CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-575

SUMMARY REVIEW

MEMORANDUM

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

DATE: February 26, 2010
TO: Julie Beitz, MD
Director, Office of Drug Evaluation III

FROM: Donna Griebel, MD
Director, Division of Gastroenterology Products

SUBJECT: Approval Action - NDA 022575 VPRIV (velaglucerase alfa)
Lyophilized powder for Intravenous Injection
200 Units/vial and 400 Units/vial
Shire Human Genetic Therapies

I concur with the recommendations of the reviewers that NDA 022575 for VPRIV (velaglucerase alfa) should receive an Approval action for the indication for long-term enzyme replacement therapy (ERT) for pediatric and adult patients with type 1 Gaucher disease, with the post marketing commitments described below. Velaglucerase alfa is a recombinant glucocerebrosidase produced by gene-activation technology in the human fibrosarcoma cell line HT 1080.

This application received a priority review designation, and I agree with the clinical reviewers that the phase 3 trials submitted in support of this indication provide substantial evidence of efficacy. I concur that the proposed dose of 60 U/kg every other week, administered intravenously has been adequately supported in this NDA. The main safety database includes 94 pediatric and adult patients. The clinical reviewers determined that velaglucerase alfa is well tolerated. The application was not taken to 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.

The currently marketed enzyme replacement therapy for Type 1 Gaucher disease, Cerezyme (imiglucerase) has had manufacturing issues that have resulted in drug shortage. Ceredase (alglucerase), a placenta-derived enzyme approved in 1991, is rarely used. Velaglucerase alfa has been available through a treatment protocol, which was approved on July 30, 2009, to minimize the impact of the Cerezyme drug shortage.

The summary findings of each review discipline are listed below:

CMC/Quality Review – The Division of Therapeutic Proteins reviewers have recommended approval of NDA 022575. They concluded the data in the application

support that the manufacture of the product is well controlled and yields a pure and potent product. The manufacturing processes were found to have been adequately validated and result in a consistent product from different production runs. There were no issues identified related to sterility assurance and endotoxin. The applicant's proposal for drug product shelf life of 24 months when stored at 2-8°C was adequately supported. The product labeling states that it should be protected from light because light exposure causes aggregation and fragmentation.

Dr. Lacana determined that the velaglucerase alfa product utilized in trial 025, which was produced by —— was not comparable to the product used in trials **032**, **034** and **039**, which was produced in the ——. The —— product was utilized in phase 1 and 2 trials. The product utilized in trials **032** and **039** is referred to as "AF1". In trial **034**, both AF1 and AF2 were used. AF2 is the to-be-marketed product. The reviewers determined that AF1 and AF2 are chemically comparable. This impacted the selection of trials reviewed by the clinical pharmacology reviewers and the clinical reviewers to support product labeling. b(4)

The CMC reviewers have recommended the following PMC's, and I concur with their recommendations:

1) 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.

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

3) 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.

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

5) Shire commits to demonstrate the clearance capability of the process to remove —— through —— spike studies. The results will be included in the final report.

6) 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.

7) 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 — in RP-HPLC, and for peak — in the glycan map. b(4)

8) 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.

9) Shire commits to include the cellular uptake bioassay for drug product release testing.

10) Shire commits to provide a report containing the sub-visible particulates — analyses, risk assessment and risk mitigation strategies. b(4)

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

12) 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.

CMC/Immunogenicity Review –

The applicant submitted the following types of immunogenicity data in this NDA: non isotype-specific screening for anti-velaglucerase and anti-imiglucerase antibodies, confirmatory evaluation for IgG antibodies, evaluation for IgE antibodies, and evaluation for antibodies capable of neutralizing velaglucerase and imiglucerase enzyme activity. Samples that were positive in an antibody screening assay were evaluated with confirmatory assays. Radioimmunoprecipitation (RIP) was utilized to test for IgG and electrochemiluminescence (ECL) was utilized to test for IgE.

One of 94 patients treated with velaglucerase alfa was found to be positive for antibodies that were characterized as IgG and neutralizing. There were 2 additional patients who experienced hypersensitivity. One developed a mild allergic skin reaction at 214 days, and required hospitalization. The patient was able to continue on velaglucerase alfa with premedication after the event. A second patient experienced an anaphylactic reaction with the first dose. This patient was being transitioned from imiglucerase to velaglucerase alfa. Test results were negative for antibodies.

The reviewer, Dr. Mills, expressed a concern that the cutpoint for assay positivity for the methods used for evaluation of ECL and RIP results were inappropriately high.

The reviewers have recommended the following PMCs to revise and reassess the antibody assays and to develop a new neutralizing assay, and I concur with their recommendations:

1) 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.

2) 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.

3) 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.

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

Nonclinical – The pharmacology/toxicology reviewers determined that velaglucerase alfa has been adequately tested in a series of toxicology studies using bolus intravenous administration. They have not recommended any PMCs or PMRs.

Clinical Pharmacology – There were manufacturing process changes during product development. The product designations for each of the manufacturing processes are: ——— process product (phase ½ material), AF1 (phase 2/3 material) and AF2 (to-be-marketed material). The CMC reviewer determined that the —— material was not comparable to the to-be-marketed material; however, AF1 and AF2 were comparable. The Clinical Pharmacology reviewer focused on the pharmacokinetic data obtained from trial **032** for labeling purposes because relevant doses were evaluated in that trial and the product utilized, AF1, was chemically comparable to the to-be-marketed product. b(4)

Two dose levels of velaglucerase alfa were evaluated in **032**, 45 U/kg and 60 U/kg, administered as 1-hour infusions every other week x 51 weeks. Serum samples were analyzed by ELISA (for velaglucerase protein content) and colorimetric assay (for velaglucerase activity) at Weeks 1 and 37. Patients in the trial ranged in age from 4 years to 62 years. Serum velaglucerase alfa concentrations declined rapidly, with a mean half life of 11 to 12 minutes. The mean velaglucerase alfa clearance ranged from 6.72 to 7.56 mL/min/kg. The mean volume of distribution at steady state ranged from 82 to 108 mL/kg (8.2% to 10.8% of body weight). The Clinical Pharmacology reviewers found no firm evidence for changes of AUC or clearance with increasing age and concluded that the same body weight-normalized dose could be recommended for both pediatric and adults.

The Clinical Pharmacology reviewers found that the in-process velaglucerase alfa assay performance was insufficient because only duplicates of the quality control samples were utilized in the sample runs. For this reason, the reviewers concluded that the PK parameters might not be accurate for labeling. They determined that in light of drug shortage issues, this issue could be managed with a PMC. The reviewers have recommended the following PMCs, and I concur with their recommendations:

1) 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.

2) 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).

Clinical/Statistical– The clinical reviewers recommended approval of velaglucerase alfa for treatment of Type 1 Gaucher Disease. The major trials that supported the efficacy of velaglucerase were two randomized, double-blind, parallel trials (trials **032** and **039)** that enrolled patients who had not received previous enzyme replacement treatment or had not received enzyme replacement treatment for the past 30 months in **032** or for the past 12 months in **039** (considered treatment-naïve), and one open label, single arm trial (trial **034**) that evaluated patients who were switched to velaglucerase alfa after being on a stable dose of imiglucerase (previously treated). In **032**, two doses of velaglucerase alfa were compared, 45 Units/kg and 60 Units/kg (duration 12 months, N=25). In **039,** velaglucerase alfa 60 Units/kg and imiglucerase 60 Units/kg were studied (duration 9 months, N=35). Trial **034** (duration 12 months, N=40) was conducted to evaluate patients 9 years of age and older who were switched to velaglucerase alfa after a minimum history of 30 months of imiglucerase. The dose of velaglucerase matched each patient's previous dose of imiglucerase. The youngest patient who entered **032** was 4 years of age and the youngest in **039** was 3 years. The youngest treated with velaglucerase alfa in **034** was 9 years old.

The primary endpoint of change in hemoglobin from baseline was evaluated in each of the 3 studies. Platelet count, liver volume, and spleen volume were major secondary endpoints. Liver and spleen volumes were measured with MRI.

The primary analysis in **032** was a paired t-test of Month 12 vs. Baseline hemoglobin in the group receiving 60 Units/kg. The mean increase in hemoglobin from Baseline to Week 53 observed on the 60 Units/kg arm of trial **032** was 2.4 g/dL±0.3 [SE, CI=1.7-3.1]. Mean baseline hemoglobin was 10.7 g. A similar improvement was observed in the 45 Units/kg group, 2.4 g/dL±0.4 [SE, CI=1.5-3.4]. Mean platelet counts also increased, and the changes appeared greater on the 60 Units/kg arm. Reduction in liver and spleen

volumes were observed, although the changes in liver volume were not statistically significant.

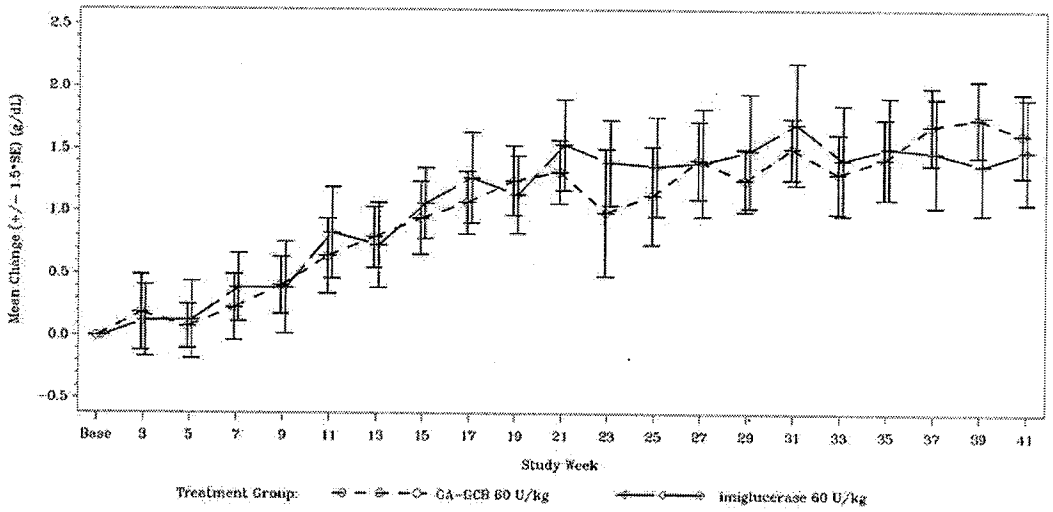
Mean Change from Baseline to Month 12 for Clinical Parameters in Patients with Type 1 Gaucher Disease Initiating Therapy with VPRIV (velaglucerase alfa) in Study 032

Clinical Parameter	Mean Changes from Baseline ± Std. Err. of the Mean	
	VPRIV Dose (given every other week)	
	45 Units/kg N = 13	60 Units/kg N = 12
Hemoglobin concentration change (g/dL)	2.4 ± 0.4*	2.4 ± 0.3**
Platelet count change (x 10^9/L)	41 ± 14*	51 ± 12*
Liver volume change (% BW)	-0.30 ± 0.29	-0.84 ± 0.33
Spleen volume change (% BW)	-1.9 ± 0.6*	-1.9 ± 0.5*

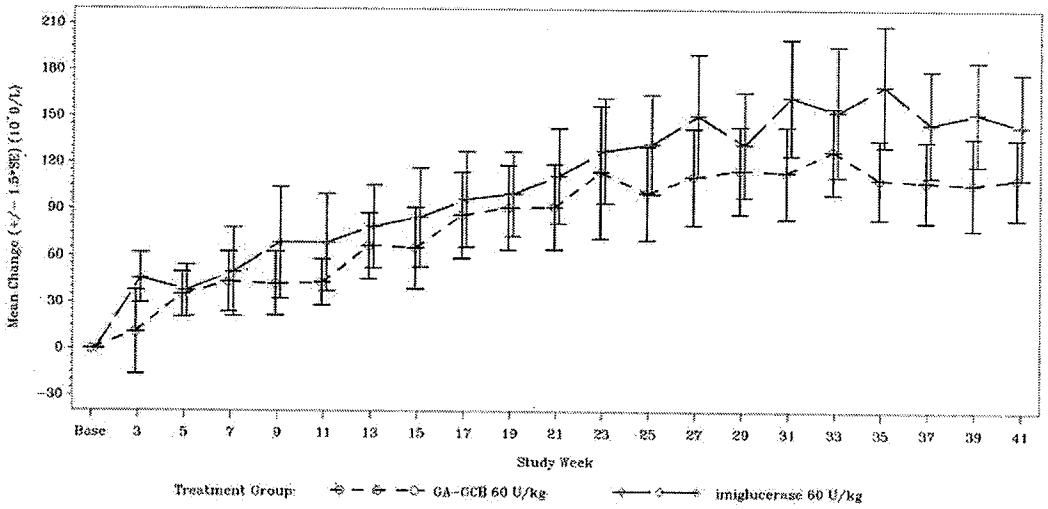
** Primary study endpoint was hemoglobin concentration change in the 60 Unit/kg group, $p < 0.001$

* Statistically significant changes from baseline after adjusting for performing multiple tests

In trial **039**, a trial designed to show noninferiority between velaglucerase 60 Units/kg and imiglucerase 60 Units/kg in change of hemoglobin from baseline, the observed mean absolute change of hemoglobin from baseline to Week 41 was 1.6 g in the velaglucerase alfa arm and 1.5 g/dl in the imiglucerase group. The treatment difference in mean change from baseline to Week 41 [velaglucerase minus imiglucerase] was 0.135 g/dL ± 0.4 (SE). In the noninferiority analysis, the lower bound of the 97.5% one-sided confidence interval was -0.6 g/dL in both the ITT population (n=34) and the per protocol population (N=30). The predefined noninferiority margin was -1 g/dl. The Biostatistical reviewers concluded that noninferiority had been shown. The mean change in hemoglobin from baseline over time in each treatment arm is summarized in the figure below, which is reproduced from the Clinical Reviewer's review.



The platelet data are similarly summarized in the figure below, which is reproduced from the Clinical Reviewer's review. There were no statistically significant differences between velaglucerase alfa and imiglucerase for changes in platelet counts.



There were no statistically significant differences observed between velaglucerase alfa and imiglucerase in changes in liver and spleen volumes.

In **trial 034** imiglucerase therapy was stopped, and treatment with velaglucerase alfa was initiated at the same dose in units as the patient's previous imiglucerase dose. After 12 months of treatment with velaglucerase alfa the median hemoglobin concentration was 13.5 g/dL (range: 10.8, 16.1) vs. the baseline value of 13.8 g/dL (range: 10.4, 16.5), and the median platelet count after 12 months was 174 x 10^9/L (range: 24, 408) vs. the baseline value of 162 x 10^9/L (range: 29, 399). Over one third of the patients who entered this study were on doses of approximately 15 Units/kg, and many patients were

on doses of approximately 30 Units/kg. The Biostatistical reviewer concluded that the results were marginally supportive of the noninferiority results of trial **039**, and the Clinical reviewer concluded that the data appeared to demonstrate clinical stability of the hemoglobin and platelet counts.

The main safety database for this application consisted of 54 patients who received velaglucerase alfa as initial therapy, and 40 who were switched from imiglucerase. Of these 94 patients, 90 completed treatment for 9 months, 73 received treatment for 12 months, and 8 received treatment for 51 months. There were no deaths reported, and there were 12 serious adverse events (SAEs). The Clinical Reviewer considered two of these likely related: anaphylaxis and allergic dermatitis requiring hospitalization. There was a case of convulsions that occurred immediately after infusion that the reviewer considered to be a possible infusion reaction. She felt the other 9 cases were likely due to underlying disease or unrelated. The most common adverse reactions were headache, dizziness, infusion related reaction, pyrexia, upper respiratory infection, abdominal pain, back pain, joint pain, pyrexia, prolongation of aPTT, and nausea. Dizziness, infusion related reactions, pyrexia, prolonged aPTT, and joint pain were more commonly reported in the treatment naïve patients than patients who had been previously treated with imiglucerase.

The clinical reviewers did not recommend PMCs or PMRs.

Division of Scientific Investigations – Two clinical sites were inspected, one in Israel and one in Paraguay. DSI found that the data from those two sites appeared reliable to support approval of the application. In addition, the CRO for the study, was inspected because the source records and MRI images were sent to the CRO for interpretation and archiving instead of being retained at the clinical sites. MRI was used to evaluate the important secondary endpoints of changes in liver and spleen volumes in the phase 3 trials. No major issues that preclude product approval were identified. b(4)

Additional Regulatory Issues:

Financial Disclosure: The Clinical Reviewer's review of the financial disclosures identified a number of investigators who were paid large consultant fees. She noted that the potential for bias from these financial arrangements was minimized by the blinded treatment assignment, central blinded analysis of MRI, PK, and GA-GCB antibodies, and monitoring of protocol adherence by monitors.

Pediatrics: Because the application is for an orphan indication, PREA requirements for pediatric studies do not apply.

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/

DONNA J GRIEBEL
02/26/2010