CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-575

OFFICE DIRECTOR MEMO

MEMORANDUM

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

DATE: February 26, 2010

FROM: Julie Beitz, MD

SUBJECT: Office Director Memo

TO: NDA 022575 VPRIV (velaglucerase alfa) for injection
Shire Human Genetic Therapies, Inc.

Summary

Gaucher disease is a serious disease that affects approximately 1 in 40,000 people in the general population.[1] An autosomal recessive inherited disorder, Gaucher disease results in a deficiency of the lysosomal enzyme glucocerebrosidase (GCB) and causes an accumulation of glucocerebroside within macrophages (Gaucher cells). This leads to multi-organ dysfunction involving the liver, spleen, and bone marrow. In a minority of patients, central nervous system (CNS) involvement leads to progressive neurological decline. Of the three clinical types of Gaucher disease, Type 1 accounts for more than 90% of all cases, affecting 30,000 worldwide. Typical manifestations of Type 1 Gaucher disease which may range from mild to severe include hepatomegaly, splenomegaly, thrombocytopenia, bleeding tendencies, anemia, hypermetabolism, bone pain and fractures, growth retardation, and pulmonary disease. Type 1 disease does not involve the CNS.

Enzyme replacement therapy (ERT) designed to compensate for the underlying enzymatic defect has been the cornerstone of treatment for Gaucher disease. ERT has been commercially available since 1991 with the approval of Genzyme's Ceredase (alglucerase), a placentally-derived GCB. This product was eventually replaced by Genzyme's recombinant product, Cerezyme (imiglucerase), approved in 1994. ERT has been shown to reduce organomegaly and improve hematological parameters. Although there is some evidence that ERT improves the bone-related complications of Gaucher disease, longstanding osseous complications of Gaucher disease may remain refractory to ERT. Since ERT has not been shown to pass the blood brain barrier, it has limited effects on CNS manifestations.

VPRIV (velaglucerase alfa) is a GCB produced by gene activation technology in a human fibroblast cell line. Velaglucerase alfa has an identical amino acid sequence to naturally occurring GCB, but has undergone post-manufacturing processing so that it can be effectively taken up by Gaucher cells. Velaglucerase alfa catalyzes the hydrolysis of glucocerebroside to glucose and ceramide in the lysosomes. Velaglucerase alfa differs from Cerezyme by one amino acid, and has an identical amino acid sequence to Ceredase.

This memo documents my concurrence with the Division of Gastroenterology Product's (DGP's) recommendation to approve VPRIV (velaglucerase alfa) for adult and pediatric patients with Type 1 Gaucher disease. Discussions regarding product labeling and postmarketing commitments have concluded satisfactorily.

Dosing

Velaglucerase alfa is available as a lyophilized powder (in 200 U and 400 U single-use vials) to be reconstituted and diluted for infusion. The recommended dose of velaglucerase alfa is 60 Units/kg

[1] Emory Genetics Laboratory. (2009, Dec 20). *Gaucher Disease.* Retrieved from http://genetics.emory.edu/egl/test.php?test_id=102

administered as a 60 minute infusion every other week. Dosage adjustments can be made based on achievement and maintenance of each patient's therapeutic goals. Patients previously treated with Cerezyme for Type 1 Gaucher disease may be switched to velaglucerase alfa at the same dose.

Regulatory History

Velaglucerase alfa received orphan designation for the treatment of Type 1 Gaucher disease on June 8, 2009. A treatment protocol was submitted and allowed to proceed on July 30, 2009 that provided patients with Gaucher disease access to ERT at a time when supplies of Cerezyme were compromised by manufacturing problems.

NDA 022575, submitted by Shire on August 31, 2009, and received on August 31, 2009, was filed and granted a priority review. An Advisory Committee was not held due to the product's similarity to other approved enzyme replacement therapies for Type 1 Gaucher disease.

Efficacy

The efficacy of velaglucerase alfa was assessed in a total of 82 patients with Type 1 Gaucher disease who were 4 years of age and older.

Treatment-naïve Type 1 Gaucher disease. Study TKT032 was a 12-month, randomized, double-blind, controlled trial in 25 patients aged 4 years and older. Patients were required to have Gaucher disease-related anemia and either thrombocytopenia or organomegaly. No disease-specific therapy was permitted in the preceding 30 months. Patients were randomized to receive velaglucerase alfa at a dose of either 45 Units/kg (n=13) or 60 Units/kg (n=12) every other week. After twelve months of therapy, patients in both dose groups showed a 2.4 g/dL increase in the mean change from baseline in hemoglobin concentration. Both dose groups also demonstrated increases in the mean change from baseline in platelet counts (41,000 and 51,000), respectively. Reductions in spleen volumes as assessed by MRI were also noted. No significant changes from baseline in liver volumes were observed.

Study TKT039 was a 9-month, randomized, double-blind, active-controlled trial in 34 patients with Type 1 Gaucher disease. Patients were required to have disease-related anemia and either thrombocytopenia or organomegaly. No disease-specific therapy was permitted in the preceding 12 months. Patients received either 60 Units/kg of velaglucerase alfa (n=17) or 60 Units/kg of imiglucerase (n=17) every other week. The mean absolute increase from baseline in hemoglobin concentration was 1.6 g/dL (± 0.2 SE) following 9 months of treatment with velaglucerase alfa. The mean treatment difference in change from baseline to 9 months (velaglucerase alfa – imiglucerase) was 0.1 g/dL (± 0.4 SE).

Previously treated Type 1 Gaucher disease. Study TKT034 was a 12-month, open-label trial in 40 patients aged 9 years and older who had been receiving treatment with imiglucerase at doses ranging from 15 Units/kg to 60 Units/kg for a minimum of 30 consecutive months. Patients were required to be on a stable dose of imiglucerase for at least 6 months prior to enrollment. Following discontinuation of imiglucerase, treatment with velaglucerase alfa was initiated at the same dose as that of imiglucerase. Hemoglobin concentrations and platelet counts remained stable through 12 months of velaglucerase alfa treatment. No patient required an adjustment in the dose of velaglucerase alfa.

Conclusion. Treatment with velaglucerase alfa is effective for both treatment-naïve patients with Type 1 Gaucher disease, and those previously treated with imiglucerase.

Safety

The safety of velaglucerase alfa was assessed in 94 patients with Type 1 Gaucher disease who received doses ranging from 15 Units/kg to 60 Units/kg every other week in clinical trials. Patients ranged in age between 4 and 71 years, and included 46 male and 48 female patients. Fifty-four patients were naïve to ERT, while 40 patients switched from imiglucerase to treatment with velaglucerase alfa. Of the 94 patients, 90 received velaglucerase alfa treatment for 9 months, and 73 received treatment for 12 months.

The most serious adverse reactions in patients treated with velaglucerase alfa were hypersensitivity reactions. The most commonly reported adverse reactions were infusion-related reactions which were reported in 52% of treatment-naïve patients and in 23% of patients previously treated with imiglucerase. Adverse reactions reported more commonly in pediatric patients compared to adult patients included rash, upper respiratory infection, prolonged aPTT, and pyrexia.

In clinical trials, 1 of 54 treatment-naive patients treated with velaglucerase alfa developed IgG neutralizing antibodies to velaglucerase alfa. No infusion-related reactions were reported for this patient. It is unknown whether the presence of IgG anti-velaglucerase alfa antibodies is associated with a higher risk of infusion reactions.

Pediatric Considerations

Pediatric Use. The safety and effectiveness of velaglucerase alfa have been established in Type 1 Gaucher disease patients aged 4 -17 years evaluated in clinical trials. Twenty of the 94 (21%) patients treated with velaglucerase alfa were pediatric patients. Safety and efficacy were similar between pediatric and adult patients. The safety of velaglucerase alfa has not been established in pediatric patients younger than 4 years of age.

Required Pediatric Assessments. Because velaglucerase alfa for this indication has an orphan drug designation, Shire is exempt from conducting required pediatric studies under the Pediatric Research Equity Act (21 USC 355c).

Chemistry, Manufacturing and Controls Considerations

The following deficiencies involving chemistry, manufacturing and controls do not preclude approval and can be addressed as postmarketing commitments. Shire commits to: 1) develop and implement a kinetic assay with a physiologically relevant substrate for drug substance and drug product release and stability testing, 2) develop and implement a quantitative method that measures total carbohydrate content, 3) replace the non-quantitative SDS-PAGE Silver stain method with a quantitative SDS-PAGE Coomassie test, 4) demonstrate that [redacted] is well-controlled to ensure no impact on product quality, 5) demonstrate the clearance capability of the process to remove [redacted] through [redacted] spike studies, 6) re-evaluate drug substance and drug product release and stability specifications, 7) provide updated specifications for SEC, RP-HPLC, and the glycan map, and include acceptance criteria for the leading shoulder in SEC-HPLC, for peaks [redacted] in RP-HPLC, and peak [redacted] in the glycan map, 8) update the peptide map specification using new acceptance criteria to reflect control of impurities, 9) include the cellular uptake bioassay for drug product release testing, 10) provide a report containing the sub-visible particulates analyses, risk assessment, and risk mitigation strategies, 11) include drug substance and drug product stress conditions in the annual stability program, and 12) evaluate the impact of pH on the in-use stability of the drug product and provide assurance that procedures are in place to control this risk to product quality.

The following postmarketing commitments involve immunogenicity issues. Shire commits to: 1) utilize an antibody screening cut point based on a mean +1.645 standard deviation for assay values from treatment-naïve Gaucher patients, and use the same methodology to calculate the anti-imiglucerase ECL cut point, 2) 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) re-assess the IgE cut point for the current ECL methodology using a chemically synthesized hybrid control, and 4) develop an assay to measure the ability of patient antibodies to block the uptake of velaglucerase alfa and imiglucerase into target cells.

Clinical Pharmacology Considerations

Pharmacokinetic (pK) assessments were performed in Study TKT032 at Weeks 1 and 37 in patients receiving 45 Units/kg or 60 Units/kg every other week. During the infusion, velaglucerase alfa serum concentrations rose rapidly for the first 20 minutes. The mean half life was 11 to 12 minutes for both dose

groups at Weeks 1 and 37. No significant accumulation in serum velaglucerase alfa concentrations was observed with repeated doses of 45 or 60 U/kg and velaglucerase alfa pK parameters did not appear to change over time (i.e., when measured at Week 1 vs. Week 37).

Upon review, it was determined that only duplicates rather than 5 replicates of quantity control samples were assayed. Thus, the pK information submitted in the NDA could not be considered reliable for labeling purposes. However, considering the supply shortage of the currently marketed Cerezyme, and the demonstrated clinical efficacy and safety of velaglucerase alfa, definitive pK characterization will be deferred post-approval as provided for under 21 CFR §320.22(e).

The pK samples from Study TKT032 are still viable for re-analysis. Shire commits to re-analyze all archived samples and recalculate velaglucerase alfa pK parameters. If these parameters cannot be adequately characterized, Shire commits to conduct a prospective pharmacokinetic study in patients with Type 1 Gaucher disease.

Tradename Review

The Division of Medication Error Prevention and Analysis (DMEPA), in consultation with the Division of Drug Marketing, Advertising, and Communications (DDMAC), have concluded that the tradename "VPRIV" is acceptable.

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Julie Beitz, MD
Director,
Office of Drug Evaluation III
CDER, FDA

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/

JULIE G BEITZ
02/26/2010