences can be fatal and there are no approved intrathecal rescue agents for IT MTX overdose. The safety and efficacy of intravenous Voraxaze as a rescue agent for toxic plasma MTX concentrations has been established with the present approval of this BLA submission. Intrathecal use of Voraxaze is expected to provide additional therapeutic benefit to the existing standard of care for IT MTX overdose.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

There is a reasonable likelihood that once approved for the reduction of systemic, toxic methotrexate concentrations, commercially available Voraxaze will be administered intrathecally if and when IT MTX overdose occurs. BTG International provided anecdotal information from 9 subjects who received investigational glucarpidase to reduce methotrexate levels in cerebrospinal fluid following IT MTX overdose. Clinical data cannot be obtained to evaluate the safety and efficacy of IT Voraxaze use because the number of accidental IT MTX overdose cases constitutes a small subset of patients that experience methotrexate overdose, and it would be unethical to conduct a placebo-controlled clinical trial to establish the safety and efficacy of intrathecal Voraxaze in this setting. Therefore, BTG International must evaluate intrathecal administration of Voraxaze under conditions of the "Animal Rule" (21 CFR 601.90 for biological products) in order to assess the risks and benefits of its use to treat IT MTX overdose. Safety and efficacy data derived from the evaluation of intrathecal Voraxaze use in a non-human primate model will be included in future product labeling and will inform clinical decisions about the timing and dosage of intrathecal Voraxaze following accidental IT MTX overdose. An initial pilot animal study is being requested as a PMR to allow BTG to optimize the MTX dose(s) that result in clinically meaningful toxicity following the IT route of administration, the supportive care the animals will receive, and the timing of the Voraxaze intervention following IT MTX overdose. BTG and FDA have agreed to discuss the pilot study results prior to the design and initiation of the definitive animal study.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☒ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

FDA is requiring and the applicant has agreed to conduct a pilot animal safety and efficacy study to evaluate Voraxaze treatment of IT MTX overdose under the conditions of the "Animal Rule" (21 CFR 601.90 for biological products). This pilot animal safety and efficacy study conducted under 21 CFR 601.90 is expected to provide data that will establish a dosing regimen of Voraxaze to be used in a future, definitive animal study that will define the clinically meaningful benefit of Voraxaze in patients with IT MTX overdose.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?

☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☑ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

1/12/12

(signature line for BLAs)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Silver Spring, MD
Tel. 301-796-4242

Memorandum

PROJECT MANAGER'S REVIEW

Application Number:	STN 125327/0
Name of Drug:	Voraxaze® (Glucarpidase)
Applicant:	BTG International Inc.
Material Reviewed:	Voraxaze® (Glucarpidase) Carton and Container Labels Prescribing Information
Submission Date:	June 30, 2010, November 30, 2011, and December 20, 2011

EXECUTIVE SUMMARY

The carton and container labels for Voraxaze® (Glucarpidase) were reviewed and found to comply with most of the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, 12/1/11-4/30/12, USP 34/NF 29. Labeling deficiencies were identified and mitigated. Please see comments in the conclusions section. The labels are acceptable.

Background

STN 125327/0 for glucarpidase is an original Biologic License Application (BLA) indicated for (b) (4) reduction of toxic methotrexate concentrations due to impaired renal function.

Labels Reviewed:

Voraxaze® (Glucarpidase) Container and Carton
-1000 Unit

Review

(b) (4)

[redacted]

I. Container

A. 21 CFR 610.60 Container Label

1. Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:
   a. The proper name (established name) of the product, Glucarpidase– is displayed along with the Tradename (proprietary name), Voraxaze. This conforms to the regulation.

   b. The name, addresses, and license number of the manufacturer – The complete address should be listed, along with the U.S. license number. (b) (4) is listed. This does not conform to the regulation. Per the definition of manufacturer, revise Manufactured for and add license number.

   c. The lot number or other lot identification – The lot number is located on the container label. This conforms to the regulation.

   d. The expiration date – The expiration date is displayed on the container label. This conforms to the regulation.

   e. The recommended individual dose, for multiple dose containers – This product is supplied in a single use vial. This regulation does not apply.

   f. The statement "Rx only" for prescription biologicals – The statement "Rx Only" is located on the label. This conforms to the regulation.

   g. If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label – A medication guide is not required. This regulation does not apply.

2. Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. – The container is enclosed in a package (carton). This regulation does not apply.

3. Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. – the product bears a full label. This regulation does not apply.

4. No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. – This container bears a label. This regulation does not apply.

5. Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. Information not provided. This does not comply with the regulation.

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. Per 21 CFR 207.35, the last five digits of the NDC number represent the Product-Package Code configuration in either a 3-2 or 4-1 configuration. The NDC configuration appears as, "NDC 50633-210-11" on the vial label. This conforms to the regulation.

C. 21 CFR 201.5 Drugs; adequate directions for use – A reference to the prescribing information appears on the vial label as "See package insert for dosage and other information." This conforms to the regulation.

D. 21 CFR 201.6 Drugs; misleading statements – The only names that appear on the label are the trade name (proprietary name), Voraxaze and the proper name (established name), Glucarpidase. This conforms to the regulation.

E. 21 CFR 201.10 Drugs; statement of ingredients – The placement and prominence of the proper name (established name) and Tradename (proprietary name) do not appear to comply with the regulation. This product is exempt from 21 CFR 610.62. This does not conform to the regulation. Placement and prominence are incorrect.

F. 21 CFR 201.15 Drugs; prominence of required label statements –The "Rx Only" is more prominent than other required statements. This does not conform to the regulation.

G. 21 CFR 201.17 Drugs; location of expiration date – The expiration date appears under the lot number in the format "MMM YY". This conforms to 21 CFR 610.60 and 21 CFR 201.17.

H. 21 CFR 201.25 Bar code label requirements –A bar code is located on the label. This conforms to the regulation.

I. 21 CFR 201.50 Statement of identity – The proper name (established name), Glucarpidase is stated on the label with the tradename (proprietary name), Voraxaze. This conforms to the regulation.

J. 21 CFR 201.51 Declaration of net quantity of contents – The net quantity is declared, "1000 Units/vial". This conforms to the regulation.

K. 21 CFR 201.55 Statement of dosage – The statement, "See package insert for dosage and information." is listed on the label. This conforms to the regulation.

L. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of "Rx Only" and other pertinent information. This conforms to the regulation.

(b) (4)

(b) (4)

[redacted]

II. Carton

A. 21 CFR 610.61 Carton/Package Label –

a. The proper name (established name) of the product Glucarpidase– is displayed along with the (proprietary name), Voraxaze®. This conforms to the regulation.

b. The name, addresses, and license number of the manufacturer – The complete address should be listed, along with the U.S. license number. (b) (4) [redacted] is listed on the side panel of the carton. This does not conform to the regulation.

c. The lot number or other lot identification – The lot number is located near the bottom of the carton label. This conforms to the regulation.

d. The expiration date – The expiration date is listed below the lot number in the format "EXP: MMM YY". This conforms to the regulation.

e. The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative" – (b) (4) This does not conform to the regulation.

f. The number of containers, if more than one –The product is supplied in a single-use vial. This conforms to the regulation.

g. The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable – The amount of product is expressed as "1000 Units/vial". This conforms to the regulation.

h. The recommended storage temperature – The statement, "Store at 2° to 8°C (36° to 46°F) is displayed on the side panel of the carton. This conforms to the regulation.

i. The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product –This conforms to the regulation.

j. The recommended individual dose if the enclosed container(s) is a multiple-dose container –Single-use vial. This regulation does not apply.

k. The route of administration recommended, or reference to such directions in and enclosed circular – The statement "for intravenous injection" is located on the side panel of the carton. This conforms to the regulation. Recommend moving route to primary panel.

l. Known sensitizing substances, or reference to enclosed circular containing appropriate information –none listed. This conforms to the regulation.

m. The type and calculated amount of antibiotics added during manufacture – none listed. This conforms to the regulation.

n. The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information. The inactive ingredients are listed on the side panel of the carton, in alphabetical order. This conforms to the regulation. Include amounts in the format, ingredient (amount).

o. The adjuvant, if present –none listed. This conforms to the regulation.

p. The source of the product when a factor in safe administration –none listed. This conforms to the regulation.

q. The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information. – *Escherichia coli* is listed in the Description section of the package insert. This conforms to the regulation.

r. (b) (4) (b) (4) This does not conform to the regulation.

s. The statement "Rx only" for prescription biologicals – The statement "Rx Only" is located on the carton. This conforms to the regulation.

t. If a Medication Guide is required under part 208 of this chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label –A

statement is not provided on either the container or carton label. This does not conform to the regulation.

B. 21 CFR 610.62 Proper name; package label; legible type *[Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]* – This product is a "specified" biological product and is exempt from this regulation. This regulation does not apply.

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown –This regulation does not apply.

D. (b) (4) (b) (4) This does not conform to the regulation.

E. 21 CFR 610.65 Products for export – This product will not be distributed outside the US use. This conforms to the regulation.

F. 21 CFR 610.67 Bar code label requirements
Biological products must comply with the bar code requirements at §201.25 of this chapter. – A bar code appears on the carton label. This conforms to the regulation.

G. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. Per 21 CFR 207.35, the last five digits of the NDC number represent the Product-Package Code configuration in either a 3-2 or 4-1. The NDC configuration, "NDC 50633-210-11" appears on the carton. This conforms to the regulation.

H. 21 CFR 201.5 Drugs; adequate directions for use – The label states "See package insert for dosage and other information." This conforms to the regulation.

I. 21 CFR 201.6 Drugs; misleading statements – The only names that appear on the label are the trade name (proprietary name), Voraxaze and the proper name (established name), glucarpidase. This conforms to the regulation.

J. [redacted] This does not conform to the regulation.

K. [redacted] This does not conform to the regulation.

L. 21 CFR 201.17 Drugs; location of expiration date – The expiration date appears under the lot number on the bottom of the label in the format MMM YY". This conforms to 21 CFR 610.61 and 21 CFR 201.17.

M. 21 CFR 201.25 Bar code label requirements – A bar code appears on the carton label. This conforms to the regulation.

N. 21 CFR 201.50 Statement of identity – The proper name (established name), Glucarpidase is stated on the label with the tradename (proprietary name), Voraxaze. This conforms to the regulation.

O. 21 CFR 201.51 Declaration of net quantity of contents – The net quantity is declared as "1000 Units/vial". This conforms to the regulation.

P. 21 CFR 201.55 Statement of dosage –The statement "See package insert for dosage and other information." appears on the label. This conforms to the regulation.

Q. 21 CFR 201.100 Prescription drugs for human use – The label bears statements "Rx Only" and other pertinent information. This conforms to the regulation.

Conclusions

The following deficiencies and recommendations were noted in the review of the Voraxaze® container and carton labels.

1. Container label
   a. Add the US License number per 21 CFR 610.60 (a)(2). Change made and acceptable.
   b. Under 21 CFR 601.2, this product is an exempt 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. Change made and acceptable.
   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. Consider adding the dosage form "For Injection" immediately following the proper name.
*See recommended format below. Change made and acceptable.

d. [redacted] to increase readability and create space for other revisions. Change made and acceptable.

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

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. Change made and acceptable.

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). Information provided and acceptable.

*Recommended format:

Voraxaze®
(Glucarpidase)
For Injection

2. Carton label

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

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

c. Revise storage information to "Store vial at …." And remove the statement, [redacted] Change made and acceptable.

d. Remove the statement, [redacted] from the primary panel and the statement, [redacted] Complete reconstitution directions are located in the Prescribing Information. Change made and acceptable.

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

f. Under 21 CFR 601.2, this product is an exempt biologic. Revise the placement and prominence of the trade name and proper name to comply with 21 CFR 201.10. **See recommended format below. Change made and acceptable.

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. Consider adding the dosage form "For Injection" immediately following the proper name. **See recommended format below. Change made and acceptable.

h. Consider moving the route of administration, "For intravenous injection" to the primary presentation of the trade name and proper name immediately following the strength. **See recommended format below. Change made and acceptable.

f. Add the statements, "Single-use vial: Discard unused portion." immediately following the route of administration. ** See recommended format below.

** Recommended format for the primary panel:

Voraxaze®
(Glucarpidase)
For Injection

1000 Units/ vial

For Intravenous Injection
Single-use vial; Discard unused portion.

3. Vial cap and ferrule

a. Please provide all proposed printed information on the vial cap and or ferrule. The applicant provided, "The batch number will be ink-jetted on the aluminum ferrule. No printed information will appear on the blue vial cap."

1/3/2012

Kimberly Rains, Pharm.D
Regulatory Project Manager
CDER/OPS/OBS

Comment/Concurrence:

Howard Anderson, Ph.D
Product Reviewer
Division of Therapeutic Products
CDER/OPS/OBP

Barry Cherney, Ph.D.
Deputy Director
Division of Therapeutic Products
CDER/OPS/OBP

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

Memorandum

Date: 12/22/11 ESL 12/22/11

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

Subject: BTG Interational Inc.; BLA STN 125327; TB-EER request

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From: Laughner, Erik
Sent: Thursday, December 22, 2011 10:05 AM
To: CDER-TB-EER
Subject: Request for EER (compliance check); Pending BLA STN 125327 (BTG International); Voraxaze
Importance: High

Good Afternoon,

DOP2 is preparing to take an approval action on BLA STN 125327 (PDUFA date 01/17/12) and wishes to request the final EER check. Please see attached form which contains the list of sites.

Sincerely,

Erik Laughner, RPM


125327 TB- EER BTG Internation...


Establishment Info.pdf (23 KB)...

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:
The review team should email this form to the email account "CDER-TB-EER" to submit:

1) an initial TB-EER within 10 business days of the application filing date
2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing[1] locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

Action Date: 01/17/12

Applicant Name: BTG International Inc.
U.S. License #: 1861
STN(s): 125327
Product(s): VORAXAZE
Short summary of application: DOP2 is completing the review of new original BLA STN 125359 for VORAXAZE (glucarpidase)

FACILITY INFORMATION

SEE ATTACHED.

[1]The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

Form FDA 356h Continuation Sheet

Establishment Information for Voraxaze™ (Glucarpidase)

Facility Name and Address	Contact Person Title Telephone Number	Registration Number (CFN)	Manufacturing Steps and/or Type of Testing	Ready for Inspection?
[redacted] (b) (4)		None	Storage of Master Cell Bank (MCB) and Working Cell Bank (WCB)	Yes
		None	Storage of MCB and WCB	Yes
Eurogentec S.A. Liege Science Park Rue du Bois Saint Jean 14 4102 Seraing Belgium	(b) (4)	3003830126	Storage of MCB and WCB Manufacture and in-process testing of drug substance (DS) Release testing of DS • Protein Concentration • Specific activity • Endotoxin • Bioburden Stability testing of DS • Endotoxin • Bioburden Release of DS	Yes
[redacted]	(b) (4)		Residual DNA testing of in-process and drug substance samples	Yes
			Release testing of DS with the exception of: • Residual DNA • Protein Concentration • Specific Activity • Endotoxin • Bioburden Stability storage and stability testing of DS with the exception of: • Endotoxin • Bioburden Release testing of drug product (DP) with the exception of: • Sterility • Endotoxin Stability storage and stability testing of DP with the exception of: • Sterility • Endotoxin	Yes

Facility Name and Address	Contact Person Title Telephone Number	Registration Number (CFN)	Manufacturing Steps and/or Type of Testing	Ready for Inspection?
Cangene bioPharma Inc. (CBI) 1111 South Paca Street Baltimore, MD 21230 USA	(b) (4)	1123903/BLT	(b) (4) In-process testing Lyophilization Vial inspection Sterility and Endotoxin testing of DP at release and stability	Yes
Protherics UK Limited Blaenwaun Ffostrasol, Llandysul Ceredigion, Wales SA44 5JT United Kingdom		3001417487	Release of the DP by Qualified Person	Yes

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Therapeutic Proteins
Rockville, MD 20852
Tel. 301-827-1709

MEMORANDUM

Date: 10/31/2011

To: File: BLA 125,327

From: Laura I. Salazar-Fontana, Ph.D. 12/19/11
Susan L. Kirshner, Ph.D. Susan L. Kirshner 12/19/2011
Associate Chief, Laboratory of Immunology
Division of Therapeutic Proteins
Office of Biotech Products
CDER/FDA

Through: Amy Rosenberg,M.D., Ph.D 12-19-11
Director
Division of Therapeutic Proteins
Office of Biotech Products
CDER/FDA

Subject: Immunogenicity review for Glucarpidase (Voraxaze™) sterile powder for injection.

Indication: (b) (4) reduction in toxic Methotrexate (MTX) levels in patients due to impaired renal function.

Sponsor: Protherics, Inc.

REVIEWER RECOMMENDATIONS: Approval with request of a PMC for a validated neutralizing antibody assay and immunogenicity data on presence of neutralizing antibodies in the binding antibody positive population.

RISK ASSESSMENT

Glucarpidase is a recombinant carboxypeptidase (CPG2) of bacterial origin produced in *E. coli*. The recombinant protein is secreted as a homodimer with a molecular weight of 83kDa. Its MOA is hydrolysis of the C-terminal glutamate residue from folic acid and folate-analogs, such as methotrexate (MTX) and leucovorin (LV). MTX is hydrolyzed into the inactive metabolites 4-deoxy-4amino-N10-methylpteroic acid (DAMPA) and glutamate, which are both metabolized by the liver. The proposed route of administration for Glucarpidase is slow i.v. infusion (b) (4) in patients experiencing increased MTX toxicity due to impaired renal function.

The presence of anti-glucarpidase antibodies (AGA) was evaluated in a total of 96 patients from three pivotal studies (5 from study 012, 82 from study 016, and 9 from study 017). The data base includes patients receiving one and two doses of glucarpidase. From the total number of studied patients, 78 received only one dose of glucarpidase, and 18 patients, two doses. Almost 17% (16/96) of the glucarpidase-treated patients developed treatment-related AGAs. Antibody testing was performed at baseline, at weeks 1-2 and 4-6, and follow ups between months 2-4 and 5-7. Mass equivalent antibody concentrations relative to a positive control antibody show that most patients had amounts below limit of detection (<62.5 ng/ml); 3 out of 16 patients belonging to the group of patients that received 2 doses of glucarpidase remained positive 5-7 months post-treatment.

Glucarpidase shows a high degree of immunogenicity in humans: almost 17% of patients develop antibodies after only one i.v. administration. No data are available as to how many of the AGA positive patients develop AGAs with neutralizing activity. Given the immunosuppressed status of the target population, the limited course of treatment, and the low degree of homology between carboxipeptidases from bacterial and human origin, I would predict that development of AGAs with neutralizing activity should be rare, and if present, the short treatment time should not allow for observation of a major impact in the efficacy of glucarpidase. The catalytic domain is highly conserved between human and bacterial carboxypeptidases so there may be some immune tolerance to this domain in particular. Moreover, this domain is embedded in the core of the homodimer making it less likely to be a primary target of an antibody response. Since the treatment will be carried out under clinical monitoring, the risk for an unattended infusion or hypersensitivity reaction should be minimal. For the reasons mentioned above, I would recommend approval of glucarpidase for the proposed indication with request for evaluation of neutralizing antibodies as a post-marketing committment (PMC).

OVERVIEW

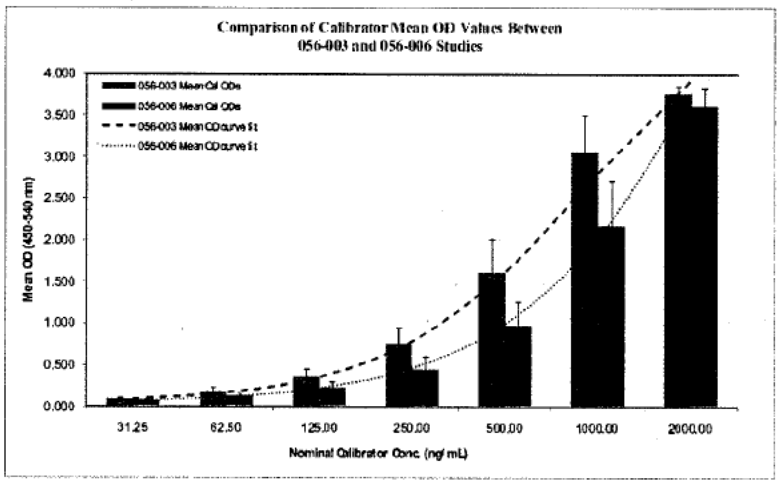
The Sponsor has provided reports on two assays for the evaluation of anti-glucarpidase antibodies (AGA): a bridging ELISA for the detection of binding anti-glucarpidase antibodies (AGAs) and a Liquid Chromatography–Mass Spectrometry LC-MS/MS measuring inhibition of enzymatic activity for the determination of neutralizing antibodies.

Regarding the detection of neutralizing antibodies, the sponsor has included a pre-validation report on a LC-MS/MS method but no final validation or clinical samples testing have been included. A formal information request was sent to the Sponsor to clarify the status of the LC-MS/MS method for determination of neutralizing antibodies.

SCREENING ASSAY

Briefly, the screening assay consists of a validated bridging ELISA where glucarpidase is adsorbed onto microtiter plates, and then blocked and incubated with human serum samples. Bridge formation occurs between the plate-bound glucarpidase and captured specific antibody. Biotinylated glucarpidase is then added and developed with ExtrAvidin peroxidase reagent. The peroxidase substrate tetramethylbenzidine (TMB) is oxidized and colorimetric reading is performed by measuring absorbance at 450 nm.

The test has been validated and re-optimized by (b) (4) (b) (4) The re-optimization of the assay was decided upon observation of a drift in the readings obtained for the quality controls (QC) during several validation exercises. The graph below shows OD readings obtained for the standard curve in 2 different validation exercises.



The method was modified to address the potential causes of assay drift and to improve assay precision. The key parameters changed were:

- Final concentration of the developing agent (ExtrAvidin) was reduced 5-fold with the corresponding increment (2-fold) in color development time.
- Reduction in the standard curve positive control concentrations now ranging from 15.6 ng/ml to 1000 ng/ml. The original concentration range was from 31.3 to 2000 ng/ml.
- Use of a new dilution of the high positive control (HQC): 750 ng/ml instead of 1500 ng/ml.
- Plate wash was changed by hand wash to minimize variability.

The Sponsor used different pools of human serum samples during the re-optimization exercise: TB03 and TB05 for optimal ExtrAvidin concentration, dose response curve, and development time; TB06, TB07, and TB10 for recalculation of assay cut-point using the revised method.

	Biotinylated Voraxaze lots		**Pooled human serum samples**
Date of Receipt	Reference number	Number received	Used in Batches
25 Apr 2008	RS08-121	15	TB02 & VB01 to VB13
14 May 2009	RS09-128	12	TB03 to TB19
08 Apr 2010	RS10-045	15	TB21 & TB22

Each vial contained (b) (4) 1000 units Voraxaze™. The expiry/re-test date was initially specified as (b) (4)

The Sponsor calculated a new assay cut-point using a new batch of 50 individual serum samples that were run on three different occasions. A new negative pool was generated for use in the preparation of QC samples and normalization of assay cut point.

Comment: The sponsor has used a statistically representative number of samples for the calculation of the final cut point for the binding assay. Therefore, I consider that the screening assay threshold for detection of positive samples is acceptable.

In order to evaluate assay variability and QC drift, seven different dilutions of the rabbit anti-glucarpidase QC replicates were run at the same time in two different plates, with two ExtrAvidin dilutions, (the new dilution of 1:10,000 in comparison to the former dilution of 1:2,000) and mean OD readings were then compared after 4 different developing times: 8, 10, 12, and 14 minutes. Data below show the positional effect on mean OD at two concentrations of ExtrAvidin measured after 15 minutes of incubation time.

Figure A1: Absorbance unit response measurements for calibration curve concentrations across the microtitre plate using ExtrAvidin diluted 1 in 2000

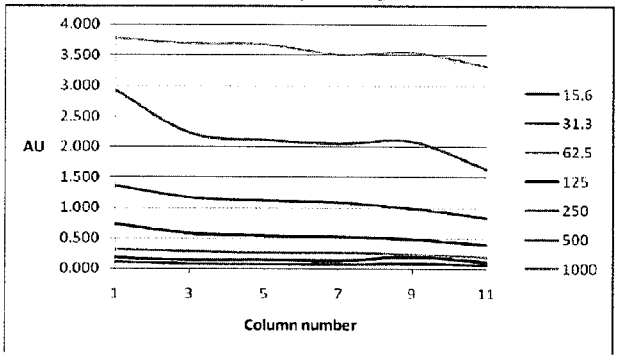


Figure A2: Absorbance unit response measurements for calibration curve concentrations across the microtitre plate using ExtrAvidin diluted 1 in 10,000

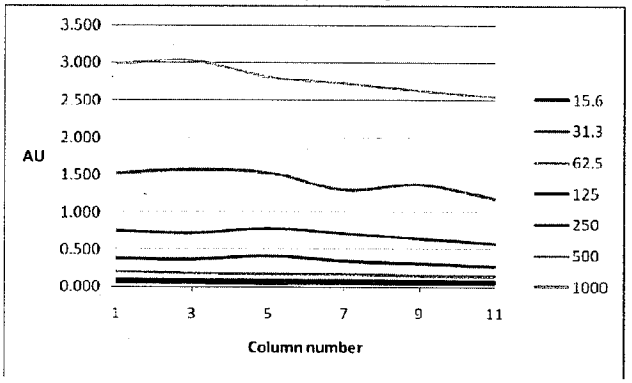


Table A8

Pre-Study Validation of an Analytical Procedure to Detect Antibodies to Voraxaze™ in Human Serum by Bridging ELISA

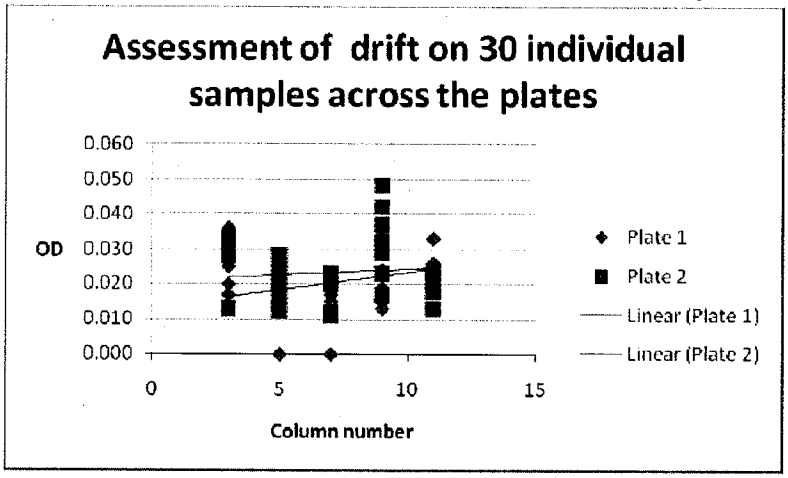
TB05: Summary of back-calculated Calibrator Recoveries for Plates 1 and 2

Nominal Calibrator Conc. (ng/mL)	Plate number: Plate 1 Mean (n=6) Observed conc' (ng/mL)	Plate 1 Precision (%CV)	Plate 1 Accuracy (%RE)	Plate 2 Mean (n=6) Observed conc' (ng/mL)	Plate 2 Precision (%CV)	Plate 2 Accuracy (%RE)
15.6	14.9	36.6	-4.5	15.6	9.9	-0.1
31.3	33.4	26.8	6.9	31.2	9.7	-0.1
62.5	59.8	19.2	-4.3	62.4	12.1	-0.2
125.0	125.9	20.7	0.7	125.3	14.0	0.3
250.0	247.2	16.2	-1.1	250.4	9.7	0.2
500.0	519.5	23.3	3.9	498.1	10.7	-0.4
1000.0	987.1	6.7	-1.3	1,001.9	7.4	0.2
	1:2,000			**1:10,000**		

Comment: I concur with the Sponsor in that selection of a 1:10,000 dilution for the ExtrAvidin reagent not only reduces the trend in reduction of OD readings of the QC samples with respect to sample position, but also results in reduced assay variability (%CV).

Despite the variability observed with the positive control samples, minimal to no drift could be observed in the antibody negative and blank samples with either assay condition.

Figure A3: – OD measurement trends of blank samples across the plate



Comment: I concur with the Sponsor in that assay drift in the negative samples is within expected limits for this type of assay.

The assay cut point was calculated in one initial occasion (TB10) but further assay qualification was performed since a trend in reduced HQC readings was still observed in the calibration curves.

Table A14

Pre-Study Validation of an Analytical Procedure to Detect Antibodies to Voraxaze™ in Human Serum by Bridging ELISA.

Re-establishment of Cut-Point Determination from Individual Sera; Batches TB06, TB07 and TB10

Individual Serum Number	Serum ID	Analysis Occasion					
		1		2		3	
		OD	Batch Number	OD	Batch Number	OD	Batch Number
1	07H133	0.012	TB06	0.014	TB07	0.012	TB10
2	07H134	0.015	TB06	0.017	TB07	0.017	TB10
3	07H138	0.011	TB06	0.014	TB07	0.012	TB10
4	07H140	0.023	TB06	0.016	TB07	0.014	TB10
5	07H141	0.023	TB06	0.031	TB07	0.019	TB10
6	07H143	0.021	TB06	0.022	TB07	0.028	TB10
7	07H146	0.013	TB06	0.012	TB07	0.012	TB10
8	07H148	0.018	TB06	0.019	TB07	0.021	TB10
9	07H151	0.032	TB06	0.045	TB07	0.036	TB10
10	07H153	0.048	TB06	0.030	TB07	0.018	TB10
11	07H154	0.029	TB06	0.050	TB07	0.041	TB10
12	07H157	0.023	TB06	0.019	TB07	0.024	TB10
13	07H158	0.017	TB06	0.020	TB07	0.018	TB10
14	07H159	0.020	TB06	0.021	TB07	0.024	TB10
15	07H160	0.042	TB06	0.044	TB07	0.079[x1]	TB10
16	07H163	0.037	TB06	0.040	TB07	0.019	TB10
17	10HIS014	0.020	TB06	0.044	TB07	0.034	TB10
18	10HIS015	0.020	TB06	0.037	TB07	0.042	TB10
19	10HIS016	0.017	TB06	0.036	TB07	0.032	TB10
20	10HIS017	0.016	TB06	0.037	TB07	0.019	TB10
21	10HIS018	0.025	TB06	0.046	TB07	0.046	TB10
22	10HIS019	0.014	TB06	0.112[x1]	TB07	0.021	TB10
23	10HIS020	0.017	TB06	0.021	TB07	0.013	TB10
24	10HIS024	0.019	TB06	0.031	TB07	0.040	TB10
25	10HIS025	0.021	TB06	0.031	TB07	0.039	TB10
26	10HIS026	0.017	TB06	0.036	TB07	0.020	TB10
27	10HIS027	0.021	TB06	0.031	TB07	0.032	TB10
28	10HIS028	0.019	TB06	0.028	TB07	0.021	TB10
29	10HIS029	0.024	TB06	0.041	TB07	0.037	TB10
30	10HIS030	0.020	TB06	0.028	TB07	0.019	TB10
31	10HIS031	0.042[x1]	TB06	0.097[x1]	TB07	0.054	TB10
32	10HIS032	0.011	TB06	0.018	TB07	0.012	TB10
33	10HIS033	0.013	TB06	0.017	TB07	0.011	TB10
34	10HIS051	0.015	TB06	0.019	TB07	0.013	TB10
35	10HIS052	0.015	TB06	0.037	TB07	0.028	TB10
36	10HIS053	0.019	TB06	0.039	TB07	0.033	TB10
37	10HIS054	0.030	TB06	0.034	TB07	0.033	TB10

Table continued on next page

Table A14 continued

Individual Serum Number	Serum ID	Analysis Occasion					
		1		2		3	
		OD	Batch Number	OD	Batch Number	OD	Batch Number
38	10HIS055	0.035	TB06	0.045	TB07	0.050	TB10
39	10HIS056	0.026	TB06	0.036	TB07	0.022	TB10
40	10HIS058	0.033	TB06	0.047	TB07	0.028	TB10
41	10HIS059	0.026	TB06	0.031	TB07	0.036	TB10
42	10HIS060	0.022	TB06	0.031	TB07	0.031	TB10
43	10HIS062	0.033	TB06	0.032	TB07	0.028	TB10
44	10HIS063	0.029	TB06	0.025	TB07	0.026	TB10
45	10HIS064	0.013	TB06	0.019	TB07	0.014	TB10
46	10HIS065	0.028	TB06	0.041	TB07	0.023	TB10
47	10HIS066	0.018	TB06	0.025	TB07	0.023	TB10
48	10HIS068	0.023	TB06	0.037	TB07	0.018	TB10
49	10HIS069	0.028	TB06	0.040	TB07	0.021	TB10
50	10HIS070	0.027	TB06	0.040	TB07	0.043	TB10
Cut-point determination – all values							
Mean		0.023		0.034		0.027	
Std Dev (n-1)		0.0084		0.0179		0.0132	
n		50		50		50	
Cut-point (Mean + 1.645SD)		0.037		0.063		0.049	
95th percentile		0.040		0.049		0.048	
Cut-point determination – Grubbs test outliers removed							
Mean		0.022		0.031		0.026	
Std Dev (n-1)		0.0081		0.0104		0.0110	
n		49		48		49	
Cut-point (Mean + 1.645SD)		0.035		0.048		0.044	

Footnotes:
x1 = Value identified as statistical outlier from batch (n = 50) by Grubbs test

Table A11
Pre-Study Validation of an Analytical Procedure to Detect Antibodies to Voraxaze™ in Human Serum by Bridging ELISA.

Precision and Accuracy of Calibration Standards ($1/y^2$ Weighting)

Batch	Plate number	Back-calculated Concentrations (ng/mL)						
		Nominal Calibrator concentration (ng/mL)						
		15.63	31.25	62.50	125.00	250.00	500.00	1000.00
TB06	1	14.58	33.93	89.87 x1x2	103.17	236.53	511.45	1069.94
TB06	2	14.80	33.82	61.65	121.29	247.51	521.64	983.62
TB07	1	15.95	30.07	62.57	134.19	233.06	522.29	991.10
TB07	2	14.89	32.42	65.95	126.33	231.20	495.88	1046.43
TB10	1	15.40	31.88	62.97	120.81	256.91	497.44	999.36
TB10	2	14.05	37.45	59.18	118.11	270.85	489.99	1000.47
Mean (ng/mL)		14.9	33.3	67.0	120.7	246.0	506.4	1015.2
Standard deviation (n-1)		0.66	2.49	11.40	10.28	15.59	13.93	34.69
Precision (%)		4.4	7.5	17.0	8.5	6.3	2.8	3.4
RE (%)		-4.6	6.6	7.2	-3.4	-1.6	1.3	1.5
n		6	6	6	6	6	6	6

Footnotes:
x1 = %CV > 30
x2 = %RE > 20

Comment: I agree with the sponsor in that calculation of this initial cut point was done following current guidelines.

Therefore, the sponsor addressed the effect of incubation temperature, stability of biotinylated Voraxaze, and plate versus hand plate washing. Although the stability of biotinylated Voraxase greatly impacts the performance of the assay it did not show a direct correlation with assay drift. Only plate washing did, thus the protocol was changed to include hand plate washes to reduce assay variability.

The final cut point for the assay was established with the modifications described above and in three different test batches: TB19, 21, and 22. The same 50 individual sera samples used in batch TB10 were used for this calculation.

Table A44
Pre-Study Validation of an Analytical Procedure to Detect Antibodies to Voraxaze™ in Human Serum by Bridging ELISA
Inter-assay Precision and Accuracy of Quality Control Samples
Combined Data from Batches TB19, TB21 & TB22

Batch	Plate	Replicate	QC Level					
			QC Concentration (ng/mL)					
			LoQC		MeQC		HiQC	
			100.0	% RE	400.0	% RE	750.0	% RE
TB19	1	1	123.0	23.0	493.7	23.4	900.8	20.1
		2	111.2	11.2	449.1	12.3	809.4	7.9
		3	105.8	5.8	415.5	3.9	810.2	8.0
	2	1	119.2	19.2	441.3	10.3	807.8	7.7
		2	109.2	9.2	419.3	4.8	831.3	10.8
		3	125.9	25.9	458.6	14.7	781.8	4.2
TB21	1	1	81.6	-18.4	362.2	-9.4	797.5	6.3
		2	96.4	-3.6	393.4	-1.7	762.5	1.7
		3	82.6	-17.4	332.6	-16.9	669.6	-10.7
	2	1	96.2	-3.8	343.4	-14.2	672.1	-10.4
		2	85.9	-14.1	356.3	-10.9	671.5	-10.5
		3	81.7	-18.3	352.4	-11.9	663.5	-11.5
TB22	1	1	85.3	-14.7	354.0	-11.5	666.3	-11.2
		2	85.7	-14.3	353.2	-11.7	669.4	-10.8
		3	84.9	-15.1	333.7	-16.6	654.4	-12.8
	2	1	86.6	-13.4	344.2	-13.9	610.1	-18.7
		2	95.0	-5.0	340.7	-14.8	605.0	-19.3
		3	94.2	-5.8	350.2	-12.5	634.5	-15.4
Mean (ng/mL)			97.2	-	383.0	-	723.2	-
Standard deviation (n-1)			14.88	-	50.26	-	88.49	-
Precision (%)			15.3	-	13.1	-	12.2	-
RE (%)			-2.8	-	-4.3	-	-3.6	-
Total error %			18.1	-	17.4	-	15.8	-
n			18	-	18	-	18	-

Comment: I agree with the sponsor in that the changes made to the original validation protocol have effectively reduced the variability observed in the readings of the QC.

Table A45
Pre-Study Validation of an Analytical Procedure to Detect Antibodies to Voraxaze™ in Human Serum by Bridging ELISA.

Cut-Point and Outlier Determinatio (b) (4)
Data from batches TB19, TB21 & TB22. Analy

Serum ID	Mean OD	Log	Mean OD	Log	Mean OD	Log
	TB19		TB21		TB22	
07H133	0.017	-1.7696	0.024	-1.6198	0.024	-1.6198
07H134	0.025	-1.6021	0.021	-1.6778	0.017	-1.7696
07H138	0.025	-1.6021	0.019	-1.7212	0.022	-1.6576
07H140	0.019	-1.7212	0.019	-1.7212	0.020	-1.6990
07H141	0.029	-1.5376	0.023	-1.6383	0.022	-1.6576
07H143	0.018	-1.7447	0.014	-1.8539	0.014	-1.8539
07H146	0.020	-1.6990	0.015	-1.8239	0.011	-1.9586
07H148	0.036	-1.4437	0.019	-1.7212	0.023	-1.6383
07H151	0.033	-1.4815	0.035	-1.4559	**0.057**	-1.2441
07H153	0.034	-1.4685	0.018	-1.7447	0.022	-1.6576
07H154	0.034	-1.4685	**0.046**	-1.3372	**0.055**	-1.2596
07H157	0.024	-1.6198	0.022	-1.6576	0.021	-1.6778
07H158	0.025	-1.6021	0.023	-1.6383	0.024	-1.6198
07H159	0.024	-1.6198	0.034	-1.4685	0.030	-1.5229
07H160	**0.052**	-1.2840	0.032	-1.4949	0.041	-1.3872
07H163	0.037	-1.4318	**0.045**	-1.3468	0.044	-1.3565
10HIS014	0.032	-1.4949	0.024	-1.6198	0.020	-1.6990
10HIS015	0.036	-1.4437	0.029	-1.5376	0.024	-1.6198
10HIS016	0.030	-1.5229	0.020	-1.6990	0.025	-1.6021
10HIS017	0.029	-1.5376	0.020	-1.6990	0.022	-1.6576
10HIS018	0.038	-1.4202	0.042	-1.3768	**0.056**	-1.2518
10HIS019	0.030	-1.5229	0.018	-1.7447	0.017	-1.7696
10HIS020	0.023	-1.6383	0.016	-1.7959	0.014	-1.8539
10HIS024	0.037	-1.4318	0.034	-1.4685	0.042	-1.3768
10HIS025	0.035	-1.4559	0.028	-1.5528	0.027	-1.5686
10HIS026	0.031	-1.5086	0.031	-1.5086	0.027	-1.5686
10HIS027	0.028	-1.5528	0.027	-1.5686	0.026	-1.5850
10HIS028	0.038	-1.4202	**0.055**	-1.2596	0.035	-1.4559
10HIS029	0.036	-1.4437	0.037	-1.4318	0.022	-1.6576
10HIS030	0.039	-1.4089	0.030	-1.5229	0.021	-1.6778
10HIS031	**0.051**	-1.2924	**0.054**	-1.2676	0.045	-1.3468
10HIS032	0.026	-1.5850	0.015	-1.8239	0.016	-1.7959
10HIS033	0.026	-1.5850	0.017	-1.7696	0.017	-1.7696

Table continued on next page

Table A45 continued

Serum ID	Mean OD	Log	Mean OD	Log	Mean OD	Log
	TB19		TB21		TB22	
10HIS051	0.025	-1.6021	0.018	-1.7447	0.018	-1.7447
10HIS052	0.027	-1.5686	0.021	-1.6778	0.021	-1.6778
10HIS053	0.032	-1.4949	0.025	-1.6021	0.026	-1.5850
10HIS054	0.028	-1.5528	0.030	-1.5229	0.028	-1.5528
10HIS055	0.041	-1.3872	0.034	-1.4685	0.029	-1.5376
10HIS056	0.042	-1.3768	**0.047**	-1.3279	0.032	-1.4949
10HIS058	0.044	-1.3565	**0.045**	-1.3468	0.038	-1.4202
10HIS059	0.035	-1.4559	0.028	-1.5528	0.030	-1.5229
10HIS060	0.035	-1.4559	0.024	-1.6198	0.023	-1.6383
10HIS062	0.038	-1.4202	0.036	-1.4437	0.034	-1.4685
10HIS063	0.031	-1.5086	0.023	-1.6383	0.018	-1.7447
10HIS064	0.026	-1.5850	0.020	-1.6990	0.013	-1.8861
10HIS065	0.031	-1.5086	0.022	-1.6576	0.027	-1.5686
10HIS066	0.030	-1.5229	0.036	-1.4437	**0.049**	-1.3098
10HIS068	0.035	-1.4559	0.022	-1.6576	0.024	-1.6198
10HIS069	0.042	-1.3768	0.036	-1.4437	0.039	-1.4089
10HIS070	0.044	-1.3565	0.043	-1.3665	0.039	-1.4089
Cut-point determination - all values						
Mean	0.032	-1.507	0.028	-1.576	0.028	-1.589
Std Dev (n-1)	0.0078	0.1083	0.0105	0.1554	0.0114	0.1691
n	50	50	50	50	50	50
Cut-point (Mean + 1.645SD)	0.045	-1.329	0.045	-1.320	0.047	-1.311
Average cut-point			0.046			
95th percentile	0.044		0.044		0.044	
Mean NCS	0.034		0.029		0.028	
Normalisation factor	1.31		1.55		1.68	
Average Normalisation Factor				1.51		

Footnotes:
Values in bold ≥ cutpoint

Comment: As per the data depicted in table A45, your final cut point calculation includes outliers in the final value. The inclusion of these high responders results in a higher assay threshold that could preclude detection of low positive sample. The sponsor explains that Grubb's test failed to identify any outliers and that the data followed a normal distribution according to the Shapiro-Wilkes test (for TB21 and TB22). Given that this test allows determining how far from the mean of a given data population is one individual value by taking into consideration the mean value and the SD of a normal distribution., I consider that the assay cut point has been adequately determined.

NEUTRALIZING ASSAY

Regarding the detection of neutralizing antibodies, the sponsor has included a preliminary report that describes the adaptation of a LC-MS/MS method. This method was originally developed by (b) (4) (b) (4) for the detection of MTX in human plasma (PR001-NCL-BA017). The principle of this method variation will be to measure inhibition of MTX hydrolysis if antibodies with neutralizing activity are present in the clinical samples.

Comment: No data are available in the current submission on the number of patients who may have developed anti-glucarpidase Abs with neutralizing activity. Although not a safety concern (see immunogenicity risk assessment above), the presence of NAbs could alter the efficacy of this product in the event that treatment with glucarpidase is required beyond a single administration. Therefore, the sponsor will be asked to present a validated neutralizing assay as well as data on the detection of NAbs in clinical samples obtained from patients included in the pivotal studies as part of a post-marketing commitment (PMC).

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Promotion

Internal Consult

****Pre-decisional Agency Information****

To: Erik Laughner, Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology Oncology Products

From: Carole C. Broadnax, R.Ph., Pharm.D., Regulatory Review Officer
Division of Professional Promotion
Office of Prescription Drug Promotion (OPDP)

C Broadnax 12/1/11

Date: December 1, 2011

Re: **VORAXAZE (glucarpidase) injection for intravenous infusion**
STN BL 125327
OPDP Comments on proposed labeling

In response to the Division of Oncology Products 2 (DOP 2) July 20, 2011, consult request, OPDP has reviewed proposed labeling (PI, carton and container) for VORAXAZE (glucarpidase).

OPDP's comments for the PI are based on the draft labeling sent via electronic mail to OPDP from DOP 2 on November 18, 2011. OPDP's PI comments are provided directly in the attached document.

The carton and container labeling used in this review can be found in the original application (folder 0006) at: \\cber-fs3\m\eCTD Submissions\STN125327\125327.enx.

OPDP does not have comments for the carton and container labeling at this time.

Thank you for your consult. If you have any questions regarding the PI or the carton/container labeling, please contact Carole Broadnax at 301-796-0575 or Carole.Broadnax@fda.hhs.gov.

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

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 28, 2011

TO: Patricia Keegan, M.D.
Director
Division of Oncology Products 2 (DOP2)

FROM: Jyoti B. Patel, Ph.D.
Young Moon Choi, Ph.D.
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, R.Ph., Ph.D. JoshH/Michael F Skelly 10/31/11
Chief, Bioequivalence Branch,
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: Review of EIR Covering BLA 125327, *Voraxase (glucarpidase)*, sponsored by BTG International Inc. (Protherics)

At the request of the Division of Oncology Products 2 (DOP2), the Division of Bioequivalence and GLP Compliance, Office of Scientific Investigations conducted an audit of bioanalytical portion of the following studies:

Study Number: **PR001-CLN-002**
Study Title: "Special exception protocol for the use of carboxypeptidase G2 ± thymidine for MTX toxicity and renal failure"

Study Number: **PR001-CLN-006**
Study Title: "Special exception protocol for the use of carboxypeptidase G2 for MTX toxicity"

The inspection and data audit of the analytical portions of these studies were conducted from (b) (4) at (b) (4)

under the supervision of [redacted] (b) (4) The measurements of plasma concentrations of methotrexate (MTX) and 2, 4-diamino-N^{10}-methylpteroic acid (DAMPA) were intended as surrogate measures of efficacy of glucarpidase in the treatment of MTX toxicity.

Please note that a complete bioanalytical report with HPLC chromatograms and data for study **PR001-CLN-002 was not available for review prior to the conduct of the inspection**. At the start of the inspection [redacted] (b) (4) provided us a summary of information for both studies **[Attachment 1]**. Following the inspection, no Form FDA-483 was issued, on the advice of counsel from the Office of Scientific Investigations, Office of Compliance. However, we discussed factual inspectional observations at the close of the inspection. Provided below are these observations and DBGC's evaluation of them for the two studies.

Study PR001-CLN-002:

Protherics was not involved in the design, patient management, or analysis of patient plasma samples under Study PR001-CLN-002. HPLC analysis of plasma MTX and DAMPA for 83 patients under this study was done **without a formal method validation at that time**.

Plasma samples from patients #70 through #83 were analyzed after Clinical Laboratory Improvement Amendments (CLIA) registration of the laboratory was received in 1999, to qualify use of this particular method for MTX and DAMPA. Note that the terms "validation" and "verification" have special meanings under CLIA, 42 CFR part 493. This EIR Review uses the term validation to mean demonstration of the accuracy, precision, and overall performance of the method under the conditions of use in these studies.

The inspection audited chromatograms of randomly selected patients from this study on an [redacted] (b) (4) computer, which was specifically designated for the study data, as printed hard copy chromatograms for the HPLC analysis were not available. No formal laboratory notebooks were maintained to documented day to day study related activities. The following are inspectional findings and our evaluations.

1. **Failure to adequately document all aspects of sample collection, receipt, handling and integrity.**

Specifically, for plasma samples from patients 1 - 69, no definite procedures were followed in terms of sample collection by the clinical sites; and receipt and handling of the samples by the analytical site (b) (4) All the samples were analyzed at (b) (4) irrespective of the condition of the samples upon receipt.

a. No consistent procedure was followed to inactivate carboxypeptidase-G2 (CPDG2) in plasma samples during collection. Early in the study plasma samples were heat inactivated; later hydrochloric acid was added to plasma samples to inactivate CPDG2 [Different versions of (b) (4) Special Exception Protocol from patients #2, #17, #67, and #73 representing changes in Pharmacokinetic sample collection procedure are provided in **Attachment 2**].
b. For many plasma samples, there was no documentation or correspondence, to describe the condition of plasma samples during shipment and upon receipt at (b) (4) Not all the samples were received in frozen (on dry ice) condition **[Attachment 4, Table showing records of randomly audited 34 patient]**
c. There was no verification that samples were protected from light. MTX is known to be light-sensitive.
d. There was no record of how the samples were transferred in and out of the freezer (-80^{0}C), and how they were processed for HPLC analysis.

The failure to document all of these conditions of handling and storage prevents assurance of accuracy in the reported concentrations. It cannot be distinguished whether apparent reductions in MTX concentrations resulted from *in vivo* therapeutic action of CPDG2, or from *ex vivo* pre-analytical variables.

2. **Failure to use adequate Quality Controls (QCs) during analysis of plasma samples to accept or to reject analytical runs.**

a. During analysis of plasma samples from patients 1-69 no QC samples were used for run acceptance/rejection. Only aqueous 1 µM and 10 µM solutions were analyzed at the beginning and end of each run.
b. During analysis of plasma samples from patients 70-83, the calibration standards and QC samples were prepared from the same stock solution. Thus, the measured QC concentrations do not necessarily demonstrate accuracy in this reflexive measurement of essentially identical calibrators and QCs. QC samples at 0.5 µM (mid) and 5.0 µM (high) concentrations were analyzed in singlet; no QC sample at the lower limit of quantitation (LLOQ) was

used. The QC acceptance criterion was that both singlet results should be within 30% of the nominal concentration.

Due to the absence of adequate QCs, the accuracy of MTX results from patients 1-69 cannot be assured. For patients 70-83, the concentration of MTX well below 0.5 µM cannot be assured.

3. Failure to demonstrate stability of MTX in stock solution and in samples with variable storage and handling conditions.

(b) (4) did not evaluate stability of MTX in stock solutions and plasma samples. All the samples were analyzed irrespective of the condition of the samples upon receipt. The opinion expressed by investigators at (b) (4) that MTX would be stable under these conditions, was not supported by experimental data. In the absence of demonstration of stability, the integrity of MTX in study samples cannot be assured.

4. Failure to use the same anticoagulant for QCs as used during sample collection of study samples.

For patients 70-83, heparin (green top tubes coated with heparin) was used during collection; however the QC samples used during analysis were prepared in "citrated plasma" **[Attachment 3]**. It is unclear whether this was transfusion plasma (diluted with a significant volume of citrate-phosphate-dextrose-adenine) or from "blue top" tubes ordinarily used for blood clotting diagnostic samples. Therefore, it is unclear whether assay performance with these QCs reflected accuracy, stability, etc. for study samples.

5. Failure to demonstrate interaction of concomitant medication on MTX.

All the patients were given leucovorin and thymidine "rescue" treatment. The selectivity of the method for MTX in the presence of the concomitant medications was not demonstrated. Interfering peaks were observed to overlap MTX chromatographic peaks in a number of sample chromatograms.

Additionally there were 6 patients 195, 207, 213, 215, 216, and 218 who were given the same lot of CPDG2 (Lot 004) as used for the 83 patients from study PR001-CLN-002. However, analysis of plasma MTX and DAMPA for these patient samples collected in 2003-2004 was done in 2005 after CLIA certification and HPLC method validation. (b) (4) failed to adequately document all aspects

of sample collection, receipt, handling and integrity **[Attachment 4]**.

Study PR001-CLN-006:

Analyses of MTX and DAMPA in plasma samples from 27 patients in Study PR001-CLN-006 were conducted in 2005 after CLIA certification and the limited method validation. Unlike Study PR001-CLN-002, no clinical decision for the patients was made based on results of HPLC analysis of plasma MTX under Study PR001-CLN-006.

The [redacted] (b) (4) for these patients specified plasma collection in heparin-coated green top tubes followed by transfer of plasma to red top tubes, which included hydrochloric acid (HCL) for CPDG2 inactivation, storing the samples at -20°C to -70°C and shipping overnight on dry ice. The red top tubes with HCL were provided by [redacted] (b) (4) to the clinical investigators. Samples once received at [redacted] (b) (4) were stored at -80°C till analyzed.

No formal laboratory notebooks were maintained to documented day to day study related activities. The following are inspectional findings and our evaluations.

1. **Failure to adequately document all aspects of sample receipt, handling and integrity.**
   a. The conditions of samples upon receipt were not documented consistently. Some samples had marginal notes on the 'MTX Pharmacokinetic Worksheet," but about 10 of 27 patients had no notes or shipping correspondence **[Attachment 4]**. Not all the samples were received in frozen (on dry ice) condition; some were thawed, shipped at room temperature or on wet ice.
   b. There was no verification that samples were protected from light. MTX is known to be light-sensitive.
   c. Plasma samples were stored at -80°C at [redacted] (b) (4) for about 6 months before they were analyzed for MTX and DAMPA concentration. There was no record of how the samples were transferred in and out of the freezer (-80°C), and how they were processed for HPLC analysis.

The failure to document all of these conditions of handling and storage prevents assurance of accuracy in the reported concentrations. It cannot be distinguished whether apparent reductions in MTX concentrations resulted from *in vivo*

therapeutic action of CPDG2, or from *ex vivo* pre-analytical variables.

2. **Failure to use adequate Quality Controls (QCs) during analysis of plasma samples to accept or to reject analytical runs.**

a. Only a single stock solution of MTX or DAMPA was used for both calibration standards and QC samples, in both pre-study validation and within-study conduct. There was no documentation to verify the weights of MTX or DAMPA used for preparation of stock solutions used to prepare calibration standards and QCs. Calibration standards and QCs were not prepared fresh for each analytical run. 20 sets of QC samples were prepared at one time, aliquotted and stored at -20°C to -70°C until analyzed.
b. The calibration standards ranged from 0.05 µM to 1.0 µM. However, the accuracy and precision of the method was validated using QC samples at 1 µM, 2.5 µM and 10.0 µM concentrations; no QC sample at the lower limit of quantitation (LLOQ) was used. QC samples at 0.5 µM and 5.0 µM were used during analysis of patient samples. During several analytical runs, the mid QC (0.5 µM) was analyzed in singlet. The QC acceptance criterion was that QC results should be within 30% of the nominal concentration.
c. Some of the plasma samples were diluted during analysis, especially the pre-CPDG2 and 15 min post-CPDG2 plasma samples; however, no validation for dilution of plasma samples was demonstrated.

Due to the failure to use independent stock solutions for calibration standards and QCs, the measured QC concentrations do not necessarily demonstrate accuracy in this reflexive measurement of essentially identical calibrators and QCs. The concentration of MTX well below 0.5 µM cannot be assured.

3. **Failure to demonstrate stability of MTX in stock solution and in samples with variable storage and handling conditions.**

(b) (4) did not evaluate stability of MTX in stock solutions and plasma samples. All the samples were analyzed irrespective of the condition of the samples upon receipt. No short term, long term, freeze thaw and process stability of MTX was demonstrated. The opinion expressed by investigators at (b) (4) that MTX would be stable under these conditions, was not supported by experimental data.

In the absence of demonstration of stability, the integrity of MTX in study samples not received in frozen and acidified condition cannot be assured.

4. Failure to demonstrate interaction of concomitant medication on MTX.

All the patients were given leucovorin "rescue" treatment. The selectivity of the method for MTX in the presence of the concomitant medications was not demonstrated. Interfering peaks were observed to overlap MTX chromatographic peaks in a number of sample chromatograms.

Number of deficiencies and inconsistency were observed during this inspection. Lack of proper documentation and record keeping for sample condition, handling along with absence of adequate quality controls and stability studies are some of the significant issues observed during the inspection.

Conclusions:

Following the above inspection, the Division of Bioequivalence and GLP Compliance (DBGC), OSI recommends

- **Due to the inconsistency and multiple deficiencies observed especially for study PR001-CLN-002 patients 1-69, plasma concentrations of MTX cannot be assured. Data from these patients should not be considered for review.**
- **MTX concentrations above 0.5 µM from study PR001-CLN-006 can be assured if stability data for MTX can be provided.**

After you have reviewed this transmittal memo, please append it to the original BLA submissions.

Jyoti B. Patel, Ph.D.

Young Moon Choi, Ph.D.

Final Classifications:
VAI: (b) (4)

CC:
CDER OSI PM TRACK
OSI/Ball/Moreno
OSI/DBGC/Salewski/Haidar/Skelly/Patel/Choi/Dejernett/Matthews/CF
HFR-CE250/Christine Smith (DIB)/Cynthia Harris (BIMO)
HFR-CE2535/Hector Colon
OND/OODP/DBOP/Patricia Keegan/Erik Laughner/ Patricia Dinndorf
OTS/OCP/DCP5/Hong Zhao/Lillian Zhang
Draft: JBP 10/18/2011, 10/27/2011
Edit: MFS 10/18/2011, 10/28/2011
DSI: 6255; O:\BE\EIRCOVER\125327.btg.glu.doc
FACTS: 1316495

Attachments:

Attachment 1: Information provided by (b) (4)
Attachment 2: Different versions of (b) (4) **Protocol**
Attachment 3: Copy of document describing anticoagulant used for preparing QC samples
Attachment 4: Table showing sample records of randomly audited 34 patients from study PR001-CLN-002
Attachment 5: Table showing sample records of patients from study PR001-CLN-006

14 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

Maternal Health Team Review

Date: October 25, 2011 **Date Consulted:** July 25, 2011

From: Jeanine Best, MSN, RN, PNP
Senior Clinical Analyst, Pediatric and Maternal Health Staff (PMHS)

Through: Lisa Mathis, MD MD 10/25/2011
OND Associate Director, Pediatric and Maternal Health Staff (PMHS)

To: Division of Oncology Products 2 (DOP2)

Drug: Voraxaze (glucardipase), BLA 125327

Subject: Pregnancy and Nursing Mothers Labeling

Materials Reviewed:

- Draft Voraxaze labeling dated July 18, 2011

Consult Question: DOP2 requests that PMHS/MHT review and comment on the proposed Pregnancy and Nursing Mothers subsections of Voraxaze labeling.

INTRODUCTION

On July 18, 2011, BTG International Inc. submitted the final portion of the rolling BLA (125327) for Voraxaze (glucardipase) for purposes of activating the review clock. Voraxaze is proposed for the (b) (4) reduction of toxic methotrexate concentrations due to impaired renal function.

The Division of Oncology Products 2 (DOP2) consulted the Pediatric and Maternal Health Staff-Maternal Health Team (PMHS-MHT) on July 25, 2011, to review the proposed Pregnancy and Nursing Mothers subsections of Voraxaze labeling.

BACKGROUND

Glucardipase

Glucardipase is a recombinant bacterial enzyme that rapidly hydrolyzes the carboxyl-terminal glutamate residue from folic acid and classical antifolates such as methotrexate (as well as folic acid and other folates) and converts methotrexate to its inactive metabolites 4-deoxy-4-amino-N^{10}-methylpteroic acid (DAMPA) and glutamate. Because both DAMPA and glutamate are metabolized by the liver, glucopardase allows for an alternative route of methotrexate elimination in patients with renal dysfunction during high-dose methotrexate treatment. Glucopardase does not cross the blood brain barrier or cellular membranes due its large molecular size (83 kiloDaltons); therefore, it cannot counteract the intracellular antineoplastic effects of high-dose methotrexate, and administration of leucovorin is still necessary to protect normal cells from methotrexate toxicity. In addition, glucopardase does not reverse pre-existing renal damage that can occur from methotrexate administration, but instead removes methotrexate to reduce the risk of sustaining further renal toxicity.

REVIEW OF LABELING

Proposed Labeling dated July 18, 2011

(b) (4)

(b) (4)

DISCUSSION AND CONCLUSIONS

Pregnancy and Nursing Mothers Labeling

The Pregnancy and Nursing Mothers subsections of labeling should describe available animal and human data in a manner that allows clinicians, who are prescribing medication for pregnant patients and female patients of reproductive potential, to balance the benefits of treating the patient with the potential risks to the mother, fetus and/or infant. PMHS- maternal health labeling recommendations comply with current regulations but incorporate "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). Usually the first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management.

No human pregnancy data is available for Voraxaze and no animal reproduction studies were conducted with the product. The Sponsor is seeking an indication for Voraxase that only involves use of the product with methotrexate, a known human teratogen and abortifacient. Animal reproduction studies should be conducted with Voraxaze if other indications are considered that include females of reproductive potential.

(b) (4)

PMHS-MHT LABELING RECOMMENDATIONS

PMHS-MHT has the following recommended pregnancy and nursing mothers labeling revisions for Voraxaze.

(b) (4)


(b) (4)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	October 4, 2011
Reviewer(s):	Manizheh Siahpoushan, Pharm.D., Safety Evaluator 10/4/11 Division of Medication Error Prevention and Analysis
Team Leader	Zachary Oleszczuk, Pharm.D., Team Leader 10/4/11 Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, R.Ph., Director 10/4/11 Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Voraxaze (Glucarpidase) Powder for Injection 1000 Units
Application Type/Number:	BLA 125327
Applicant/sponsor:	BTG International Inc.
OSE RCM #:	2011-2549

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the container label, carton labeling, and Prescribing Information for Glucarpidase Powder for Injection 1000 Units, for areas of vulnerabilities that could lead to medication errors. This review is in response to the June 30, 2011 submission from BTG International Inc.

1.1 BACKGROUND OR REGULATORY HISTORY

The Applicant submitted a request for review of the proprietary name, Voraxaze, BLA 125327 on July 18, 2011, which is reviewed separately in OSE Review #2011-2548. The proprietary name Voraxaze was reviewed under IND 11557 in OSE Review #06-0178, dated July 31, 2006, and was found to be acceptable from both a promotional and safety perspective. The Applicant also sumbitted container labels, carton, and Prescribing Information labeling for review by the Agency at the time of the proporietary name submission. DMEPA's review of the label and labeling identified areas of improvement to reduce potential for medication errors, and made recommendations in OSE Review #06-0178, dated July 31, 2006.

1.2 PRODUCT INFORMATION

Voraxaze (Glucarpidase) Injection 1000 Units is indicated for the (b) (4) reduction of toxic Methotrexate concentration due to impaired renal function. The healthcare professional will administer a single dose of 50 Units/kg, (b) (4) , by bolus intravenous injection over 5 minutes. (b) (4) Leucovorin may compete with Methotrexate for Voraxaze binding sites. It is recommended that Leucovorin not be administered within the 2 hours before or after Voraxaze dosing. Voraxaze is supplied as a lyophilized powder in 3 mL single use vials. Each vial contains 1000 Units of Glucarpidase and the excipients lactose, zinc, and tris-HCL-containing buffer. Voraxaze should be stored at 2°C to 8°C (36°F to 46°F). Reconstituted Voraxaze should be used immediately (b) (4) .

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis[1], the principals of human factors, and the lessons learned from postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following (see Appendix A for the carton and container labels):

- Container Label submitted 6/30/11
- Carton Labeling submitted 6/30/11
- Prescribing Information submitted 6/30/11

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 DISCUSSION OF DEFICIENCIES IDENTIFIED

Our review of the container labels, carton labeling, and Prescribing Information identified the following deficiencies:

3.1 CONTAINER LABELS

- The route of administration is not located on the principal display panel and lacks prominence.
- The statement 'Discard unused portion' does not appear on the container label.

3.2 CARTON LABELING

- The route of administration statement does not appear on the principal display panel.
- The statement 'Discard any unused portion' does not appear on the container label.

3.3 PRESCRIBING INFORMATION LABELING

- Presence of trailing zeros throughout the Prescribing Information.
- Use of dangerous symbols '>','<', '≥', '≤', and the abbreviation μg.

4 CONCLUSIONS AND RECOMMENDATIONS

The Applicant addressed most of DMEPA's recommendations in OSE Review #06-0178, dated July 31, 2006, however, the Applicant did not relocate the route of administration statement (i.e. for intravenous injection) to the primary display panel. our evaluation of the container labels, carton labeling, and Prescribing Information noted additional areas of vulnerability that can lead to medication errors because of the deficiencies identified. We recommend the following:

4.1 COMMENTS TO THE DIVISION

A. Prescribing Information

1. Remove all instances of trailing zeros (i.e. 13.0), the symbols '>','<', '≥', and '≤', and the abbreviation 'μg' from the Prescribing Information, (i.e. change '13.0' to read '13' and use 'greater than', 'less than', 'greater than or equal to', and 'less than or equal to'). The use of trailing zeros is error-prone and can result in ten-fold dosing error if the decimal is not seen. The symbols '>' and '<' can be misinterpreted as opposite of intended, mistakenly use incorrect symbol, or '< 10' can be misinterpreted as '40'.

   Additionally, the unit of measurement 'μg' can be misinterpreted as 'mg'. Use 'mcg' in all instances that 'μg' appears in the Prescribing Information. As part of a national campaign to prevent the use of error-prone dose designations such as trailing zeros in prescribing, FDA agreed not to

approve error-prone dose designations in labeling because they are carried on to the prescribing practice.

4.2 COMMENTS TO THE APPLICANT

A. Container Labels

1. Per 21 CFR 201.100 (b)(3), 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. This will ensure that healthcare practitioners will accurately administer the drug. As currently presented, the route of administration statement lacks prominence and is difficult to locate.

2. Revise the side panel to reorganize the information such that the information for reconstitution and administration are stated first and the 'Rx only' statement is made smaller and relocated to the end of the information. Additionally, include the statement 'Discard any unused portion' to appear immediately after (b) (4) (b) (4) The presentation on the side panel should be as follows:

"See package insert for dosage and other information.
(b) (4)
(b) (4) Discard any unused portion.
(b) (4)
Manufactured (b) (4) BTG International Inc.
(b) (4)
Lot: XXXXXX
EXP: MMM YY"

B. Carton Labeling (trade and sample)

1. It is not clear which of the proposed panels is intended to be the principal display panel (PDP) of the carton labeling. Revise the presentation so that the principal display panel includes the proprietary name, the established name, the product strength (under the established name), the route of administration displayed in a prominent manner (i.e. bold letters) below the product strength, and the NDC number. The Lot and expiration dates, the reconstitution instructions, the package content, and the storage information, can be displayed on the side panel. The 'Rx only' statement may appear at the bottom of the principal display panel or the side panel of the carton labeling.

2. Include the statement 'Discard unused portion' to follow the statement (b) (4) ,

APPENDICES

Appendix A: Carton labeling and container label

Carton Labeling

Container Label

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Review Date: September 9, 2011

Division of Biologic Oncology Products

Application Number: BLA STN 125327

Name of Drug: VORAXAZE

Applicant: BTG Internaional Inc.

Material Reviewed:

Initial Proposed Package Insert Labeling Submitted with Clinical Portion of Rolling Application: June 30, 2011

Submission Date of Structure Product Labeling (SPL): June 30, 2011

Type of Labeling Reviewed: WORD/SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

This is a preliminary format review of the proposed labeling submitted in this application. The attached label contains the review comments to go to the Applicant in the filing letter (no 74-day letter is planned).

Recommendations

I completed a preliminary review of the proposed PLR labeling submitted in this application largely based on 21 CFR Parts 201.56 and 201.57, the preamble to the Final Rule, and FDA Guidance documents. The applicant complied with the major requirements for a PLR label in

terms of required sections, headings/sub-headings, font size, etc. A search for the most common formatting deficiencies routinely encountered identified a few issues that will have to be addressed by the Applicant. A list of deficiencies are embedded as comments in the Applicant's initial proposed package insert which will be attached to the filing letter. The clinical reviewer had also provided a number of "first cut" revisions to the label to allow for a better starting point for substantial team review and revision of this label which would begin after the mid-cycle meeting. These revisions are reflected in the label attached to this review.

09/09/11

Erik Laughner, M.S. RAC (US)
Senior Regulatory Health Project Manager

Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

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