CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-575

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022575

NDA APPROVAL

Shire Human Genetic Therapies, Inc.
Attention: Nikhil Mehta, Ph.D.
Vice President, Global Regulatory Affairs
700 Main Street
Cambridge, MA 02139

Dear Dr. Mehta:

Please refer to your new drug application (NDA) dated August 31, 2009, received August 31, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VPRIV (velaglucerase alfa for injection).

We acknowledge receipt of your submissions dated July 30, August 31, September 17, 22, and 28, October 1, 9, 12, 23, and 29, November 16 and 20, December 1, 4, 15, 18, 22, and 31, 2009, and January 13, 14, 15, 26, and 27, and February 1, 8, 9, 17, 19, and 25, 2010.

This new drug application provides for the use of VPRIV (velaglucerase alfa for injection) for long-term enzyme replacement therapy (ERT) for pediatric and adult patients with type 1 Gaucher disease.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

Your application was not referred to an advisory committee because this drug is not the first in its class, the clinical study design was acceptable, the application did not raise significant safety or efficacy issues, the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment or prevention of a disease, and outside expertise was not necessary.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the submitted labeling (package insert submitted February 25, 2010). For administrative purposes, please designate this submission, "**SPL for approved NDA 022575.**"

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your February 19, 2010, submission containing final printed carton and container labels.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments in your submission dated February 25, 2010. These commitments are listed below.

1600-01 Shire commits to utilize an antibody screening cut point based on a mean + 1.645 standard deviation for assay values from treatment naïve Gaucher patients. Shire will utilize the same methodology to calculate the anti-imiglucerase ECL cut point.

Final Report Submission: May 31, 2010

1600-02 Shire commits to revise the cut point for the confirmatory anti-velaglucerase and anti-imiglucerase screening assays to a level that is less than or equal to the cut point of the screening assay.

Final Report Submission: May 31, 2010

1600-03 Shire commits to re-assess the IgE cut point for the current ECL methodology using a chemically synthesized hybrid control. Shire commits to support assay validation using patient baseline values.

Final Report Submission: May 31, 2010

1600-04 Shire commits to develop an assay to measure the ability of patient antibodies to block the uptake of velaglucerase and imiglucerase into target cells.

Final Report Submission: November 30, 2010

1600-05 Shire commits to re-analyze all archived pharmacokinetic (PK) samples for Study TKT032 (using adequate in-process quality controls and standard curves) and recalculate velaglucerase alfa PK parameters.

Study Completion Date: May 31, 2010
Final Report Submission: June 30, 2010

1600-06 Shire commits to conduct a prospective PK study in patients with Type 1 Gaucher disease in the case that Shire fails to adequately characterize velaglucerase alfa PK using the archived PK samples (discussed under PMC #1600-05 above).

Final Protocol Submission: December 31, 2010
Study Completion Date: March 31, 2013
Final Report Submission: September 30, 2013

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

We remind you of your postmarketing commitments in your submission dated February 25, 2010. These commitments are listed below.

1600-07 Shire commits to develop and implement a kinetic assay with a physiologically relevant substrate for drug substance and drug product release and stability testing. Results and specifications will be included in the final report.

Final Report Submission: December 31, 2011

1600-08 Shire commits to develop and implement a quantitative method that measures total carbohydrate content. Results and specifications will be included in the final report.

Final Report Submission: February 28, 2011

1600-09 Shire commits to replace the non-quantitative SDS-PAGE Silver stain method with a quantitative SDS-PAGE Coomassie test. Results and specifications will be included in the final report.

Final Report Submission: February 28, 2011

1600-10 Shire commits to demonstrate that [redacted] is well controlled to ensure no impact on product quality. The results will be included in the final report. b(4)

Final Report Submission: February 28, 2011

1600-11 Shire commits to demonstrate the clearance capability of the process to remove [redacted] through [redacted] spike studies. The results will be included in the final report. b(4)

Final Report Submission: November 30, 2010

1600-12 Shire commits to re-evaluate drug substance and drug product release and stability specifications. Shire will submit the revised specifications and supporting data in the final report.

Final Report Submission: December 31, 2011

1600-13 Shire commits to update the specifications for SEC, RP-HPLC, and the glycan map, and to include acceptance criteria for the leading shoulder in SEC-HPLC, for peaks [redacted] in RP-HPLC, and for peak [redacted] in the glycan map. b(4)

Final Report Submission: July 1, 2010

1600-14 Shire commits to update the peptide map specification using new acceptance criteria to reflect control of impurities. Shire commits to add the peptide map as a drug substance and drug product release and stability test with the new acceptance criteria.

Final Report Submission: July 1, 2010

1600-15 Shire commits to include the cellular uptake bioassay for drug product release testing.

Final Report Submission: April 1, 2010

1600-16 Shire commits to provide a report containing the sub-visible particulates [redacted] analyses, risk assessment and risk mitigation strategies. b(4)

Final Report Submission: September 30, 2010

1600-17 Shire commits to include drug substance and drug product stress conditions in the annual stability program. The revised stability protocols will be included.

Final Protocol Submission: April 1, 2010

1600-18 Shire commits to evaluate the impact of pH on the in-use stability of the drug product and to provide assurance that procedures are in place to control this risk to product quality.

Final Protocol Submission: December 31, 2010

Submit clinical protocols to your IND 061220 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

If you have any questions, call Wes Ishihara, Regulatory Project Manager, at (301) 796-0069.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Package Insert