CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	August 19, 2014
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Deputy Director:	Reema Mehta, Pharm.D., M.P.H., DRISK, Acting Deputy Director
Subject:	Review evaluates if a REMS is needed for Cerdegla
Drug Name:	Cerdegla (eliglustat)
Therapeutic Class:	Glucosylceramide synthase inhibitor
Dosage form:	Oral tablet
Application Type/Number:	NDA 205494
Applicant/sponsor:	Genzyme
OSE RCM #:	2013-537

CONTENTS

1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Cerdegla (eliglustat), NDA 205494.. The NDA for Cerdegla (eliglustat) was received by the Division of Gastrointestinal and Inborn Errors Products (DGIEP)) from Genzyme Corporation on September 20, 2013. The Applicant did not propose a REMS for Cerdegla.

1.1 PRODUCT BACKGROUND

Eliglustat is a specific inhibitor of glucosyleramide synthase and acts as a substrate reduction therapy (SRT). Inhibition of glucosylamide synthase partially inhibits the synthesis of glucosylceramide (GL-1), thereby decreasing its accumulation and treating clinical manifestations of Gaucher Disease Type 1 (GD-1). The proposed indication is the long term treatment of adult patients with GD-1, a rare metabolic disorder, who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test.

The proposed dosing for eliglustat is 84 mg orally BID for CYP2D6 IMs and EMs. The recommended dosage in CYP2D6 PMs is 84 mg once daily. Patients who are CYP2D6 ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of Cerdelga to achieve a therapeutic effect. Some inhibitors of CYP2D6 and CYP3A are contraindicated with Cerdelga depending on the patient's metabolizer status. Co-administration of Cerdelga with other CYP2D6 and CYP3A inhibitors may require dosage adjustment depending on the patient's CYP2D6 metabolizer status to reduce the risk of potentially significant adverse reactions.

1.2 DISEASE BACKGROUND

GD is the most common of approximately fifty lysosomal storage diseases (LSDs) and is caused by the deficiency of B-glucosidase. The lack of this enzyme results in an accumulation of GL-1 which in turn causes hepatosplenomegaly, anemia, thrombocytopenia, skeletal disease, and rarely, lung or liver impairment. GD is an orphan disease and occurs in approximately 1/100,000 people in the general population. The majority of these patients have GD-1. The life expectancy of patients with GD-1 varies depending on the severity of the disease and some may lead a near normal life expectancy.

LSDs were historically treated with supportive care (bed rest, transfusion, analgesia, surgery) based on the specific organs impacted by the disease and degree of impairment. However, after the advent of enzyme replacement therapies (ERTs), these therapies are the mainstay treatment for GD and three ERTs are approved by FDA for the treatment of GD (see Table 1).

One alternative treatment approach is oral SRT. Currently, Zavesca (miglustat) a glucosylceramide synthase inhibitor, is the only approved SRT to treat GD-1. Zavesca is associated with neurological and other adverse effects, targets a different part of the glucosylceramide synthase enzyme substrate from eliglustat, and has a limited indication (mild to moderate GD-1 for whom ERT is not an option) due to the drug's unique benefit-risk profile.

Table 1. Drugs used to treat patients with GD-1

Drug	Recommended dosage	Comments
Cerezyme (imiglucerase)	60 U/kg IV every 2 weeks	Warnings for anaphylaxis and hypersensitivity; ERT
Vpriv (velaglucerase)	60 U/kg IV every 2 weeks	Warnings for anaphylaxis and hypersensitivity; ERT
Elelyso (taliglucerase)	Recommended dose is 60 U/kg IV once every 22 weeks	Warnings for anaphylaxis and allergic and infusion reactions; ERT
Zavesca (miglustat)	100 mg PO BID	Warnings for peripheral neuropathy, tremor or exacerbation of existing tremors, diarrhea and weight loss; SRT

1.3 REGULATORY HISTORY

September 20, 2013: Genzyme Corporation submitted a NDA for Cerdegla. The submission did not include a proposed REMS.

January 9, 2014: At the mid-cycle meeting with the Sponsor, FDA communicated that the need for a REMS was still under review.

June 6, 2014: FDA informed Genzyme in the Late Cycle Meeting Background Package that a REMS was not necessary to ensure the benefits outweighed the risks for eliglustat.

2 MATERIALS REVIEWED

The following is a list of internal materials that informed our review:

- Berry K. Clinical safety review for Cerdegla (eliglustat), DGIEP, dated August 15, 2014.
- Genzyme Corporation. Summary of Clinical Safety for Cerdegla (eliglustat), received September 20, 2013.
- Genzyme Corporation. Summary of Clinical Efficacy for Cerdegla (eliglustat), received September 20, 2013.
- CDER DCRP QT Interdisciplinary Review Team, QT-IRT Consult to DGIEP, February 28, 2014.
- Strongin B., Chief, Project Management, DGIEP, Information Request, March 19, 2014.
- Shang E., Office of Clinical Pharmacology Reviewer, Clinical Pharmacology Review, June 16, 2014.

Below is a list of other materials that informed our review:

- Hughes DA and Pastores GM. Haematological manifestations and complications of Gaucher disease. Curr Opin Hematol 2013;20:41–47.
- Agency for Healthcare Research and Quality. Enzyme-Replacement Therapies for Lysosomal Storage Diseases. Technical Brief, January 2013.
- Zavesca (miglustat), Prescribing Information, Last updated February 2014.

3 REVIEW FINDINGS FOR CERDEGLA

3.1 OVERVIEW OF CLINICAL PROGRAM FOR CERDEGLA

A total of 379 subjects were exposed to eliglustat while enrolled in Phase 1 clinical studies and 395 patients were exposed to eliglustat while enrolled in Phase 2 or Phase 3 clinical studies. A summary of the Phase 2 and 3 studies is as follows:

- Phase 2 study (GZGD00304) was an open label, multi-center study that included 26 patients who were treated with at least one dose of eliglustat. The primary objective of the trial was to evaluate the efficacy, safety, and PK of eliglustat, administered as an oral dose of either 50 mg BID or 100 mg BID, to patients with GD1 for 52 weeks. The secondary objective was to determine the long-term efficacy, safety, and PK effects of eliglustat at doses of 50, 100, or 150 mg BID administered to the same patients from approximately Week 54 through trial completion.
- Phase 3 ENGAGE study (GZGD02507), a double-blind, randomized, placebo-controlled, was to confirm the efficacy and safety of eliglustat after 39 weeks of treatment in patients with GD1. The secondary objectives were to determine the long-term efficacy, safety and pharmacokinetics (PK) of eliglustat in patients with GD1. The study consisted of 20 patients who received eliglustat and 20 patients who received placebo; and,
- Phase 3 ENCORE study (GZGD02607), an open-label, active comparator trial, was to assess the efficacy and safety of eliglustat compared with Cerezyme® (imiglucerase) after 52 weeks of treatment in patients with GD1 who have reached therapeutic goals with ERT. The secondary objective was to demonstrate that, in patients with GD1 who have reached therapeutic goals with ERT, the majority of patients who receive eliglustat remain stable after 52 weeks of treatment. The study included 160 patients who were randomized to treatment with eliglustat (n=106) or Cerezyme (n=54).

The two Phase 3 and one Phase 2 trial were reviewed for this submission and form the basis for determining efficacy for eliglustat. In addition to the above studies, study GZGD03109 (EDGE) was included in the pooled safety data. This study is a Phase 3b, randomized, multi-center, multi-national, double-blind trial to evaluate the efficacy, safety and pharmacokinetics of once daily versus twice daily dosing of eliglustat in GD-1 who have demonstrated clinical stability on a twice daily dose of GD-1. EDGE is an ongoing long-term safety and efficacy study; however, the Applicant has only submitted lead-in safety data for this study.

3.1.1 Efficacy

The primary efficacy endpoints in GZGD00304 were the changes in hemoglobin and platelet levels and the percent change in spleen volume during the Primary Analysis Period, from baseline through Week 52. The trial consisted of several phases: Screening, dose adjustment/ treatment, initial steady-state treatment, a treatment interruption period, long-term steady-state treatment, and safety follow-up. On Day 1, each patient received an open-label 50 mg dose of eliglustat; on Day 2, patients began receiving 50 mg eliglustat BID. Following PK sampling on Day 20, if a patient's Day-10 PK results indicated that trough plasma concentration of eliglustat was less than 5 ng/mL, the patient received a dose increase to 100 mg BID eliglustat for the remainder of the treatment period; if trough plasma concentration was greater than or equal to 5

ng/mL, the patient remained on 50 mg BID for the remainder of the treatment period. Patients were eligible for a further dose adjustment to 150 mg BID if they had been on treatment for at least 24 months and met certain efficacy criteria. Twenty-four patients received 50 mg eliglustat BID from Day 2 through Day 20, after which doses could be adjusted. Six (25%) patients continued to receive 50 mg BID, and 18 (75%) were dose-adjusted to 100 mg BID.

In the ENGAGE study, the eliglustat treatment group showed a percentage reduction in spleen volume (MN) by the first post-Baseline assessment at Week 26 (mean = -25.16%), and a reduction in spleen volume through Week 39 (mean = -27.58%). In contrast, the placebo group showed small mean percentage increases in spleen volume at both time points (mean = 0.73% and 2.07%, respectively) ($p<0.0001$).

In the ENCORE study, the efficacy endpoint was the percentage change in spleen volume (MN) from baseline to Week 52 (non-inferiority). The study demonstrated that the eliglustat group was -5.00% compared to -3.26% in the Cerezyme group ($p=0.292$). Stability in the composite endpoint, including hemoglobin and platelet values and spleen and liver volumes, was maintained after 52 weeks of treatment in 84% of patients in the eliglustat group and 94% in the Cerezyme group (the lower bound of the 95% CI in the difference in percentage (-18.6%) was within the pre-specified threshold of -25%).

3.1.2 Safety

Common adverse events

Overall, 334 of 393 of eliglustat-treated patients (85%) experienced a treatment emergent adverse event (TEAE). The majority of patients had events which were considered not related to eliglustat treatment by the Investigators (312/334; 79%). Most of the TEAEs experienced were mild or moderate in severity (78% and 44% of patients, respectively). The most frequent TEAEs included: headache (17%), arthralgia (14%), nasopharyngitis (13%), upper respiratory tract infection (11%), diarrhea (10%), and dizziness (10%).

Serious adverse events

Forty-five patients (11%) experienced 68 TEAEs which were considered severe. A total of 35 patients (9%) experienced 42 events that were treatment-emergent serious adverse events (SAEs), the majority of which were also considered not related to eliglustat treatment by the Investigators (31 patients [89%]; 36 SAEs). Five patients (1%) had SAEs that were considered related to eliglustat treatment. There were 3 deaths that occurred; however, the medical officer determined they were unrelated to study drug.

Drug-Drug Interactions

Eliglustat is primarily metabolized by CYP2D6 isoenzymes, although it is also metabolized to a lesser degree by CYP3A4 isoenzymes. Patients on strong CYP2D6 and 3A4 inhibitors and/or poor metabolizers were generally not studied in the clinical trials and eliglustat was stopped if a

patient needed to take one of these types of drugs (e.g., a time-limited antibiotic course).[1] At a given dose, the systemic exposure (Cmax and AUC) depends on the CYP2D6 phenotype. In CYP2D6 EMs and IMs, the eliglustat pharmacokinetics is time-dependent and the systemic exposure increases in a more than dose proportional manner. After multiple oral doses of 84 mg twice daily in EMs, eliglustat systemic exposure (AUC_{0-12}) increased up to about 2-fold at steady state compared to after the first dose ($AUC_{0-\infty}$). The pharmacokinetics of eliglustat in CYP2D6 PMs is expected to be linear and time-independent. Compared to EMs, the systemic exposure following 84 mg twice daily at steady state is 7- to 9-fold higher in PMs.

QT prolongation

Eliglustat has the potential to prolong the QT interval. QTc interval prolongation was studied in a double-blind, single dose, placebo- and positive-controlled crossover study in 42 healthy subjects. Concentration-related increases were observed for the placebo-corrected change from baseline in the PR, QRS, and QTc intervals. Based on PK/PD modeling, eliglustat plasma concentrations of 500 ng/mL are predicted to cause mean (upper bound of the 95% one-sided confidence interval) increases in the PR, QRS, and QTcF intervals of 22 (26), 7 (10), and 13 (19) msec, respectively. At the highest geometric mean concentrations of 237 ng/mL following a single supratherapeutic dose tested in the thorough QT study, Cerdelga did not prolong the QT/QTc interval to any clinically relevant extent.

Despite these study results, there is a concern that in the postmarket real world setting patients who are PMs and/or who are taking strong CYP2D6 and/or 3A4 inhibitors were not represented in the trials and may be at increased risk of QT prolongation, which may lead to sudden cardiac death.

Pursuant to these concerns, DGIEP asked the Applicant to provide adverse event data stratified by patients with trough levels less than and greater than 5 mg/dL. The Applicant's response demonstrated that the percent of non-serious and serious adverse events experienced by these two groups were generally comparable. Further, DGIEP requested that the Applicant conduct additional simulation modeling to assess the potential impact of drug-drug interactions stratified by the metabolizer status, including ultra-rapid, extensive, intermediate, and poor metabolizer status (i.e., the impact of concomitant use of strong inhibitors of CYP2D6 and CYP3A4 stratified by these groups). Based on this simulation modeling, the Office of Clinical Pharmacology recommends an 84 mg QD dosing for poor metabolizers and an 84 mg BID dose for intermediate and extensive metabolizers.

4 DISCUSSION

Gaucher disease is a rare, orphan condition that causes significant morbidity and decreased quality of life. Although ERTs (glycoprotein products) are efficacious when compared to placebo, there is a need for non-biologic therapies and safer and more efficacious oral therapies to treat patients who fail ERT or seek to initiate treatment with a non-injectable product.

[1] Although a small percentage of patients studied were either poor metabolizers (7 patients (4%)) or taking strong 2D6 or 3A4 inhibitors, they did not receive the proposed maintenance dose but rather a lower dose.

In the clinical trials, eliglustat was found to be efficacious versus placebo and non-inferior to Cerezyme (imiglucerase) with an acceptable safety profile. Eliglustat use was associated with a low incidence of serious safety issues and incidence of non-serious safety issues.

As mentioned above, serious risks associated with the only other SRT approved to treat GD, miglustat, include: peripheral neuropathy, tremor or exacerbation of existing tremors, diarrhea and weight loss. Based on the available data for eliglustat, the neurologic symptoms associated with miglustat have not been associated with the administration of eliglustat.

Regarding the drug-drug interactions and the potential for increased drug concentrations and potential QT prolongation, DGIEP and DRISK believe labeling is sufficient to describe this risk. (b) (4)

The Warnings and Precautions section of the label will state that use of eliglustat in patients with pre-existing cardiac disease, long QT syndrome, and concomitant use of Class IA and Class III antiarrhythmic medications is not recommended. Drug-drug interactions and PM is discussed extensively in the drug interactions section of the label, and the once daily dosing for PMs is highlighted in the dosing and administration section. The totality of the evidence does not support a boxed warning for this safety issue.

DRISK believes that a REMS is not necessary to ensure the benefits outweigh the risks for eliglustat when used in GD-1 for the following reasons:

- The GD is an orphan disease and occurs in approximately 1/100,000 people in the general population.
- Due to the significant morbidity and decreased quality of life associated with the disease, patients are managed closely typically by a specialist (hematologist and/or a geneticist).
- The drug has demonstrated efficacy in patients from the clinical trials and provides a therapeutic alternative to ERT
- The risk of drug-drug interactions is described extensively in the label and does not require additional risk mitigation beyond labeling at this time
- The available data from the clinical trials suggests that the risk of QT prolongation is predicted to occur as substantially elevated levels of Cardelga; and is therefore contraindicated in this at risk population (i.e., EMs/IMs taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor; or IMs/PMs taking a strong CYP3A inhibitor).

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, risk mitigation measures beyond professional labeling are not warranted for eliglustat. Eliglustat has proven efficacy in the treatment of GD-1. The serious risk of concern associated with eliglustat is QTc prolongation in specific patients which will be included in the Warnings and Precautions, drug-drug interactions, as well as doing and administration sections

of the labeling. Thus, the benefit-risk profile for eliglustat is favorable and the risks can be mitigated though professional labeling.

Should DGIEP have any concerns or questions, or feel that a REMS may be warranted for this product, please send a consult to DRISK.

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/s/

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08/19/2014

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