CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-575

OTHER REVIEW(S)

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-Amendment

Application Number: NDA 22-575

Name of Drug: VPRIV™ (velaglucerase alfa for injection)

Sponsor: Shire Human Genetic Therapies, Inc.

Material Reviewed: VPRIV™ (velaglucerase alfa for injection) Carton and Container Labels

OBP Receipt Date: September 1, 2009

Amendment Reviewed: February 18, 2010

Background:

VPRIV™ (velaglucerase alfa for injection) is a New Drug Application (NDA) indicated for long-term enzyme replacement therapy (ERT) for pediatric and adult patients with type I Gaucher disease. The product is supplied as a lyophilized powder in single use vials for reconstitution with Sterile Water for Injection at concentrations of 200 units or 400 units.

Labels Reviewed:

VPRIV™ (velaglucerase alfa for injection) Container Label
- 200 Units
- 400 Units

VPRIV™ (velaglucerase alfa for injection) Carton Labels
- 200 Units
- 400 Units

EXECUTIVE SUMMARY

The carton and container labels for VPRIV™ (velaglucerase alfa for injection) were reviewed and found to comply with 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 Pharmacopoeia, 8/1/09-12/1/09, USP 32/NF 27. Labeling deficiencies were identified and mitigated. Please see comments in the conclusions section. The carton and container labels are acceptable.

Review

The carton and container labels for VPRIV™ (velaglucerase alfa for injection) were reviewed and found to be adequate under most of the following regulations: 21 CFR 201.1 through 21 CFR 201.18; 21 CFR 201.25; and 21 CFR 201.50 through 21 CFR 201.55 through 21 CFR 200.57; 21 CFR 201.100 and United States Pharmacopeia, 8/1/09-12/1/09, USP 32/NF27. Please see comments in the conclusions section.

I. Container

A. Vial Label

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer or distributor-
   Manufactured By: Shire Human Genetic Therapies, Inc.
   700 Main Street
   Cambridge, MA 02139
   This conforms to the regulation.

2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers- The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 54092-XXX-XX. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.

3. 21 CFR 201.5 Drugs; adequate directions for use-Adequate directions for use does not appear on the label, however "See package insert for reconstitution and dosing instructions." appears. This conforms to the regulation.

4. 21 CFR 201.6 Drugs; misleading statements- There is a single ingredient in this product. This conforms to the regulation.

5. 21 CFR 201.10 Drugs; statement of ingredients- The established name, velaglucerase alfa is not used in type at least half as large as the proprietary name, VPRIV™. The prominence of the velaglucerase alfa, is not commensurate with the prominence and typography of VPRIV™. The established name appears as velaglucerase alfa and does not include the dosage form. This does not conform to the regulation.

6. 21 CFR 201.15 Drugs; prominence of required label statements-

All required statements ("Rx Only", "Do not freeze", "Protect from Light"). This conforms to the regulation.

7. 21 CFR 201.17 Drugs: location of expiration date-The expiration date and the lot identification number do not appear on the label. This does not conform to the regulation.

8. 21 CFR 201.25 Bar code label requirements – The bar code is located on the right of the label with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.

9. 21 CFR 201.50 Statement of identity- The established name, velaglucerase alfa, appears on the label, but does not include the dosage form, for injection. The prominence of velaglucerase alfa is not commensurate with VPRIV™. This does not conform to the regulation.

10. 21 CFR 201.51 Declaration of net quantity of contents – The label prominently states the net quantity of contents in terms of units. This conforms to the regulation.

11. 21 CFR 201.55 Statement of dosage- The label states "See package insert for reconstitution and dosing instructions." This conforms to the regulation.

12. 21 CFR 201.100 Prescription drugs for human use- The label bears statements for "Rx Only", storage conditions, and reference to the package insert. An identifying lot number, is not present on the label. The route of administration is not displayed. This does not conform to the regulation.

13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of 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. This does not apply.

3 Page(s) Withheld

_____ Trade Secret/Confidential (b4)

_X_ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Other Reviews Section-*_____

400 Units Carton

b(4)

II. Carton

A. Carton Label

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer or distributor-

   Manufactured By: Shire Human Genetic Therapies, Inc.
   700 Main Street
   Cambridge, MA 02139

   This conforms to the regulation.

2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers- The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 54092-XXX-XX. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.

3. 21 CFR 201.5 Drugs; adequate directions for use-Adequate directions for use does not appear on the label, however "See package insert for reconstitution and dosing instructions." appears on the side panel. This conforms to the regulation.

9. 21 CFR 201.6 Drugs; misleading statements- There is a single ingredient in this product. This conforms to the regulation.

4. 21 CFR 201.10 Drugs; statement of ingredients- The established name, velaglucerase alfa not used in type at least half as large as the proprietary name, VPRIV™. The prominence of the velaglucerase alfa, is not commensurate with the prominence and typography of the VPRIV™. The established name appears as velaglucerase alfa and does not include the dosage form. This does not conform to the regulation.

5. 21 CFR 201.15 Drugs; prominence of required label statements- All required statements ("Rx Only", "Do not freeze", "Protect from Light"). This conforms to the regulation.

6. 21 CFR 201.17 Drugs: location of expiration date-The expiration date and lot identification number do not appear on the label. This does not conform to the regulation.

7. 21 CFR 201.25 Bar code label requirements – The bar code is located on the bottom right panel of the label with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.

9. 21 CFR 201.50 Statement of identity- The established name, velaglucerase alfa, appears on the label, but does not include the dosage form, for injection. The prominence of velaglucerase alfa is not commensurate with VPRIV™. This does not conform to the regulation.

10. 21 CFR 201.51 Declaration of net quantity of contents – The label states the net quantity of contents in terms of units. This conforms to the regulation. Declaration lacks prominence.

11. 21 CFR 201.55 Statement of dosage- The label states "See package insert for reconstitution and dosing instructions." This conforms to the regulation.

12. 21 CFR 201.100 Prescription drugs for human use- The label bears statements for "Rx Only", storage conditions, and reference to the package insert. An identifying lot number, is not present on the label. The route of administration is not displayed. This does not conform to the regulation.

13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of 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. This does not apply.

III. Conclusions

A. The proposed carton and vial labeling are acceptable only upon the following changes:

1. Carton

a) The following statements are BLA requirements that may be removed:

(1) Contains one vial

(2) Contains no preservative

(3) No U.S. standard of potency

Recommendations accepted and items removed.

2. Container

a) See Carton and Container comments.

3. Carton and Container

a) Per 21 CFR 201.10 and 201.100, Please revise the prominence and typography of the established name, Velaglucerase alfa commensurate with the most prominent presentation of the proprietary name, VPRIV™.

Change made and acceptable.

b) Per 21 CFR 201.17, Please add the lot identification

number and the expiration date.
Changes made and acceptable.

c) Per 21 CFR 201.50, Please add the dosage form, for injection to the listed established name velaglucerase alfa. The established name should read, velaglucerase alfa for injection.
Change made and acceptable.

d) Per 21 CFR 201.51, please increase the font size of the net quantity statement listed on the container labels for improved readability. Consider relocating the quantity statement and route of administration to reflect the following presentation.

VPRIV
(velaglucerase alfa for injection)
XXX units
For Intravenous use

Change made and acceptable.

e) Per the United States Pharmacopoeia, 8/1/09-12/1/09, USP 32/NF 27, General Chapter <1091> Labeling of Inactive Ingredients, Please alphabetize the inactive ingredient listing in the "Description" section of the Package Insert.
Change made and acceptable.

Discussion points:

The Division of Medication Error Prevention and Anaylsis (DMEPA) has requested a color change for the 400 Units strength presentation on the vial and carton label. The DMEPA safety evaluator has requested that the firm change the light green text to increase contrast and improve readability of the strength. The label text was revised to blue. DMEPA finds the label acceptable with the revision.

Revised Carton and Container Labels (2/17/10)

b(4)

b(4)

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

Comment/Concurrence:

Emanuela Lacana, Ph.D.
Product Reviewer
Division of Therapeutic Proteins
CDER/OPS/OBP/

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY M RAINS
02/25/2010

EMANUELA LACANA
02/25/2010

BARRY W CHERNEY
02/26/2010

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

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

Memorandum

Date: January 28, 2010

To: Wes Ishihara, Regulatory Project Manager
Division of Gastroenterology Products (DGP)

From: Shefali Doshi, Regulatory Review Officer
Kathleen Klemm, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Robert Dean, DTC Group Leader
Lisa Hubbard, Professional Group Leader
DDMAC

Subject: NDA 22-575
DDMAC labeling comments for VPRIV (velaglucerase alfa) for injection

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DDMAC has reviewed the proposed product labeling (PI) for VPRIV (velaglucerase alfa) for injection submitted for consult on October 23, 2009, and offers the following comments.

The version of the draft PI used in this review is titled, "09-0831 vela PI Shire orig.doc" accessed via the DGP eRoom on January 26, 2010. This document was last modified on January 22, 2010, at 3:53pm.

DDMAC's comments are provided directly on the marked up version of this document, attached below.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the PI up to section 17, please contact Katie Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov. If you have any questions regarding section 17 of the PI, please contact Shefali Doshi at 301.796.1780 or Shefali.Doshi@fda.hhs.gov.

20 Page(s) Withheld

_____ Trade Secret/Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Other Reviews Section-*_____

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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/s/

SHEFALI S DOSHI
01/28/2010

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: January 27, 2010

TO: Richard Ishihara, Regulatory Project Manager
Il-Lun Chen, Medical Officer
Division of Gastroenterology Products

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA 22575

APPLICANT: Shire Human Genetic Therapies, Inc.

DRUG: Gene-Activated Glucocerebrosidase (GA-GCB, DRX009A), Velaglucerase Alfa

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: For the long-term enzyme replacement therapy (ERT) for patients with type 1 Gaucher disease.

CONSULTATION REQUEST DATE: 10/15/2009

DIVISION ACTION GOAL DATE: 02/26/2010

PDUFA DATE: 02/26/2010

I. BACKGROUND:

Shire Human Genetics Therapy, Inc. seeks approval of Velaglucerase alfa (GA-GCB) for the long-term enzyme replacement therapy (ERT) for patients with type 1 Gaucher disease. The applicant presents data from three phase III studies, TKT032, TKT034 and HGT-GCB-039; however, TKT032 is the pivotal study, entitled, "A Multicenter, Randomized, Double-Blind, Parallel Group, Two-Dose Study of Gene-Activated® Human Glucocerebrosidase (GA-GCB) Enzyme Replacement Therapy in Patients with Type 1 Gaucher Disease." In addition, the applicant provides key data from 2 additional studies, TKT025 and TKT025EXT.

Three phase III studies TKT032 (pivotal), TKT034 and HGT-GCB-039, and 2 phase II supportive studies TKT025 and TKT025EXT were targeted for inspection. The data generated by all of these studies is deemed critical by the review division in understanding the efficacy and safety parameters of this ERT for type I Gaucher disease.

There were no concerns regarding safety or efficacy signals associated with the data generated by the 2 sites targeted for inspection. As such, this assignment was a routine audit request to assess data integrity and human subject protection for the clinical trials identified above and submitted in support of this application.

Two clinical sites were inspected in accordance with the CDER Clinical Investigator Data Validation Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.811); that of Dr. Ari Zimran, Site number 071, and that of Dr. Derlis Emilio Gonzales Rodriguez, Site number 152. These sites were selected by the product review division because there are insufficient domestic data and these sites were high enrolling sites.

In addition, the NDA applicant and study sponsor, Shire Human Genetic Therapies, Inc, and a CRO [redacted] were inspected in accordance with the CDER Sponsor/Monitor/CRO Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.810). The applicant was inspected because the drug product represents a new molecular entity. The CRO was inspected because the CRO was singularly responsible for MRI interpretations, generating the secondary efficacy endpoint data (changes in liver and spleen volumes) for the three phase III studies submitted to the agency in NDA 22575. In addition, it was discovered during the audits of the clinical investigators that the source records and media (MRI images) were not retained at the sites, but instead were forwarded to this CRO for interpretation and archiving. Therefore, the reliability of the secondary efficacy endpoint data for liver and spleen volumes for all three phase III studies could only be verified by audit of this CRO.

b(4)

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
CI#1: Dr. Ari Zimran **Site #071** Address: Gaucher Clinic	Studies TKT025 (Phase I/II): 12/12 subjects	December 7-10, 13-18, and 20th, 2009	Pending (EIR is pending)

The Hebrew University Haddassah Medical School Shaare Zedek Medical Center 12 Hans Bayt Jerusalem 91031, Israel Phone: 972 2-6555143 Cell: 972 55 728284 Fax: 972 2 6517979 Email: azimran@gmail.com Email: gaucher@szmc.org.il	TKT025EXT: 8/10 subjects TKT032: 7/25 subjects TKT034: 9/40 subjects HGT-GCB-039: 3/34 subjects		
CI#2: Derlis Emilio Gonzales Rodriguez, M.D. **Site #152** Address: Sociedad Espanola de Socorros Mutuos (Santorio Espanol) Gobernador Irala y Coronel Lopez Barrio Sajonia, Asuncion, Paraguay Phone: (595)21-420.888 Direct: (595)21-423-603 Cell: (595)971-223286 Fax: (595)21-420.888 Email: degonzal@conexion.com.py Email: gderlis@conexion.com.py	TKT032: 11/25 subjects HGT-GCB-039: 5/34 subjects	January 4-8, 2010	Pending (EIR is pending)
Sponsor: **Shire Human Genetic Therapies, Inc.** POC: Nikhil Mehta, Ph.D. Senior Vice President, Global Regulatory Affairs 700 Main Street Cambridge, Massachusetts 02139-3543 Phone: 781-482-4900 Fax: 617-613-4444 Email: nmehta@shire.com	Studies TKT025: 12 subjects TKT025EXT: 10 subjects TKT032: 25 subjects TKT034: 40 subjects HGT-GCB-039: 34 subjects	December 8-11, 14-15, and 17th, 2009. January 7, 2010	Pending (EIR is pending)
CRO:	TKT032: 25 subjects TKT034: 40 subjects HGT-GCB-039: 34 subjects	January 8, 11 and 12th, 2010	Pending (EIR is pending)

b(4)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. **CI#1: Dr. Ari Zimran**
   (Site Number 071)
   Gaucher Clinic
   The Hebrew University, Haddassah Medical School
   Shaare Zedek Medical Center
   12 Hans Bayt
   Jerusalem 91031, Israel

   a. **What was inspected**: The study records of subjects enrolled at this site for 5 protocols (TKT025, TKT025EXT, TKT032, TKT034 and HGT-GCB-039) were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed the reliability of all primary and secondary efficacy endpoints as per protocol (hemoglobin levels, platelet counts, liver and spleen volumes) submitted to NDA 22575 for all subjects and all time points in all 5 studies. The FDA investigator also assessed consent forms.

      i. **TKT025:** The site screened 13 subjects, 12 of those were enrolled and all 12 completed the study. The study records of 4 enrolled subjects (0003, 0004, 0007, 0009) were audited.
      ii. **TKT025EXT:** The site screened 10 subjects, all 10 of those were enrolled and 8 were continuing in the ongoing study. The study records of 2 subjects (0005, 0008) were audited.
      iii. **TKT032:** The site screened 12 subjects, 7 of those were enrolled and all 7 completed the study. The study records of all 7 enrolled subjects were audited.
      iv. **TKT034:** The site screened 10 subjects, 9 of those were enrolled and all 9 completed the study. The study records of 5 enrolled subjects (0001, 0003, 0005, 0007, 0009) were audited.
      v. **HGT-GCB-039:** The site screened 4 subjects, 3 of those were enrolled and all 3 completed the study. The study records of all 3 enrolled subjects were audited.

   Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. General observations/commentary: Generally, the investigator's execution of each protocol was found to be adequate. The primary efficacy endpoint data listings, specifically, hemoglobin and platelet count data listings submitted to NDA 22575 were verifiable by comparison to source data available at the clinical site (— and/or local lab test results). There were no discrepancies. However, the liver and spleen volume source data were not retained at the site for any of the 5 studies audited. b(4)

The FDA field investigator was informed during the inspection that for Studies TKT025 and TKT025EXT the liver and spleen volume MRIs were not retained by the site and the interpretations/source records were generated and maintained by a CRO, at an alternate location. These MRIs and source records were maintained by the CRO who conducted the organ volume assessments, — b(4)
— Those records were transported from the CRO, —
— to the site of Dr. Ari Zimran, for data integrity validation. The FDA field investigator was then able to assess the liver and spleen volumes submitted to NDA 22575 for Studies TKT025 and TKT025EXT. No discrepancies were noted between liver and spleen volume source records from the CRO — and the data listings provided in NDA 22575. However, it should be noted that CRO — was not audited under the BIMO program so his procedures were not verified.

Regarding studies TKT032, TKT034 and HGT-GCB-039 the liver and spleen volume data were not able to be verified at this site because the source data for these parameters were generated by a CRO, —
— . The sponsor, Shire, contracted with —
— for measuring and reporting liver and spleen volumes. The MRIs from which the volumetric measurements were obtained were performed by another contract firm, — b(4)
The electronic MRI files were initially sent from — to the clinical site on CDs, however, the clinical site did not retain copies of the electronic MRI files and sent the CDs containing the electronic MRI files on to — (Form FDA-483 observation 1). The liver and spleen volumes determined by — were subsequently sent directly to the sponsor, Shire, and were not provided to the clinical site.

The CRO was responsible for MRI interpretation for liver and spleen volumes of subjects enrolled in studies TKT032, TKT034 and HGT-GCB-039 for all study sites. A subsequent FDA BIMO inspection of this CRO was conducted in early January 2010 in order to audit the critical secondary efficacy endpoints of liver and spleen volume, generated by site 071/Dr. Ari Zimran, for Studies TKT032, TKT034 and HGT-GCB-039. No discrepancies were noted between b(4)
liver and spleen volume source records from the CRO — and that provided in NDA 22575.

The inspection also found a number of record keeping violations related to records retention of study specific MRIs of lumbar spine and femoral neck, and bone density scans. The inspection also found that drug accountability records appeared to contain conflicting information related to timing of drug preparations. Inspectional observations also raised concerns regarding study medication controls, documentation of receipt, storage, and disposition. In one instance expired study medication was administered to a subject. In Study TKT025, one subject was enrolled that failed to meet inclusion/exclusion criteria.

The inspectional observations were shared via email and discussed with the review division Medical Officer, Dr. Ii-Lun Chen, during December 2009 and early January 2010. DSI reviewer Dr. Lauren Iacono-Connors and Dr. Chen discussed the possibility that the inspectional observations with respect to the few protocol deviations, procedural on-site record keeping violations, and study medication storage and controls may not be clinically significant. Briefly, efficacy endpoint source records not found at the site were generated and retained at the corresponding CRO sites b(4)
and efficacy endpoint data listings, liver and spleen volumes, could be, and were, verified by audit of the CRO source records. Study medication storage was not likely significant since temperature excursions were short and just slightly above the sponsor-required temperature range for short periods of time (personal communication from the FDA field investigator). According to the FDA field investigator, the sponsor provided additional information indicating there is some extended stability data for the study drug. The FDA field investigator informed that while he did observe conflicting dose preparation times (Form FDA 483, item 4) they in fact would have little affect on the study since in all but one circumstance (Form FDA 483, item 5) the prep times and administration were still within the 3 hour time limit specified as expiration time limit.

Consistent with the routine clinical investigator compliance program assessments, the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. A Form FDA 483 was issued citing 8 Observations. The review division may wish to consider each violation, outlined in the Form FDA 483, and summarized below, as it pertains to individual study subjects, and the review division may wish to sensor subject-specific data as appropriate.

1. For Studies TKT032, TKT034 and HGT-GCB-039, failure to maintain source data records. For example,
    a. MRIs used to calculate liver and spleen volumes (secondary efficacy criteria);
    b. MRIs of the lumbar spine and femoral neck; and

c. DXAs (bone density scans) used to determine Gaucher-related local and systemic bone disease.

2. Failure to adequately control the storage and disposition of study medication. For example,
   a. For all five studies, study medication was stored throughout the studies in an unlocked refrigerator in the hospital pharmacy, where it was accessible to non-study personnel, including non-study pharmacists, pharmacy technicians and pharmacy warehouse personnel.
   b. For all five studies, procedures utilized for the disposition of used, partially used, and unopened vials of study medications did not provide assurance the vials were not diverted to persons not authorized to receive them. For example, for Studies TKT032, TKT034 and HGT-GCB-039, used, partially used and unopened vials were placed into unsealed boxes and delivered to a non-study person (pharmacy storekeeper), after which a study pharmacist assumed the vials would be destroyed and completed a destruction record. The storekeeper subsequently placed the vials in an unlabeled and unsealed drum in the pharmacy warehouse area where it was accessible to non-study personnel, and where it remained unsealed for up to two months. When full, the unsealed drum was taken from the pharmacy warehouse by a hospital cleaning person for delivery to a central pick-up area. The central pickup area remained accessible to hospital cleaning staff, and the drum remained unsealed until sufficient drums were accumulated to warrant pickup by a waste disposal company.
   c. Study records fail to document the date or time study drug shipments were received at the clinical site, the date or time they were placed into controlled temperature storage, the identity of the carrier or individual that delivered the drugs, the identity of the person that received the drugs, or the location where the drugs were placed for storage (such as pharmacy refrigerator 1, pharmacy refrigerator 2, etc.). However, a packing slip and invoice were received with each shipment of study drug.

3. Incorrect versions of informed consent forms were administered to four study subjects, including Subject R-B for study TKT032, Subject 0002/BXS for Study TKT025EXT, and Subjects 0001 and 0002 for Study HGT-GCB- 039.

4. Study records contain conflicting information for the preparation times of study medications. Preparation times, which were used to calculate the 3-hour medication expiry periods, differed by as much as 1 hour (Study TKT034, Subject 0009, Week 7) between the prep times recorded by the pharmacist on the label they attached to each infusion record, and the prep time recorded by the pharmacist on the physician script.

5. For Study TKT032 records indicate that on week 29, expired medication was administered to subject 0007. Records show the medication was prepared at

"9:35" but not infused until "12:50", exceeding the 3-hour expiry period from preparation to infusion. There is no record of any interim storage under controlled temperature conditions.

6. For Study TKT025, liver and spleen volumes calculated for study subjects were not included in study records, and paper printouts of the volumetric analysis data signed by the technician that masked the data were not retained as required by the blinding procedure SOP.

7. For Studies TKT032, TKT034, and HGT-GCB- 039, numerous instances were noted where source data for dose preparation was not retained. In these cases, source data for medication preparation was recorded by a pharmacist directly on a fax copy of a prescription script. That data was subsequently transcribed from the fax onto the original prescription script, and in many instances, the fax copies containing the source data were discarded.

8. Study Subject 0009 was entered into Study TKT025 despite failing to meet inclusion criteria 2(b). The criteria required that the patient's hemoglobin be at least 1 gm/dL below the lower limit of normal for age and sex. The lower limit for a male is reportedly "14.0", and this subject's hemoglobin was measured at 13.1. This was not identified as a protocol deviation and no exemption was granted by the sponsor.

The general observations and actions on inspection are based on preliminary communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

c. **Assessment of data integrity**: Based on discussions between the DSI reviewer and the Review Division MO, and consideration of the informal explanations from the FDA field investigator the findings are unlikely to significantly impact data integrity. The data for Dr. Zimran's site, associated with Studies TKT025, TKT025EXT, TKT032, TKT034 and HGT-GCB-039 submitted to the Agency in support of NDA 22-575, appear reliable based on available information, despite the various regulatory violations noted.

2. **CI#2: Dr. Derlis Emilio Gonzales Rodriguez**
(Site Number 152)
Sociedad Espanola de Socorros
Mutuos (Santorio Espanol)
Gobernador Irala y Coronel
Lopez Barrio
Sajonia, Asuncion, Paraguay

a. **What was inspected**: The study records of subjects enrolled at this site into 2 protocols (TKT032 and HGT-GCB-039) were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention

paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed the reliability of all primary and secondary efficacy endpoints as per protocol (hemoglobin levels, platelet counts, liver and spleen volumes) submitted to NDA 22575 for all subjects and all time points for Studies TKT032 and HGT-GCB-039. The FDA investigator also assessed consent forms.

i. **TKT032:** The site screened 12 subjects, 11 of those were enrolled and all 11 completed the study. The study records of 7 enrolled subjects were audited.
ii. **HGT-GCB-039:** The site screened 5 subjects, 5 of those were enrolled and all 5 completed the study. The study records of 4 enrolled subjects were audited.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. **General observations/commentary**: Generally, the investigator's execution of each protocol was found to be adequate. The primary efficacy endpoint data listings, specifically, hemoglobin and platelet count data listings submitted to NDA 22575 were verifiable by comparison to source data available at the clinical site. There were no discrepancies.

As with Dr. Zimran's site, this site did not generate the liver and spleen volume determinations for Studies TKT032 and HGT-GCB-039. Therefore those endpoints were not able to be verified at this site. The source data for liver and spleen volumes were generated by and retained at the CRO _____ A subsequent FDA BIMO inspection of this CRO was conducted in early January 2010 in order to audit the critical secondary efficacy endpoints of liver and spleen volume, generated by site 152/Dr. Rodriguez, for studies TKT032 and HGT-GCB-039. No discrepancies were noted between liver and spleen volume source records from the CRO — and that provided in the NDA 22575. b(4)

The inspection also found that disposition of study drug was not performed according to protocol requirements and that source data for infusions was recorded in nurse's notes but not included in study records. Informed consent procedures were inadequate in that subjects were consented with an obsolete informed consent document (ICD) version and/or were not promptly re-consented after the protocol was amended to include additional procedures.

Consistent with the routine clinical investigator compliance program assessments, the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. A Form FDA 483 was issued citing 7 Observations. The review division may wish to consider each violation, outlined in the Form FDA 483, and summarized below, as they pertain to each study, and may choose to sensor data as appropriate.

1. For both studies, the medication dosages assigned to each study subject were determined by the viewing of a limited-access computer screen by an unblinded pharmacist. The step of obtaining the assigned dosages was not documented by the pharmacist at the time it was performed, and the assigned dosages were not recorded until 1 or 2 days later when they were written in the medication preparation records. For both studies, dosage confirmation records were not provided to the site (unblinded study personnel) prior to the administration of study medication. For Study 039, the assigned dosage for Subject 001 was determined by the study monitor rather than by study personnel.

DSI Reviewer's Note: The FDA field investigator, James Kewley, provided additional insights, via personal communication, into this observation and its' impact on the accuracy of dosage and treatment of Subject 001 for Study 039. Briefly, randomization occurred when the PI/Coordinator completed the section of the eCRF regarding eligibility for enrollment. At that point, the subject was assigned to a dosage group, but the screen showing the dosage group was intended only to be accessible to the unblinded pharmacist and the monitor. However, at the start of the study, at the time the first subject was ready for infusion, the unblinded pharmacist had not yet been provided access to the software screen that would identify the assigned dosage. The monitor, who was on site at the time, accessed the dosage screen using her password, and the unblinded pharmacist viewed the screen and prepared the dosage identified. Although this was certainly a procedural error, the FDA field investigator was able to confirm that the correct dosage was prepared for administration to the subject.

2. For both studies, study records fail to include liver and spleen volume measurements determined by a contract firm from MRIs performed during the study. However, both protocols specified that for the efficacy analyses, the MRI scans were to be blinded and interpreted by an independent reviewer. The site would not be expected to retain source records that they did not generate.

3. For both studies, failure to follow the protocol requirements for disposition of all used, partially used, and unopened study medication. Section 7.5 of the protocol for Study TKT032, and Section 8.4.1 of the protocol for Study HGT-GCB-039, require that the vials be "returned to Shire HGT or destroyed on site according to instructions provided by Shire HGT". Used and unopened

vials from both studies were not returned to Shire or destroyed on site; they were placed into storage for pick-up by a commercial waste disposal firm. Although destruction records were prepared and signed, many vials remain in storage at the clinical site.

4. For both studies, source data for infusions performed from 29 March 2007 through the end of both studies were not included in study records. During this time period the study nurse recorded source data in her nurse's notes, which were retained but were not included with study records. Parameters initially recorded in the nurse's notes, which were later transcribed into the study records, include the times infusions were started, the times infusions were completed, and the times vital signs were checked during the infusions. Review of the nurse's notes found that in numerous instances pertinent data regarding the recorded information was not included, such as the dates the infusions were performed, and the identity of the subjects to which the data pertains.

DSI Reviewer's Note: The FDA field investigator, James Kewley, provided additional insights, via personal communication, into this observation and its' impact on the accuracy of dosage and treatment of Subject's in both studies after March 29, 2007. The study nurse for both studies was available during the entire inspection and was interviewed and willingly explained her procedures. The study nurse also provided all her nurses diary notes for the FDA field investigator in support of the inspection.

Briefly, according to the study nurse, infusions were administered in four separate treatment rooms. The study nurse indicated that up until the fourth subject was entered into the study [039], she was able to record the source data for the infusions directly on an "infusion worksheet," entitled "Antaciones De Enfermeria" (translates to nurse's notes) for each subject. This infusion worksheet was developed locally by the study monitor. The source data recorded on this infusion worksheet included the start & stop times of infusions, times vital signs were taken, time study drug was received from the pharmacy, and in some cases the subjects weight. Once the fourth subject was enrolled, the study nurse said it became too much for her to record the source data directly onto the infusion worksheets, so she recorded the source data in her nurse's diary notes, and subsequently transcribed the data onto the corresponding infusion worksheet for each subject. The study nurse said she normally transcribed the source data from her personal nurses diary notes to the infusion worksheets on the same day as the infusion, and normally shortly after the steps were performed. The nurse said that in instances where her nurse's diary notes were incomplete, she might have recorded the information directly on the infusion worksheet from her recollection, or may have recorded them directly into the infusion worksheets, but she said generally she did not record the data directly into the infusion worksheets after the fourth subject was enrolled. The infusion worksheet data were transcribed into the eCRF by the study coordinator at some point in the future.

The FDA field investigator conducted a random check of eCRF pages against pharmacy records and the infusion worksheets and found no deficiencies. The FDA field investigator stated that this study nurse was very forthright regarding the information she provided, and did

not appear to be hiding any information. Other than the sporadic incomplete source data for the infusion worksheets, the FDA field investigator noted no discrepancies between the study dosages prepared in the pharmacy and the assigned dosages, and no indication of any fraudulent records.

5. For Study TKT032, study Subject 011 was administered an obsolete version of the informed consent document at the time he was enrolled. The first 10 study subjects (001-010) were not promptly re-consented after the protocol was amended to include additional medical procedures and a new informed consent form (version 3) was approved for use.

6. Study records do not identify the date or time incoming shipments of study medication were placed into controlled-temperature storage.

7. Study records fail to include data queries, and the sites responses to the data queries.

The general observations and actions on inspection are based on preliminary communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

c. **Assessment of data integrity**: The data for Dr. Rodriguez' site, associated with Studies TKT032 and HGT-GCB-039 submitted to the Agency in support of NDA 22575, appear reliable based on available information. Inspectional observations revealed that the reliability of infusion records for subjects treated at this site after March 2007 could not be fully verified by source records. In some cases source records contained limited information. However, the totality of corroborating evidence, including assessments of pharmacy records and infusion worksheets, as well as nurse's diary notes, suggests that subjects were adequately infused in accordance with their respective protocols. Additional, inspectional observations related to noncompliance with protocol-specified procedures, such as study drug disposition, are not likely to affect site-generated data integrity.

3. **Sponsor:**
Shire Human Genetics Therapies, Inc.
300 Patriot Way
Lexington, MA 02421

a. **What was inspected**: The sponsor was inspected completing the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. Specifically, the inspection covered adherence to Protocols TKT025, TKT025EXT, TKT032, TKT034 and HGT-GCB-039, assessment of clinical monitoring reports, and study records and procedures.

The following studies/sites/subjects were reviewed:

Studies Reviewed	Sites Reviewed	Subjects Reviewed
Study TKT025	Dr. Ari Zimran – Site 071	12
Study TKT025EXT	Dr. Ari Zimran – Site 071	8
Study TKT032	Dr. Ari Zimran – Site 071	7
Study TKT032	Dr. D. Rodriquez – Site 152	11
Study TKT032	Dr. Lukina – Site 191	3
Study TKT034	Dr. Ari Zimran – Site 071	9
Study TKT034	Dr. Szymanska – Site 162	5
Study HGT-GCB-039	Dr. Ari Zimran – Site 071	3
Study HGT-GCB-039	Dr. D. Rodriquez – Site 152	5
Study HGT-GCB-039	Dr. Lukina – Site 191	4

Note: The EIR was not available at the time this CIS was written. The EIR for the Sponsor inspection is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. **General observations/commentary**: Records and procedures were clear, complete and well organized. There was nothing to indicate under-reporting of AEs/SAEs. Overall, site monitoring performed by ~~~~ appeared adequate. Review of monitoring reports found no major issues. Hemoglobin and platelet data listings were verifiable against electronic CRFs. Liver-spleen volume data were not verifiable since eCRFs only included the date/time image was obtained. There were numerous investigational product temperature excursions found at Sites 071 and 152; however, IP temperatures did not exceed NDA stability data.

A Form FDA 483 was issued to the Sponsor citing 2 inspectional observations.

1. An investigator who did not comply with the signed agreement, the general investigational plan, and applicable regulatory requirements was not promptly brought into compliance. Specifically, the clinical investigator at Site 071 (Zimran) had numerous, repeat, non-compliance issues. For example, items identified in the study site monitoring visit reports include, but are not limited to enrollment of subjects who did not meet inclusion criteria, informed consent issues, failure to perform study-specific visit procedures, dosing errors, investigational product temperature excursions and administration of quarantined investigational product.
2. Failure to ensure that study is conducted in accordance with the protocol and/or investigational plan. Specifically,

a. Sponsor issued protocol exemptions for Site 071 (Zimran) specific to inclusion/exclusion criteria for:
   i. 7 of 12 subjects enrolled in Study TKT025 (Subject numbers: 0001, 0002, 0003, 0005, 0006, 0007, 0012*)
   ii. 5 of 8 subjects enrolled in Study TKT025EXT (Subject numbers: 0001, 0002, 0003, 0005, 0007)
   iii. 6 of 9 subjects enrolled in Study TKT034 (Subject numbers: 0002, 0003*, 0004*, 0005*, 0006*, 0007*)
   iv. 3 of 3 subjects enrolled in Study HGT-GCB-039 (Subject numbers: 0001, 0002, 0003)

   *Note: Subjects were administered investigational product prior to receipt of protocol exemption.

b. Sponsor issued protocol exemptions for Site #152 (Rodriguez) specific to inclusion/exclusion criteria for: 2 of 11 subjects enrolled in Study TKT032: Subjects 0008* and 0010*.

   *Note: Subjects were administered investigational product prior to receipt of protocol exemption.

c. Sponsor issued protocol exemptions for Site #162 (Szymanska) specific to inclusion/exclusion criteria for: 2 of 5 subjects enrolled in Study TKT034: Subjects 0003* and 0005*.

   *Note: Subjects were administered investigational product prior to receipt of protocol exemption.

According to the FDA field investigator, Michelle Noe, the sponsor, Shire, intends to make a written response to the Form FDA 483. The sponsor was responsible for adequate monitoring and subsequent follow up on corrective actions at each site involved in each of the studies audited.

DSI Reviewer's Note: DSI informed the review division Medical Office, Dr. Chen, of these preliminary observations and discussed them in detail. The circumstances and justification for the protocol deviations/waivers was reviewed by the review division Medical Officer. Dr. Chen followed up directly with the sponsor and requested that they [Shire] provide to Dr. Chen details of their response to each protocol deviation related to the Form FDA 483. A copy of the sponsor's response to the Form FDA 483 (dated January 15, 2010) was provided to Dr. Chen on January 19, 2010. Dr. Chen discussed the sponsor response with DSI reviewer Dr. Lauren Iacono-Connors. It was concluded that the inspectional observations while violative from a compliance stand point would not likely impact the integrity of clinical research data submitted the NDA 22575.

The general observations and actions on inspection are based on preliminary communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

c. **Assessment of data integrity**: Based on preliminary review of the inspectional observations for the Sponsor, and discussions between the DSI reviewer and the Review Division MO, the findings are unlikely to significantly impact data integrity for studies submitted to the Agency in support of NDA 22575.

4. Contract Research Organization (CRO):

b(4)

a. **What was inspected**: The CRO was inspected completing the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. Specifically, Studies TKT032, TKT034 and HGT-GCB-039, performed by the investigators mentioned above, were the focus of this audit. The CRO was responsible (under contract with the sponsor, Shire) for assessing abdominal MRI images to determine liver and spleen volumes in study participants at baseline, on-study, and end of study measurements as per protocol. Changes in these organ volume measurements are considered by the agency to be critical secondary efficacy endpoints and as such the accuracy and reliability of data provided in NDA 22575 had to be assessed/verified.

It was discovered during the audits of the clinical investigators, Dr. Zimran and Dr. Rodriguez, that the MRI images were not retained at the sites, but instead were forwarded to this CRO for interpretation and archiving. Therefore, the reliability of the secondary efficacy endpoint data for liver and spleen volumes for all 3 phase III studies were assessed/verified by audit of this CRO.

Site Reviewed	Protocols Audited for Secondary Efficacy Endpoints: Liver and Spleen Volumes	Number of Subjects Source Records Reviewed for Liver and Spleen Volumes
Dr. Ari Zimran – Site 071	Study TKT032	7
	Study TKT034	8
	Study HGT-GCB-039	3
Dr. D. Rodriquez – Site 152	Study TKT032	11
	Study HGT-GCB-039	5

Note: The EIR was not available at the time this CIS was written. The EIR for the CRO inspection is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. **General observations/commentary**: The liver and spleen volumes, for the studies and subjects audited, were all verified against source records maintained by the CRO in ——— and were found to be consistant with what was submitted NDA 22575 data listings. b(4)

The CRO was responsible for checking quality of the data received, assigning a masking code, training a masked reader, supplying the software program for the readings, and transferring the data to the sponsor. A Master Research Agreement was signed by both the Sponsor (Shire) and the CRO ——— ———. Additionally, specific responsibilities for each of the three protocols (TKT032, TKT034, and HGT-GCB-039) were outlined in Work Orders, signed by both the Sponsor and CRO. All responsibilities were verified and there was evidence of regular communication between the sponsor and CRO. The validation for the software used for liver and spleen volumes was reviewed and appeared adequate. b(4)

The correspondence records indicated no problems or deviations from the protocol. The sponsor requested an intra-reader variability data collection for 10% of the data (blinded duplicate readings of 10% of the screens) but the CRO did not do anything with the data and the intra-variability reads were clearly identified to the sponsor with the data submission and not used for the application submitted to FDA.

For Protocol TKT032, week 25 data was not available for some subjects because IRB approval of the Protocol Amendment had not been given. This was clearly documented in the subject folders with a note to file.

Quality checks and verification of subject ID/data was checked for 100% of subjects for all 3 protocols for Sites 071 and 152. Any discrepancies or missing data required a data correction/query which was sent directly to the Clinical Sites for correction. The generated data queries did not indicate a compromise in the data and could be verified.

The Project Managers for Protocols TKT032, TKT034 and HGT-GCB-039 had training for the protocols and attended the Investigator's Meetings by the Sponsor (1/07 in Miami and 4/07 in Rome). Site initiation consisted of a mail/faxed form indicating the type of equipment on site. This was verified for all sites.

The data was sent/transferred to the Sponsor in a SAS file through the Shire online portal on 4/24/09, 5/20/09, and 7/8/09.

The general observations and actions on inspection are based on preliminary communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

c. **Assessment of data integrity**: The data generated at this site, as it pertains to Studies TKT032, TKT034 and HGT-GCB-039 were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The data from this CRO submitted to the agency as part and in support of NDA 22575 appear reliable.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on preliminary review of inspectional findings, the study data collected by Dr. Zimran and Dr. Rodriguez appear reliable. The inspection of the sponsor, Shire, and CRO, found that records and procedures were clear, complete and well organized, that reporting of AEs/SAEs appeared adequate, and a review of monitoring reports found no major issues. b(4)

The 2 clinical investigator sites and the sponsor were issued Form FDA 483s, Inspectional Observations. Site 071, that of Dr. Zimran, had protocol compliance and record keeping violations. Briefly, Dr. Zimran appears to have requested numerous protocol deviation waivers for all studies audited. Many of these appeared to be associated with inclusion/exclusion criteria waiver requests. Discussions with the review division Medical Officer, Dr. Ii-Lun Chen, confirms that while these protocol deviations are of concern from a protocol compliance stand point they are unlikely to significantly affect data reliability for each of the studies audited. Regarding generalized record keeping violations, the site failed to maintain source records for a number of study-specific assessments, in particular Studies TKT032, TKT034 and HGT-GCB-039 generated MRIs (media) to support determination of liver and spleen volumes. The blinded assessment of these MRIs for liver and spleen volumes were conducted by a CRO in the United States, b(4) . The CRO was responsible for retaining these source records. The data were verified during a subsequent inspection of the CRO.

Site 152, that of Dr. Rodriguez, had protocol compliance and record keeping deviations. Inspectional observations revealed that the reliability of infusion records for subjects treated at this site after March 2007 could not be fully verified by source records. In many cases source records contained limited information. However, the totality of corroborating evidence, including assessments of pharmacy records and infusion worksheets, suggests that subjects were adequately infused in accordance with their respective protocols. As with Dr. Zimran's site, this site did not retain the liver and spleen volume records and MRIs for studies TKT032 and HGT-GCB-039. The source data and records for liver and spleen volumes were retained at the CRO b(4) where the data were verified during a subsequent inspection of the CRO. The inspection also found that disposition of study drug was not performed according to protocol requirements.

Finally, the sponsor inspection revealed that numerous requested protocol deviations were granted waivers instead of bringing the sites into protocol compliance. The review division Medical Officer, Ii-Lun Chen, upon learning of these inspectional observations followed up directly with the sponsor and requested that they [Shire] provide to Dr. Chen details of their response to each protocol deviation. A copy of the sponsor's response to the Form FDA 483 (dated January 15, 2010) was provided to Dr. Chen on January 19, 2010. Dr. Chen discussed the sponsor response with DSI reviewer Dr. Lauren Iacono-Connors. It was concluded that the inspectional observations while violative from a compliance stand point would not likely impact the integrity of clinical research data submitted the NDA 22575. Also, there were numerous investigational product temperature excursions found at Sites 071 and 152; however, IP temperatures did not exceed NDA stability data.

The review division may, wish to consider each violation pertaining to protocol adherence and record keeping, outlined in each the Form FDA 483s, and described above, and sensor subject-specific or site-specific data from study analyses as appropriate. The review division may wish to consider the impact of what appears to be ubiquitous granting of protocol waivers (inclusion/exclusion criteria) in all studies audited on study results and interpretation. However, although regulatory violations were noted as described above, these are unlikely to significantly impact data reliability. The final reports (EIRs) for these inspections have not been completed to date.

Note: Observations noted above are based on the preliminary communications provided by the FDA field investigator and copies of the Form FDA 483, inspectional observations, issued. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIRs.

Follow-Up Actions: DSI will generate an inspection summary addendum if the conclusions change significantly upon receipt and review of the pending EIRs and the supporting inspection evidence and exhibits.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

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Tejashri Purohit-Sheth, M.D.
Branch Chief
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Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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/s/

LAUREN C IACONO-CONNORS
01/28/2010

TEJASHRI S PUROHIT-SHETH
01/29/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	January 27, 2010
To:	Donna Griebel, MD, Director Division of Gastroenterology Products
Through:	Todd Bridges, RPh, Team Leader Denise Toyer, PharmD, Deputy Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Deveonne Hamilton-Stokes, RN, BSN, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Vpriv (Velaglucerase alfa) for Injection 200 units/vial and 400 units/vial
Application Type/Number:	NDA 022575
Applicant:	Shire Human Genetic Therapies, Inc.
OSE RCM #:	2009-2032

CONTENTS

1 INTRODUCTION

This review is written in response to a request from the Division of Gastroenterology Products for assessment of Vpriv (Velaglucerase Alfa) for Injection labels and labeling for their vulnerability to medication errors.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis[1] (FMEA) to evaluate the labels and labeling that were submitted. The October 1, 2009 submission included the container labels and carton labeling and the November 20, 2009 submission included the insert labeling (Appendix A and B; no image of insert labeling).

3 RECOMMENDATIONS

Our evaluation noted areas where information on the labels and labeling can be clarified and improved on to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1 *(Comments to the Division)* for discussion during the review team's label and labeling meetings. Section 3.2 *(Comments to the Applicant)* contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Nitin Patel, OSE Regulatory Project Manager, at 301-796-5412.

3.1 COMMENTS TO THE DIVISION

1. Include the dosage form (for injection) to immediately follow the established name throughout the Highlights and Full Prescribing Information.
2. In June 2006, FDA launched an educational campaign with ISMP to educate healthcare practitioners not to use dangerous abbreviations or dose designations in their prescribing. As part of this campaign, FDA agreed not to allow dangerous abbreviations and dose designations in the approved labeling of products because these carry over to prescribing habits. Based on this agreement we recommend you:
   a. Revise the error prone abbreviation — to read "Units" throughout the Highlights and Full Prescribing Information. — is listed as a dangerous abbreviation on the Institute for Safe Medication Practice's (ISMP) 'List of Error-Prone Abbreviations, Symbols, and Dose Designations'. b(4)
   b. Remove throughout the package insert. are listed on the Institute for Safe Medication Practice's 'List of Error-Prone Abbreviations, Symbols, and Dose Designations', because they can lead to ten-fold dosing errors if the decimal is not seen.
3. Ensure the unit of measurement is included with the numerical portion of the strength throughout the labeling (e.g., in the Dosage and Administration section revise — to "15 units/kg to 60 units/kg"). b(4)

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

4. In Table 1 (Reconstitution Instructions), the last row includes the extractable volume. This is not useful information for healthcare providers and may cause confusion. Additionally, the table does not convey to practitioners the concentration after reconstitution. Therefore, revise the chart as follows:

Table 1: Reconstitution Instructions

	200 Units/vial	**400 Units/vial**
Volume of Sterile Water for Injection, USP for reconstitution	2.2 mL	4.3 mL
Concentration after reconstitution	100 Units/mL	100 Units/mL

5. In the Full Prescribing, Dosage Forms and Strengths section, delete ' [redacted] from each sentence as this is not useful information for practitioners. Additionally, delete the words [redacted] in order to be consistent throughout the insert labeling. b(4)
6. In Table 3 (Trade name Composition Following Reconstitution), delete : [redacted] as this information is not necessary and may lead to confusion and dosing errors, since Vpriv is dosed in units.

3.2 COMMENTS TO THE APPLICANT

A. Container Labels (200 units and 400 units)

1. The established name does not have a prominence commensurate to that of the proprietary name. Revise the established name per 21 CFR 201.10(g)(2) which states: The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
2. Include the dosage form (for injection) to immediately follow the established name. The dosage form should be presented in the same size and font as the established name.
3. Revise the product strength to read: XXX units/vial.
4. Relocate the product strength from the bottom of the principle display panel so that it immediately follows the established name and dosage form. Thus the presentation of the proprietary name, established name, dosage form and product strength will appear as follows:

   Vpriv

   (Velaglucerase alfa) for Injection

   XXX units/vial

5. The product strengths are not differentiated, thus making the labels appear identical. Revise the product strengths so that they are readily distinguishable from one another through the use of colors, borders, shading or some other means, and ensure that they do not overlap to help minimize the risk of errors.

6. Revise the statement [redacted] to read: "Single use vial. Discard unused portion". b(4)
7. Include the route of administration "for intravenous use only" on the 200 unit vial.
8. Delete or decrease the size [redacted] to allow room to incorporate the changes above.

B. Carton Labeling (200 units and 400 units)

1. See Container Labels comments A1 thru A5.
2. Revise the statement [redacted] to read: "Single use vial. Discard unused portion".
3. Include the route of administration "for intravenous use only" on the principle display panel.
4. Decrease the size [redacted] on the 200 unit carton labeling to allow room to incorporate the changes noted in comment B1 above.
5. On the side panel of the carton labels, delete the phrase [redacted] '. Revise the sentence to read: "Following reconstitution with XX mL Sterile Water for Injection, USP the resultant concentration is 100 units/mL". b(4)
6. The proprietary name and established name appear on the side panel without the product strength. Revise to include the product strength.

2 Page(s) Withheld

_____ Trade Secret/Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Other Reviews Section-*_____

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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/s/

DEVEONNE G HAMILTON-STOKES
01/27/2010

TODD D BRIDGES
01/27/2010

DENISE P TOYER
01/27/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 22575 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: VPRIV Established/Proper Name: velaglucerase alfa Dosage Form: lyophilized powder for solution for intravenous infusion Strengths: 200 unit/vial; 400 unit/vial		
Applicant: Shire Human Genetic Therapies, Inc Agent for Applicant (if applicable): NA		
Date of Application: 8/31/09 Date of Receipt: 8/31/09 Date clock started after UN: NA		
PDUFA Goal Date: 2/28/09	Action Goal Date (if different): 2/26/09	
Filing Date: 10/30/09	Date of Filing Meeting: 9/25/09	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1: NME		
Proposed indication(s)/Proposed change(s): Longterm enzyme replacement therapy for adult and pediatric patients with type 1 Gaucher disease.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☒ Fast Track ☒ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC		☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 61220	

Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

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

Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).

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

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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

Exclusivity	YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm***	X			Zavesca (miglustat) Expires: 7/31/2010
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***		X		Velaglucerase alfa is an enzyme replacement therapy and Zavesca is a small molecule substrate reducer.
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: *Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	NA			
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? *If yes, date consult sent to the Controlled Substance Staff:*			X	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			X	

Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included. **Forms** include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:** Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:** Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."*	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	Shire has notified the Field Office that the application is available electronically via EDR.

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** *Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		X		Orphan designation has been granted.
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***	X			Sequence #: 0003. This has been routed to OSE (Nina Ton).
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted. **NOTE: inclusion of the patient package insert may be a misunderstanding on the sponsors part of the PLR requirements. These enzyme replacement therapies are administered via intravenous infusion and are administered by trained professionals.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI)** ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			X	
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent: DSI sent 10/15/09; DPV sent 11/17/09.***	X			Pharmacovigilence (DPV) and Scientific Investigations (DSI).

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 1/11/2006; 6/16/2006 (cancelled) ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 8/10/2009 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

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

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 25, 2009

BLA/NDA/Supp #: NDA 22575

PROPRIETARY NAME: VPRIV

ESTABLISHED/PROPER NAME: velaglucerase alfa

DOSAGE FORM/STRENGTH: 200 unit/vial; 400 unit/vial

APPLICANT: Shire Human Genetic Therapies, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Longterm enzyme replacement therapy for adult and pediatric patients with type 1 Gaucher disease.

BACKGROUND: VPRIV (velaglucerase alfa) is an enzyme replacement therapy (ERT) for patients with type 1 Gaucher disease. This patient population is currently underserved due to ongoing product shortages with the only other approved ERT for type 1 Gaucher disease patients. The product shortage with the currently marketed ERT for type 1 Gaucher disease patients began in June 2009 and as a result Shire submitted a treatment protocol to allow patients to have access to VPRIV (velaglucerase alfa), an alternative ERT. This treatment protocol was submitted by Shire on June 30, 2009, and allowed to proceed by FDA on July 30, 2009. In addition, Shire accelerated their NDA submission timeline and requested that the NDA be submitted in portions (i.e., rolling review). On July 15, 2009, FDA granted Shire Fast Track designation for VPRIV for the treatment of patients with type 1 Gaucher disease and also authorized Shire to submit the NDA as a rolling review. The first portion of the NDA was submitted and received on July 30, 2009, and included complete Modules 3 and 4, and a partial Module 5 (study reports for TKT025 and TKT032). The second and final portion was submitted and received on August 31, 2009. The final portion completed Modules 2 and 5 and also updated Module 3 (based on FDA requested information at the August 10, 2009, pre-NDA meeting with Shire).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Wes Ishihara	Y
	CPMS/TL:	Brian Strongin	N
Cross-Discipline Team Leader (CDTL)	John Hyde		Y
Clinical	Reviewer:	Ii-Lun Chen	Y
	TL:	John Hyde	Y

Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Lanyan Fang	Y
	TL:	Jang-Ik Lee	Y
Biostatistics	Reviewer:	Behrang Vali	Y
	TL:	Mike Welch	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Tamal Chakraborti	Y
	TL:	Sushanta Chakder	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	Fred Mills	Y
	TL:	Susan Kirshner	N
Product Quality (CMC)	Reviewer:	Emanuela Lacana Howard Anderson	Y Y
	TL:	Gibbes Johnson	N
Quality Microbiology *(for sterile products)*	Reviewer:	Denise Miller	Y
	TL:	Brian Riley	N
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:	Kimberly Raines	N
	TL:		
Facility Review/Inspection	Reviewer:	Shawn Gould	Y
	TL:	Tara Gooen	N
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Lauren Iacono-Connor	N
	TL:	Tejashri Purohit-Sheth	N

Other reviewers		
Other attendees	Maria Walsh (ADRA, ODEIII) Ruyi He (Acting Deputy Director, DGP) Lynne Yao (Acting MO Team Leader, DGP) Grant Lee (SRPM, OSE)	

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: None	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: o ***this drug is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments:**	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments:** Pending receipt of assay in-process performance reports and quality control data.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES (pending review of requested data a determination will be made on the necessity of a DSI analytical site inspection based on the quality of the data submitted) ☐ NO
BIOSTATISTICS **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable

Comments:	☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Environmental Assessment	☐ Not Applicable
• Categorical exclusion for environmental assessment (EA) requested?	☒ YES ☐ NO
If no, was a complete EA submitted?	☐ YES ☐ NO
If EA submitted, consulted to EA officer (OPS)?	☐ YES ☐ NO
Comments:	
Quality Microbiology (for sterile products)	☐ Not Applicable
• Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)	☒ YES ☐ NO
Comments:	
Facility Inspection	☐ Not Applicable
• Establishment(s) ready for inspection?	☒ YES ☐ NO
▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?	☒ YES ☐ NO
Comments:	
Facility/Microbiology Review (BLAs only)	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE
Comments:	☐ Review issues for 74-day letter
CMC Labeling Review (BLAs/BLA supplements only)	
Comments:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Julie Beitz **21st Century Review Milestones (see attached)** (optional): **Comments:**	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Note: These were committed to be provided to the RPM no later than 10/23/09 and will be included in the filing letter. Review Classification: ☐ Standard Review ☒ Priority Review
ACTIONS ITEMS	
☒	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74

☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD W ISHIHARA
12/23/2009

BRIAN K STRONGIN
12/23/2009

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: NDA 22-575

Name of Drug: VPRIV® (velaglucerase alfa)

Sponsor: Shire Human Genetic Therapies, Inc.

Material Reviewed: VPRIV® (velaglucerase alfa) Carton and Container Labels

OBP Receipt Date: September 1, 2009

Amendment Reviewed:

Background:

VPRIV® (velaglucerase alfa) is a New Drug Application (NDA) indicated for long-term enzyme replacement therapy (ERT) for pediatric and adult patients with type I Gaucher disease. The product is supplied as a lyophilized powder in single use vials for reconstitution with Sterile Water for Injection at concentrations of 200 units or 400 units.

Labels Reviewed:

VPRIV® (velaglucerase alfa) Container Label
- 200 Units
- 400 Units

VPRIV® (velaglucerase alfa) Carton Labels
- 200 Units
- 400 Units

Review

The carton and container labels for VPRIV® (velaglucerase alfa) were reviewed and found to be adequate under most of the following regulations: 21 CFR 201.1 through 21 CFR 201.18; 21 CFR 201.25; and 21 CFR 201.50 through 21 CFR 201.55 through 21

CFR 200.57; 21 CFR 201.100 and United States Pharmacopeia, 8/1/09-12/1/09, USP 32/NF27. Please see comments in the conclusions section.

I. Container

A. Vial Label

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer or distributor-
   Manufactured By: Shire Human Genetic Therapies, Inc.
   700 Main Street
   Cambridge, MA 02139
   This conforms to the regulation.

2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers- The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 54092-XXX-XX. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.

3. 21 CFR 201.5 Drugs; adequate directions for use-Adequate directions for use does not appear on the label, however "See package insert for reconstitution and dosing instructions." appears. This conforms to the regulation.

4. 21 CFR 201.6 Drugs; misleading statements- There is a single ingredient in this product. This conforms to the regulation.

5. 21 CFR 201.10 Drugs; statement of ingredients- The established name, velaglucerase alfa is not used in type at least half as large as the proprietary name, VPRIV®. The prominence of the velaglucerase alfa, is not commensurate with the prominence and typography of VPRIV®. The established name appears as velaglucerase alfa and does not include the dosage form. This does not conform to the regulation.

6. 21 CFR 201.15 Drugs; prominence of required label statements- All required statements ("Rx Only", "Do not freeze", "Protect from Light"). This conforms to the regulation.

7. 21 CFR 201.17 Drugs: location of expiration date-The expiration date and the lot identification number do not appear on the label. This does not conform to the regulation.

8. 21 CFR 201.25 Bar code label requirements – The bar code is located on the right of the label with sufficient white space

surrounding to ensure for proper scanning. This conforms to the regulation.

9. 21 CFR 201.50 Statement of identity- The established name, velaglucerase alfa, appears on the label, but does not include the dosage form, for injection. The prominence of velaglucerase alfa is not commensurate with VPRIV®. This does not conform to the regulation.

10. 21 CFR 201.51 Declaration of net quantity of contents – The label prominently states the net quantity of contents in terms of units. This conforms to the regulation.

11. 21 CFR 201.55 Statement of dosage- The label states "See package insert for reconstitution and dosing instructions." This conforms to the regulation.

12. 21 CFR 201.100 Prescription drugs for human use- The label bears statements for "Rx Only", storage conditions, and reference to the package insert. An identifying lot number, is not present on the label. The route of administration is not displayed. This does not conform to the regulation.

13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of 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. This does not apply.

__2__ Page(s) Withheld

_____ Trade Secret/Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Other Reviews Section-_____

II. Carton

A. Carton Label

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer or distributor-
   Manufactured By: Shire Human Genetic Therapies, Inc.
   700 Main Street
   Cambridge, MA 02139
   This conforms to the regulation.

2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers- The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 54092-XXX-XX. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.

3. 21 CFR 201.5 Drugs; adequate directions for use-Adequate directions for use does not appear on the label, however "See package insert for reconstitution and dosing instructions." appears on the side panel. This conforms to the regulation.

9. 21 CFR 201.6 Drugs; misleading statements- There is a single ingredient in this product. This conforms to the regulation.

4. 21 CFR 201.10 Drugs; statement of ingredients- The established name, velaglucerase alfa not used in type at least half as large as the proprietary name, VPRIV®. The prominence of the velaglucerase alfa, is not commensurate with the prominence and typography of the VPRIV®. The established name appears as velaglucerase alfa and does not include the dosage form. This does not conform to the regulation.

5. 21 CFR 201.15 Drugs; prominence of required label statements- All required statements ("Rx Only", "Do not freeze", "Protect from Light"). This conforms to the regulation.

6. 21 CFR 201.17 Drugs: location of expiration date-The expiration date and lot identification number do not appear on the label. This does not conform to the regulation.

7. 21 CFR 201.25 Bar code label requirements – The bar code is located on the bottom right panel of the label with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.

9. 21 CFR 201.50 Statement of identity- The established name, velaglucerase alfa, appears on the label, but does not include the dosage form, for injection. The prominence of velaglucerase alfa is not commensurate with VPRIV®. This does not conform to the regulation.

10. 21 CFR 201.51 Declaration of net quantity of contents – The label states the net quantity of contents in terms of units. This conforms to the regulation. Declaration lacks prominence.

11. 21 CFR 201.55 Statement of dosage- The label states "See package insert for reconstitution and dosing instructions." This conforms to the regulation.

12. 21 CFR 201.100 Prescription drugs for human use- The label bears statements for "Rx Only", storage conditions, and reference to the package insert. An identifying lot number, is not present on the label. The route of administration is not displayed. This does not conform to the regulation.

13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of 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. This does not apply.

III. Conclusions

A. The proposed carton and vial labeling are acceptable only upon the following changes:

1. Carton

a) The following statements are BLA requirements that may be removed:

(1) Contains one vial

(2) Contains no preservative

(3) No U.S. standard of potency

2. Container
   a) See Carton and Container comments.

3. Carton and Container
   a) Per 21 CFR 201.10 and 201.100, Please revise the prominence and typography of the established name, Velaglucerase alfa commensurate with the most prominent presentation of the proprietary name, VPRIV®.

   b) Per 21 CFR 201.17, Please add the lot identification number and the expiration date.

   c) Per 21 CFR 201.50, Please add the dosage form, for injection to the listed established name velaglucerase alfa. The established name should read, velaglucerase alfa for injection.

   d) Per 21 CFR 201.51, please increase the font size of the net quantity statement listed on the container labels for improved readability. Consider relocating the quantity statement and route of administration to reflect the following presentation.

      VPRIV
      (velaglucerase alfa for injection)
      XXX units
      For Intravenous use

   e) Per the United States Pharmacopoeia, 5/1/09-8/1/09, USP 32/NF 27, General Chapter <1091> Labeling of Inactive Ingredients, Please alphabetize the inactive ingredient listing in the "Description" section of the Package Insert.

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

Comment/Concurrence:

Emanuela Lacana, Ph.D.
Product Reviewer
Division of Therapeutic Proteins
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Deputy Director
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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY M RAINS
11/24/2009

EMANUELA LACANA
11/24/2009

BARRY W CHERNEY
11/24/2009

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Gastroenterology Products

Application Number: NDA 22575

Name of Drug: VPRIV (velaglucerase alfa for injection)

Applicant: Shire Human Genetic Therapies, Inc.

Material Reviewed:

Submission Date: August 31, 2009

Receipt Date: August 31, 2009

Submission Date of Structure Product Labeling (SPL): August 31, 2009

Type of Labeling Reviewed: SPL

Background and Summary

This review provides a list of deficiencies 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

The following issues/deficiencies have been identified in your proposed labeling.

1. Highlights of Prescribing Information (Highlights section):

    a. The information summarized in the Highlights section should be presented in direct language (i.e., "command" language).

    b. Include for each bulleted statement a numerical reference to the corresponding section or subsection in the full prescribing information (FPI).

2. Full Prescribing Information: Table of Contents (Table of Contents):

a. The section or subsection headings and the section or subsection numerical identifier must be separated by two square em's (i.e., two squares the size of the letter "m" in 8 point type) [21 CFR 201.57(d)(7)]. In addition, periods should not be used after the number for each section or subsection heading.

3. Full Prescribing Information:

a. The section or subsection headings and the section or subsection numerical identifier must be separated by two square em's (i.e., two squares the size of the letter "m" in 8 point type) [21 CFR 201.57(d)(7)]. In addition, periods should not be used after the number for each section or subsection heading.

b. Bold type should not be used in the body of the Full Prescribing Information except as required (e.g., section and subsection headings). Other methods may be used, such as italics.

c. Cross-references within the labeling should identify the section (not subsection) followed by the numerical identifier of the section or subsection, as appropriate. For example, under subsection 13.1, Carcinogenesis, Mutagenesis, Impairment of Fertility, references are made to the Pregnancy subsection (i.e., subsection 8.1) of section 8, Use in Special Populations. The appropriate reference is as follows:

[see Use in Specific Populations (8.1)]

Recommendations

The sponsor should be requested to address the identified deficiencies/issues and re-submit labeling by December 2, 2009. The updated version of labeling will be used for further labeling discussions.

R. Wesley Ishihara
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff

Drafted: rwi/10-26-09
Revised/Initialed:

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD W ISHIHARA
10/30/2009

BRIAN K STRONGIN
10/30/2009