

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205494Orig1s000**

**OTHER REVIEW(S)**

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA # 205494  
Product Name: Eliglustat

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PMR/PMC Description: Conduct a study to evaluate the effect of renal impairment on eliglustat PK. A reduced design may be used.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/2015</u>
	Study/Trial Completion:	<u>01/2017</u>
	Final Report Submission:	<u>07/2017</u>
	Other:	<u>n/a</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Gaucher Disease Type 1 (GD-1) is a rare disease. Only a small portion of GD-1 patients have renal impairment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Renal impairment can inhibit some pathways of hepatic and gut drug metabolism and transport, and result in increase in systemic exposure to eliglustat. High systemic exposures may result in prolongation of QTc and PR intervals. Dose adjustment may be needed in patients with severe renal impairment or end-stage renal disease. The proposed study is needed for appropriate dose recommendation in these patients. The currently proposed labeling does not recommend use in patients with moderate or severe renal impairment or end-stage renal disease.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Clinical PK and safety study in patients with severe renal impairment and end-stage renal disease not on dialysis
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Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

---

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

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Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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ELIZABETH Y SHANG  
08/15/2014

SUE CHIH H LEE  
08/15/2014

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA # 205494  
Product Name: Eliglustat

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PMR/PMC Description: Conduct a clinical study to evaluate the effects of hepatic impairment on eliglustat PK.

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PMR/PMC Schedule Milestones: Final Protocol Submission: 06/2015  
Study/Trial Completion: 01/2017  
Final Report Submission: 07/2017  
Other: \_\_\_\_\_ n/a

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Gaucher Disease Type 1 (GD-1) is a rare disease and only a small portion of GD-1 patients have hepatic impairment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Eliglustat is extensively metabolized through hepatic elimination. Decrease in hepatic function is expected to result in increase in systemic exposure to eliglustat. Increased exposures are a concern because of the potential for QTc and PR interval prolongation at high systemic exposures. Dose adjustment is likely to be necessary in patients with hepatic impairment. The proposed study is needed for appropriate dose recommendation in these patients. The currently proposed labeling does not recommend use in patients with any level of hepatic impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Clinical PK and safety study in subjects with mild and moderate hepatic impairment classified by Child-Pugh classification. The patients' with hepatic impairment can be "non-Gaucher Disease Type 1" subjects. The study maybe staged by first conducting the study in subjects with moderate hepatic impairment with provisions in the study protocol to enroll a cohort of subjects with mild hepatic impairment if the results in subjects with moderate hepatic impairment show a substantial effect of reduced hepatic function on eliglustat PK compared to the healthy subjects.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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ELIZABETH Y SHANG  
08/15/2014

SUE CHIH H LEE  
08/15/2014

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA # 205494  
Product Name: Eliglustat

PMR/PMC Description: Develop 21-mg and/or 42-mg dosage strength(s) to accommodate various situations requiring further dosage adjustments. Conduct a single- and multiple-dose PK study in healthy subjects to characterize dose proportionality of 21, 42, and 84 mg dose strengths.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>n/a</u>
	Study/Trial Completion:	<u>n/a</u>
	Final Report Submission:	<u>12/2018</u>
	Other: _____	<u>n/a</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Currently, no first line oral therapy is available for the treatment of GD-1. Eliglustat potentially fills this gap.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The proposed dose of 84 mg PO once daily in CYP2D6 poor metabolizers (PMs) is acceptable but not optimal. In addition, the dose adjustment recommendations for various drug-drug interaction scenarios are not optimal. Developing a lower dosage forms will allow more flexible dosing regimens for PMs and can eliminate restrictions in some DDI scenarios. Alternate dose strengths may also allow more flexible dosing in patients with renal or hepatic impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

a) Conduct formulation development studies to develop 21 mg and/or 42 mg capsules. Provide pertinent CMC information required for approval of the lower strengths

b) a single- and multiple-dose PK study in healthy subjects to characterize dose proportionality/linearity of 21, 42, and 84 mg dose strengths.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other  
formulation development, CMC ----Sponsor agreed at LCM
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
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***If so, does the clinical trial meet the following criteria?***

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- There is not enough existing information to assess these risks
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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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ELIZABETH Y SHANG  
08/15/2014

SUE CHIH H LEE  
08/15/2014

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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**Date of This Memorandum:** July 16, 2014  
**Requesting Office or Division:** Division of Gastroenterology and Inborn Errors (DGIEP)  
**Application Type and Number:** NDA 205494  
**Product Name and Strength:** Cerdelga (eliglustat) Capsules, 84 mg  
**Submission Date:** July 23, 2014  
**Applicant/Sponsor Name:** Genzyme Corporation  
**OSE RCM #:** 2013-2203-2  
**DMEPA Primary Reviewer:** Mónica Calderón, PharmD, BCPS  
**DMEPA Team Leader:** Kendra Worthy, PharmD

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#### 1 PURPOSE OF MEMO

DGIEP requested that we review the revised carton labeling and wallet pack (Appendix A) for Cerdelga (eliglustat) Capsules to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling Memorandum.<sup>1</sup>

#### 2 CONCLUSIONS AND RECOMMENDATIONS

The revised carton labeling is acceptable from a medication error perspective. We have no further recommendations.

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<sup>1</sup> Calderon M. Memorandum: Review of Revised Label and Labeling for Cerdelga (NDA 205494). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 07 16. 32 p. OSE RCM No.: 2013-2203-1.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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MONICA M CALDERON  
07/29/2014

KENDRA C WORTHY  
07/29/2014

**Consult  
MEMORANDUM***Department of Health and Human Services  
Public Health Service  
Food and Drug Administration*

**DATE:** July 21, 2014

**RECEIVED:** December 4, 2013

**TO:** Jessica Benjamin, Senior Regulatory Health Program Manager, OMPT/CDER/OND/ODEIII/DGIEP

**FROM:** Lynn Filpi, CDRH/OIR/DCTD

**THROUGH:** Denise Johnson-Lyles, Toxicology Branch Chief, CDRH/OIR/DCTD

**SUBJECT:** ICC 1400425 - CDER consult request for NDA205494

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**Protocol Title** Not applicable

**Drug Sponsor** Genzyme

**Drug Name** Cerdelaga (eliglustat tartrate)

**Analyte Detected** CYP2D6

**Device Sponsor** Not applicable

**I. BACKGROUND**

The drug is proposed for the long term treatment of adult patients with Gaucher disease type 1. Eliglustat is primarily metabolized by the <sup>(b) (4)</sup> enzyme CYP2D6. The applicant proposes to limit use of eliglustat to patients who are CYP2D6 intermediate (IM) or extensive (EM) metabolizers (i.e., not for use in <sup>(b) (4)</sup> ultra-rapid (URM), or indeterminate metabolizers). While the appropriateness of this strategy is under review, as currently proposed, CYP2D6 genotype testing would be recommended for the safe and effective use of eliglustat.

**II. DEVICE USE IN THE TRIAL**

The sponsor used the Luminex Molecular Diagnostics xTAG CYP2D6 Kit v3 in their Phase I studies and the Roche AmpliChip CYP450 microarray in their Phase II and Phase III studies to determine the patients CYP2D6 genotype and to determine whether based on genotype, subjects could participate in studies using eliglustat.

### III. RESPONSE TO CDER QUESTIONS

1. *Are the in vitro diagnostics that are currently FDA-cleared for CYP2D6 genotyping adequate to support the proposed use of eliglustat in IMs and EMs?*

There are currently two cleared devices for genotyping CYP2D6, Luminex Molecular Diagnostics xTAG CYP2D6 Kit v3 (k130189) and Roche AmpliChip CYP450 microarray (k042259). Both tests are intended for use with DNA extracted from whole blood samples. The device cleared under k130189 uses multiplex PCR followed by multiplex allele specific primer extension for genotyping, with detection by flow cytometry. The device cleared under k042259 uses PCR amplification of purified genomic DNA, fragmentation and labeling of the amplified products, and hybridization of the amplified products to a microarray for detection. Neither test is cleared to be used to predict drug response or non-response and therefore these tests should not be used as a stand-alone for diagnostic purposes.

It is important to note that not all CYP2D6 alleles are identified by these two devices. In addition, while both devices demonstrated over 98% agreement with sequencing (the reference method), there is a possibility that a patient could be placed into the wrong metabolizer status and the drug would not have the desired effect. Rare alleles not queried by the test should receive a no call, however there is a chance that these devices could incorrectly result in a default wild-type (\*1) call (if the nucleotide change the patient has is not detected by the assay) or an incorrect allele if the patient's rare allele shares a nucleotide change with a different allele detected by the assay. However as discussed in the team meeting on January 22, 2013, due to the rarity of Gaucher disease type1 and the accuracy of these tests, the chances of a patient being placed into the incorrect metabolizer status are very low and if such an event were to occur it would likely not cause an adverse effect and would instead delay the proper treatment. Therefore, we suggest an FDA cleared genotyping test can be safely used to identify the CYP2D6 genotype and be used under a medical professional's care to determine if the patient is a candidate for this Eliglustat. Please refer to the tables below provided in the Additional Information section for a list of the CYP2D6 alleles and predicted enzyme activity that can be identified by these devices.

2. *If adequate, how should labeling for the drug product reference the available tests (e.g., as detected by an FDA-cleared test)?*

The labeling can state:

“Select patients with Gaucher disease type 1 based on the CYP2D6 metabolizer status. It is recommended patient genotypes be established using an FDA-cleared test for determining CYP2D6 genotype.”

#### IV. ADDITIONAL INFORMATION

For each of the cleared CYP2D6 genotyping devices, tables are provided below to list the genotypes (alleles) and predicted enzyme activity that can be identified by these devices.

Luminex Molecular Diagnostics xTAG CYP2D6 Kit v3 (k130189):

<b>Allele</b>	<b>SNPs detected</b>	<b>Predicted Enzyme Activity</b>	<b>Reference where the effect of the genotype on drug metabolism is described</b>
*1	None	Normal	(Kimura, Umeno et al. 1989; Marez, Legrand et al. 1997; Sachse, Brockmoller et al. 1997)
*2	-1584C>G, 1661G>C, 2850C>T, 4180G>C	Normal	(Johansson, Lundqvist et al. 1993; Panserat, Mura et al. 1994; Marez, Legrand et al. 1997; Raimundo, Fischer et al. 2000; Sakuyama, Sasaki et al. 2008)
*3	2549A>del	None	(Kagimoto, Heim et al. 1990; Marez, Legrand et al. 1997)

*4	100C>T, 1661G>C, 1846G>A, 4180G>C, 2850C>T	None	(Gough, Miles et al. 1990; Hanioka, Kimura et al. 1990; Kagimoto, Heim et al. 1990; Sachse et al, 1997; Marez et al, 1997)
*5	deletion	None	(Gaedigk, Blum et al. 1991; Steen, Molven et al. 1995)
*6	1707T>del, 4180G>C	None	(Evert, Griese et al. 1994; Saxena, Shaw et al. 1994; Daly, Leathart et al. 1995; Marez, Legrand et al. 1997)
*7	2935A>C 1661G>C, 1758G>T, 2850C>T, 4180G>C	None	(Evert, Griese et al. 1994)
*8	1661G>C, 1758G>T, 2850C>T, 4180G>C	None	(Broly, Marez et al. 1995)
*9	2613delAGA	Reduced	(Tyndale, Aoyama et al. 1991; Broly and Meyer 1993)

*10	100C>T, 1661G>C, 4180G>C	Reduced	(Yokota, Tamura et al. 1993; Johansson, Oscarson et al. 1994; Ishiguro, Kubota et al. 2004; Sakuyama, Sasaki et al. 2008)
*11	883G>C, 1661G>C, 2850C>T, 4180G>C	None	(Marez, Sabbagh et al. 1995)
*15	138insT	None	(Sachse, Brockmoller et al. 1996)
*17	1023C>T, 1661G>C, 2850C>T, 4180G>C	Reduced	(Masimirembwa, Persson et al. 1996; Oscarson, Hidestrand et al. 1997)
*29	1659G>A, 1661G>C, 2850C>T, 3183G>A, 4180G>C	Reduced	(Marez, Legrand et al. 1997; Wennerholm, Johansson et al. 2001; Wennerholm, Dandara et al. 2002)
*35	-1584C>G, 31G>A, 1661G>C, 2850C>T, 4180G>C	Normal	(Marez, Legrand et al. 1997; Gaedigk, Ryder et al. 2003)
*41	1661G>C, 2850C>T, 2988G>A, 4180G>C	Reduced	(Raimundo, Fischer et al. 2000; Raimundo, Toscano et al. 2004)

## Roche AmpliChip CYP450 microarray (k042259):

<b>Allele</b>	<b>SNPs detected</b>	<b>Predicted Enzyme Activity</b>	<b>Reference where the effect of the genotype on drug metabolism is described</b>
*9	2613-2615delAGA	Reduced	Tyndale et al, 1991 Broly & Meyer, 1993
*10AB	100C>T, 1039C>T, 1661G>C, 4180G>C	Reduced	Yokota et al, 1993 Johansson et al, 1994
*11	883G>C, 1661G>C, 2850C>T, 4180G>C	None	Marez et al, 1995
*15	T138ins	None	Sachse et al, 1996
*17	1023C>T, 1661G>C, 2850C>T, 4180G>C	None	Masimirembwa et al, 1996 Oscarson et al,
*19	1661G>C, 2539-2542delAACT, 2850C>T, 4180G>C	None	Marez et al, 1997
*20	1661G>C, 1973insG, 1978C>T, 1979T>C, 2850C>T, 4180G>C	None	Marez-Allorge et al, 1999
*29	1659G>A, 1661G>C, 2850C>T, 3183G>A, 4180G>C	Reduced	Marez et al, 1997
*35	-1584C, G31A, 1661G>C, 2850C>T, 4180G>C	Normal	Marez et al, 1997 Gaedigk et al, in press
*36	100C>T, 1039C>T, 1661G>C, 4180G>C, gene conversion to CYP23T in exon 9	Reduced	Wang, 1992 Johansson et al, 1994 Leathart et al, 1998
*40	1023C>T, 1661G>C, 1863ins(TTT CGC CCC)2; 2850C>T, 4180G>C	None	Gaedigk et al, 2002a
*41	-1548C, 1661G>C, 2850C>T, 4180G>C	Reduced	Raimundo et al., 2000 Raimundo et al., 2004

*1XN	duplicate active *1 genes (n is not determined-range 2 -13)	Increased	Dahl et al, 1995 Sachse et al, 1997
*2XN	duplicate active *2 genes (n is not determined-range 2 -13)	Increased	Johansson et al, 1993 Dahl et al, 1995
*4XN	duplicate active *4 genes (n is not determined)	None	Lovlie et al, 1997 Sachse et al, 1998
*10XN	duplicate partially active *10 genes (n is not determined)	Reduced	Garcia-Barceló etal., 2000 Ji et al., 2002 Mitsunaga et al., 2002 Ishiguro et al., 2004
*17XN	duplicate partially active *17 genes (n is not determined)	Reduced	Cai et al., 2004
*35XN	duplicate active *35 genes (n is not determined)	Increased	Griese et al, 1998
*41XN	duplicate partially active *41 genes (n is not determined)	Reduced	Candiotti et al., 2004

**Concurrence History Page**

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<b>Digital Signature Concurrence Table</b>	
Reviewer Sign-Off	
Branch Chief Sign-Off	
Division Sign-Off	

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/s/  
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JESSICA M BENJAMIN

07/22/2014

Administratively checked into DARRTS by Project Manager for reviewer.

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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**Date of This Memorandum:** July 16, 2014  
**Requesting Office or Division:** Division of Gastroenterology and Inborn Errors (DGIEP)  
**Application Type and Number:** NDA 205494  
**Product Name and Strength:** Cerdelga (eliglustat) Capsules, 84 mg  
**Submission Date:** June 26, 2014 and July 2, 2014  
**Applicant/Sponsor Name:** Genzyme Corporation  
**OSE RCM #:** 2013-2203-1  
**DMEPA Primary Reviewer:** Mónica Calderon, PharmD, BCPS  
**DMEPA Team Leader:** Kendra Worthy, PharmD

---

#### 1 PURPOSE OF MEMO

DGIEP requested that we review the revised carton labeling and wallet pack (Appendix A) for Cerdelga (eliglustat) Capsules to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>1</sup>

#### 2 CONCLUSIONS AND RECOMMENDATIONS

The revised carton labeling is unacceptable from a medication error perspective. Information regarding the (b) (4) of the drug was removed from the previously proposed labeling. We provide recommendations in Section 2.1.

##### 2.1 RECOMMENDATIONS TO THE APPLICANT

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<sup>1</sup> Calderon M. Label and Labeling Review for Cerdelga (NDA 205494). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 03 05. 32 p. OSE RCM No.: 2013-2203.

### Outer and Inner Carton Labeling

1. Add an asterisk to the strength to read as follows, "84 mg\*".
  - a. Add the following statement below the strength, "\*Each capsule contains 84 mg of eliglustat which is equivalent to 100 mg of eliglustat tartrate".
2. Revise the storage condition as follows, "The storage condition should read as: Store at 20–25°C (68–77°F); excursions permitted to 15–30°C (59–86°F)".

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/s/  
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MONICA M CALDERON  
07/16/2014

KENDRA C WORTHY  
07/16/2014

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

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

## Memorandum

**Date:** June 3, 2014

**To:** Jessica Benjamin, MPH  
Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors  
Products (DGIEP)

**From:** Adewale Adeleye, Pharm.D., MBA  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Kathleen Klemm, Pharm.D.  
Team Leader, OPDP

**Subject:** NDA # 205494  
OPDP Labeling Comments for CERDELGA (eliglustat tartate)  
capsules for oral use (Cerdelga)

---

Reference is made to DGIEP's consult request dated November 13, 2013, requesting review of the proposed Package Insert (PI) and Medication Guide (MG) for Cerdelga.

OPDP has reviewed the proposed PI. Our comments on the PI are based on the proposed draft marked-up labeling titled "NDA 205494 eliglustat draft labeling.doc" that was available in the e-room on May 20, 2014, at 9:04am. OPDP's comments on the PI are provided directly on the attached marked-up copy of the labeling (see below).

Please note that comments on the proposed MG were provided on June 3, 2014, under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or [adewale.adeleye@fda.hhs.gov](mailto:adewale.adeleye@fda.hhs.gov)

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/s/  
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ADEWALE A ADELEYE  
06/03/2014

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: June 3, 2014

To: Donna Griebel, MD  
Director  
**Division of Gastroenterology and Inborn Error Products (DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Nathan Caulk, MS, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Adewale Adeleye, Pharm.D., MBA  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): CERDELGA (eliglustat)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 205-494

Applicant: Genzyme Corporation

## 1 INTRODUCTION

On September 20, 2013, Genzyme Corporation submitted for the Agency's review an original New Drug Application (NDA) 205-494 for CERDELGA (eliglustat) capsules. The purpose of this submission is to seek approval for the proposed indication for the long-term treatment of adult patients with Gaucher disease type 1 for CERDELGA (eliglustat) capsules.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology and Inborn Error Products (DGIEP) on November 13, 2013, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for CERDELGA (eliglustat) capsules.

## 2 MATERIAL REVIEWED

- Draft CERDELGA (eliglustat) capsules MG received on September 20, 2013, and received by DMPP on November 13, 2013.
- Draft CERDELGA (eliglustat) capsules MG received on September 20, 2013, and received by OPDP on May 19, 2014.
- Draft CERDELGA (eliglustat) capsules Prescribing Information (PI) received on September 20, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 19, 2014.
- Approved ZAVESCA (miglustat) capsules comparator labeling dated February 10, 2014.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/  
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NATHAN P CAULK  
06/03/2014

ADEWALE A ADELEYE  
06/03/2014

LASHAWN M GRIFFITHS  
06/03/2014



**DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service**

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Food and Drug Administration  
Office of New Drugs - Immediate Office  
Pediatric and Maternal Health Staff  
Silver Spring, MD 20993  
Telephone 301-796-2200  
FAX 301-796-9744

**Pediatric and Maternal Health Staff – Maternal Health Review**

**Date:** May 22, 2014

**From:** Carol H. Kasten, MD, Medical Officer  
Pediatric and Maternal Health Staff, Maternal Health Team

**Through:** Melissa S. Tassinari, Ph.D. DABT, Senior Clinical Advisor,  
Pediatric and Maternal Health Staff, Maternal Health Team

Lynne P. Yao, MD, OND IO Associate Director  
Pediatric and Maternal Health Staff

**To:** Division of Gastrointestinal and Inborn Errors Products (DGIEP)

**Drug:** Cerdelga™ (Eliglustat)  
NDA 205-494  
Orphan Drug Designation 08-2654

**Subject:** Pregnancy and Nursing Mothers Labeling

**Sponsor:** Genzyme Corporation

**Consult Request:** “We are requesting your review of Section 8 of the package insert. A marked-up version of the PI can be found in the DGIEP Share Point site.”

## INTRODUCTION

Genzyme Corporation submitted NDA 205-494 for eliglustat (Cerdelga) on September 20, 2013, with the proposed indication of long term treatment of adult patients with Gaucher disease Type 1 (GD1). Eliglustat was developed under IND application 67589. The PUDFA goal date for this application is August 20, 2014.

On April 16, 2014, the Division of Gastrointestinal and Inborn Errors Products (DGIEP) consulted the Pediatric and Maternal Health Staff (PMHS) - Maternal Health Team (MHT) to evaluate and revise relevant sections of the labeling for eliglustat.

## DISEASE BACKGROUND

### *Gaucher Disease Type 1*

Gaucher Disease Type I (GD1) is an autosomal recessive disorder caused by mutations in the gene for the lysosomal hydrolase, glucocerebrosidase or acid  $\beta$ -glucosidase.<sup>1,4</sup> This enzyme is required to breakdown glucosylceramide, a glycosphingolipid. Without glucocerebrosidase, the enzyme's substrate glucosylceramide accumulates in lysosomes of macrophages.<sup>2</sup> The swollen macrophages, called 'Gaucher cells' accumulate in the liver and spleen producing hepatosplenomegaly. The hypersplenism caused by splenomegaly usually manifests as thrombocytopenia, anemia and sometimes leukopenia.<sup>3</sup> Ultimately, the abnormal macrophages also infiltrate the bone marrow deforming the bones and producing chronic bone pain, bone infarcts and osteopenia.<sup>3,4</sup> GD1 generally spares the central nervous system permitting these patients to have normal intellect.<sup>1,2</sup> GD1 patients typically present in later childhood or early adulthood. The disease is compatible with a long life span.<sup>2</sup> Ashkenazi Jews have the highest mutation carrier prevalence at 5.7%.<sup>4</sup> The most common mutation among the Ashkenazim is a change at amino acid 370 from an asparagine to a serine, a mutation which confers a mildly symptomatic or asymptomatic phenotype when homozygous.<sup>4</sup>

The first enzyme replacement therapy (ERT) for GD1 (Ceredase) was approved in the U.S. in 1991. There are now three recombinant formulations ERT, taliglucerase (NDA 22458), velaglucerase alpha (NDA 22575) and imiglucerase (NDA 20367). These drugs produce reductions in liver and spleen volumes and increases in platelets and red cells. All of these ERT formulations require bi-weekly infusions.

In 2003, miglustat (Zavesca, NDA 21348) was approved in the US. It is the first Substrate Reduction Therapy (SRT) approved for GD1. Miglustat is an oral product, and

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<sup>1</sup> Chapter 35. Disorders of Sphingolipid Metabolism.. In: Fernandes J. Saudubray JM, Van den Berghe G (eds.) Inborn Metabolic Diseases Diagnosis and Treatment, 3<sup>rd</sup> Revised Edition. ©Springer-Verlag Berlin Heidelberg 2000.

<sup>2</sup> Chapter 6. Genetic Disorders. In: Kemp WL, Burns DK, Brown TG. eds. Pathology: The Big Picture. New York, NY: McGraw-Hill; 2008. Accessed April 29, 2014.  
<http://accessmedicine.mhmedical.com/content.aspx?bookid=499&Sectionid=41568289>.

<sup>3</sup> Martins AM, Valadares ER *et al.* Recommendations on Diagnosis, Treatment, and Monitoring for Gaucher Disease. *J Peds* 155;Supp 2:S10-S18.

<sup>4</sup> OMIM Entry - # 230800 - GAUCHER DISEASE, TYPE I. Accessed May 13, 2014.  
<http://www.omim.org/entry/230800>

to be taken twice daily. SRT reduces the production of the substrate glucosylceramide which accumulates in GD1. Miglustat acts by blocking glucosylceramide synthase, the final enzyme in the transformation of ceramide to glucosylceramide. Eliglustat's mechanism of action is the same as that of miglustat reducing the quantity of substrate which GD1 patients are unable to metabolize. Eliglustat is also taken orally twice daily. The data on miglustat demonstrate that it is effective in reducing GD1 signs and symptoms even when started in ERT-naïve patients; however, it has several adverse effects (nausea, weight loss) which result in approximately a third of patients discontinuing the drug in the first year.<sup>5</sup>

#### *Effect of ERT on Pregnancy, Labor and Delivery*

Approved pharmacologic treatments of GD1 have been available since 1991. Published data demonstrates that women with GD1 suffer fewer adverse events during pregnancy, labor and delivery if they receive ERT throughout gestation.<sup>6,7,8</sup> Specifically, the reduction in the woman's hepatosplenomegaly allows the fetus enough space in the abdomen to grow.<sup>7</sup> The hematologic abnormalities caused by an enlarged spleen also regress, reducing the risk of hemorrhage during labor and delivery. The data also indicate that initiating ERT before conception permits all the benefits of ERT to begin earlier, thus maximizing the woman's health prior to pregnancy.<sup>8</sup>

## **DISCUSSION**

Animal studies with eliglustat demonstrated a teratogenic risk in rats at doses six times the recommended human dose based on surface area. However, no adverse effects were seen in pregnant rabbits exposed to eliglustat at doses ten times the recommended human dose based on surface area.

As a comparison, animal studies for miglustat were reviewed. Studies of miglustat's effect in rats receiving miglustat doses  $\geq 2$  times the human therapeutic systemic exposure from 14 days prior to conception through day 17 (organogenesis) demonstrated complete litter loss and decreased fetal weight. Pregnant rats given oral gavage doses  $\geq 2$  times human therapeutic systemic exposure of miglustat from day 6 through lactation were found to have delayed parturition and dystocia, and decreased weight gain. These findings were not seen in animal studies with eliglustat.

In male rats exposed to eliglustat, abnormal sperm morphology was noted. However, spermatogenesis was normal in Cynomolgus monkeys. See the pharmacology toxicology review for further details. Therefore, effects on males of reproductive potential were inconsistent across species and did not warrant labeling of this information. Previously, Zavesca carried a warning statement about male fertility based on studies in the rat

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<sup>5</sup> Hollak CEM, Hughes D et al. Miglustat (Zavesca<sup>®</sup>) in type 1 Gaucher disease: 5-year results of a post-authorisation safety surveillance programme. *Pharmacoepid Drug Safety*.2009; 8: 770–777.

<sup>6</sup> *J Gynecol Obstet Biol Reprod (Paris)*. 2014 May;43(5):397-400. doi: 10.1016/j.jgyn.2012.11.013

<sup>7</sup> Granovsky-Grisaru S, Belmatoug N et al. The management of pregnancy in Gaucher disease. *Eur J Obstet Gynec Reprod Biol*;2011;156: 3–8.

<sup>8</sup> Zimran A, Morris E et al. The female Gaucher patient: The impact of enzyme replacement therapy around key reproductive events (menstruation, pregnancy and menopause). *Blood Cells Molec Dis*.2009; 43:264–288

suggested that miglustat may adversely affect male fertility. However, post-marketing human data failed to demonstrate effects on male fertility and this warning was removed from Zavesca labeling.

There are no data on eliglustat in any of the databases. A database review for miglustat yielded reports in TERIS<sup>9</sup> and Shephard's® Catalog of Teratogenic Agents.<sup>10</sup> TERIS comments that the risk of teratogenesis is undetermined in humans as there are no peer-reviewed data published.<sup>9</sup> Shephard's does not comment on the risk of teratogenesis.<sup>10</sup> The database discusses two publications on the effect of miglustat on murine sperm morphology and its functional capacity to fertilize mouse oocytes. Male mice exposed to miglustat 5 to 7 weeks prior to mating were functionally sterile; however, via microsurgical injection of mouse oocytes with the abnormally shaped sperm, normal mice offspring were delivered.<sup>11</sup> There is one publication which describes a small clinical study in healthy men (without GD1) treated with miglustat demonstrating normal spermatogenesis.<sup>12</sup> There were no data on miglustat in either LactMed®<sup>13</sup> or Hale's Medications and Mother's Milk.<sup>14</sup>

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May, 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in nursing mothers labeling, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

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<sup>9</sup> TERIS is the TERatology Information Service located at University of Washington. It is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women. [http://www.micromedexolutions.com/micromedex2/librarian/ND\\_T/evidencexpert/ND\\_PR/evidencexpert/CS/](http://www.micromedexolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/) Accessed April 29, 2014.

<sup>10</sup> 2014 Shephard's®: A Catalog of Teratogenic Agents.

<sup>11</sup> Suganuma R, Walden CM et al. Alkylated imino sugars, reversible male infertility-inducing agents, do not affect the genetic integrity of male mouse germ cells during short-term treatment despite induction of sperm deformities. *Biol Reprod*; 2005;72:805-813.

<sup>12</sup> Amory, JK, Muller CH, et al. Miglustat has no apparent effect on spermatogenesis in normal men. *Hum. Reprod*; 2007;22:702-707.

<sup>13</sup> LACTMED®: The LactMed database is a National Library of Medicine database with information on drugs and lactation geared toward healthcare practitioners and nursing women. LactMed Record Number: 990; Last Revision Date: 20130907

<sup>14</sup> Hale's 2012 Medications and Mother's Milk. 15th Edition, Amarillo, TX

Given the data on the importance of ERT in women with GD1 who are pregnant or are thinking of becoming pregnant, a *Clinical Considerations* paragraph under **(8.1) Pregnancy** was added using the same verbiage as that included with miglustat.

The pregnancy subsection of the eliglustat labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. The Nursing Mothers subsection of the eliglustat labeling was revised to comply with current labeling recommendations.

## **RECOMMENDATIONS**

PMHS-MHT attended the labeling meeting with the Division on April 30, 2014. The following are the PMHS Maternal Health Team recommendations for the proposed labeling for eliglustat PLR format during that meeting. The language for each section was modified from the most recent approved labeling for eliglustat which was in non-PLR format. For the Pregnancy and Nursing Mothers sections, the information was re-formatted to conform to the structure outlined in the proposed PLLR. The original, labeling and final approved labeling are provided in Appendix A and B, respectively.

Language was provided in the following sections of the eliglustat labeling:

### **Highlights of Prescribing Information**

#### ----- **USE IN SPECIFIC POPULATIONS** -----

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Nursing mothers: Discontinue drug or nursing based on importance of drug to mother (8.3)

## **8 USE IN SPECIFIC POPULATIONS**

Pregnancy Category C

### **8.1 Pregnancy**

#### Risk Summary

There are no adequate or well-controlled studies with CERDELGA in pregnant women. However, animal reproduction studies have been conducted for eliglustat. In these animal studies, a spectrum of anomalies at doses 6 times the recommended human dose was observed in rats. No fetal harm was observed with oral administration of eliglustat to pregnant rabbits at dose levels 10 times the recommended human dose. CERDELGA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### *Clinical Considerations*

##### Disease-associated maternal and embryo-fetal risk

Women with Type 1 Gaucher disease have an increased risk of spontaneous abortion, especially if disease symptoms are not treated and controlled pre-conception and during a

pregnancy. Pregnancy may exacerbate existing Type 1 Gaucher disease symptoms or result in new disease manifestations. Type 1 Gaucher disease manifestations may lead to adverse pregnancy outcomes including, hepatosplenomegaly which can interfere with the normal growth of a pregnancy and thrombocytopenia which can lead to increased bleeding and possible hemorrhage.

#### *Animal Data*

Reproduction studies have been performed in pregnant rats at oral doses up to 120 mg/kg/day (about 6 times the recommended human dose based on body surface area) and in pregnant rabbits at oral doses up to 100 mg/kg/day (about 10 times the recommended human dose based on body surface area). In rats, at 120 mg/kg/day (about 6 times the recommended human dose based on body surface area), eliglustat increased the number of late resorptions, dead fetuses and post implantation loss, reduced fetal body weight, and caused fetal visceral variations (dilated cerebral ventricles), fetal skeletal variations (poor bone ossification) and fetal skeletal malformations (abnormal number of ribs or lumbar vertebra). Eliglustat did not cause fetal harm in rabbits at oral doses up to 100 mg/kg/day (about 10 times the recommended human dose based on body surface area). In a pre and postnatal development study in rats, eliglustat did not show any significant adverse effects on pre and postnatal development at doses up to 100 mg/kg/day (about 5 times the recommended human dose based on body surface area).

### **8.3 Nursing Mothers**

It is not known whether CERDELGA is present in human milk. Because many drugs are present in human milk, and because of the potential for serious adverse reactions in nursing infants from CERDELGA, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the lactating woman.

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/s/  
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CAROL H KASTEN  
05/22/2014

MELISSA S TASSINARI  
05/22/2014

LYNNE P YAO  
05/23/2014

MEMORANDUM

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

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**CLINICAL INSPECTION SUMMARY**

DATE: May 15, 2014

TO: Jessica Benjamin, M.P.H., Regulatory Project Manager  
Karyn Berry, M.D., Medical Officer  
Division of Gastroenterology and Inborn Errors Products

FROM: Susan Leibenhaut, M.D.  
Medical Officer  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205494

APPLICANT: Genzyme Corporation

DRUG: eliglustat tartrate

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Long term treatment of adult patients with Gaucher Disease Type 1

CONSULTATION REQUEST DATE: November 13, 2013  
INSPECTION SUMMARY GOAL DATE: May 18, 2014  
DIVISION ACTION GOAL DATE: August 20, 2014  
PDUFA DATE: August 20, 2014

## I. BACKGROUND:

Genzyme Corporation submitted an NDA for eliglustat, a new molecular entity (NME), for the indication of the long term treatment of adult patients with Gaucher Disease Type 1 (GD1). Two pivotal studies were conducted to support this application. ENGAGE enrolled treatment-naïve patients and ENCORE enrolled patients switching to eliglustat from enzyme replacement therapy. Eliglustat is a novel substrate reduction therapy (SRT). Its mechanism of action, partial inhibition of the enzyme glucosylceramide synthase, differs from that of the enzyme replacement therapies (ERTs) currently marketed to treat GD1.

The sponsor submitted the following two studies in support of the application:

1. Protocol GZGD02507 entitled “A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study Confirming the Efficacy and Safety of Genz-112638 in Patients with Gaucher Disease Type 1 (ENGAGE)” and
2. Protocol GZGD02607 entitled “A Phase 3, Randomized, Multi-Center, Multi-National, Open-Label, Active Comparator Study to Evaluate the Efficacy and Safety of Genz-112638 in Patients with Gaucher Disease Type 1 who have Reached Therapeutic Goals with Enzyme Replacement Therapy (ENCORE)”.

Protocol GZGD02507 (ENGAGE) was a randomized, double-blind, placebo-controlled study with the primary efficacy evaluation of percentage change in spleen volume in multiples of normal (MN) as assessed by MRI from Baseline to 39 weeks of treatment with eliglustat as compared to placebo. Secondary efficacy endpoints are hemoglobin levels, liver volumes (MN), and platelet counts. ENGAGE was conducted at 26 study sites from September 2009 to November 2012 (data cut-off date). Seventeen centers in Latin America, the United States (US), Canada, Middle East and Northern Africa, India, and Europe enrolled at least one eligible subject and a total of 40 subjects were randomized.

Protocol GZGD02607 (ENCORE) was a randomized, open label, active-controlled study with the primary efficacy evaluation of stability of hemoglobin, platelet count, spleen and liver volume in MN from baseline to 52 weeks. The comparator was Cerezyme, a currently available intravenous replacement therapy. ENCORE was conducted at 39 centers in Latin America, the United States (US), Canada, Australia, Middle East, and Europe from September 2009 to November 2012 (data cut-off date). One hundred sixty (160) patients were randomized in a 2:1 ratio to treatment with eliglustat (n=106) or Cerezyme (n=54). It was designed to establish the non-inferiority of eliglustat compared with Cerezyme.

The review division chose sites for inspection on the basis of several factors including numbers enrolled at each site and the efficacy results at the sites. Because this is a new molecular entity

a sponsor inspection was conducted as per usual OSI procedures. In addition, the sponsor inspection evaluated monitoring reports for Site 49 of Study 2507 located in Tunis, Tunisia. This site enrolled a high number of subjects, six subjects, and FDA was unable to schedule inspection of this site due to international safety concerns.

## II. RESULTS (by Site):

<b>Name, Address, and Type of Inspected Entity</b>	<b>Protocol #, Site #, and # of Subjects</b>	<b>Inspection Date</b>	<b>Final Classification*</b>
CI: Prof. Elena Lukina Hematology Research Center of Ministry of Healthcare of the Russian Federation Novy Zykovsky proezd 4 125167 Moscow, Russia	Protocol 2507/ Site # 01/ 10 Subjects  Protocol 2607/ Site # 01/ 9 Subjects	December 23 to 27, 2013	NAI
CI: Dr. Guillermo Isaias Drelichman Hospital de Nino's Dr. Ricardo Gutierrez Gallo 1330, 1425 – Buenos Aires Argentina	Protocol 2607/ Site # 28/ 21 Subjects	February 24 to 28, 2014	Pending* (preliminary NAI)
CI: Dr. Renata de Souza Cravo Hemorio Rua Frei Caneca 08 – sala: 315 – Centro 20211-030 Rio de Janeiro, Brazil	Protocol 2607/ Site # 29/ 12 Subjects	February 10 to 13, 2014	NAI
CI: Dr. Ana Maria Martins Instituto de Genética e Erros Inatos do Metabolismo (IGEIM) Vila Clementino 04020-041- São Paulo, Brazil	Protocol 2607/ Site # 27/ 10 Subjects	February 3 to 7, 2014	NAI
CI: Dr. Heather Lau/Gregory M. Pastores New York University 403 East 34th Street, 2nd Floor New York, NY 10016	Protocol 2507/ Site # 09/ 2 Subjects  Protocol 2607/ Site # 69/ 4 Subjects	January 27 to February 4, 2014	NAI
CI: Dr. Manisha Balwani Dept. of Genetics and Genomic Sciences Mount Sinai School of Medicine New York, NY 10029	Protocol 2607/ Site # 19/ 11 Subjects	January 14 to 21, 2014	NAI
Sponsor: Genzyme Corporation 500 Kendall Street Cambridge, MA 02142	Protocol 2507 Protocol 2607	March 18 to 25, 2014	Pending* (preliminary NAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

\*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. Prof. Elena Lukina, 125167 Moscow, Russia**

- a. **What was inspected:** At this site, Site #1 for both protocols, for Protocol 2507, a total of 12 subjects were screened and 10 subjects were enrolled and randomized. At this site, for Protocol 2607, a total of 11 subjects were screened and 9 subjects were enrolled and randomized. An audit of all of the informed consent documents was conducted. A review was conducted of test article handling and accountability. For eligibility criteria, the review included source records to confirm eligibility for every other subject enrolled in both studies.
- b. **General Observations/Commentary:** The study site was blinded to the primary efficacy data during the study. Primary efficacy endpoint data were provided by [REDACTED] <sup>(b) (4)</sup> (by email) and compared with approximately 50% of subjects in both studies. A small sample of MRIs images reviewed matched the information in the subject records. There was no evidence of under-reporting of adverse events. No significant regulatory violations were noted, and no Form FDA 483 was issued.
- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

**2. Dr. Guillermo Isaias Drelichman, Buenos Aires Argentina**

**Note:** Observations below for the sponsor inspection are based on a draft Establishment Inspection Report (EIR) and e-mail communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

- a. **What was inspected:** At this site, for Protocol 2607, a total of 23 subjects were screened and 21 subjects were enrolled and randomized. A total of 18 subjects from this site and 2 subjects transferred from another site (Subjects 5201 and 5202) completed the study. An audit of all of the informed consent documents was conducted. A review was conducted of test article handling and accountability. The following source documents were compared to the line listings that were submitted to the NDA: for all subjects: hematology results at baseline, Week 26 and Week 52; MRI spleen and liver values for seven

subjects, and adverse events and concomitant medications, and protocol deviations for five subjects.

*Reviewer note: The original consult from the review division states that there were 22 subjects at this site, but the randomization list in the NDA has 21 subjects listed for this site.*

- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. No discrepancies were noted between the line listings and the source documents and data.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the indication.

### 3. Dr. Renata de Souza Cravo, Rio de Janeiro, Brazil

- a. **What was inspected:** At this site, for Protocol 2607, a total of 16 subjects were screened and 12 subjects were enrolled and randomized. The audit included review of informed consent documents, study correspondence, source records, and test article handling and accountability. Source documents for all subjects enrolled in study GZGD02607 were reviewed.
- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. No discrepancies were noted between the line listings and the source documents and data. One objectionable condition was observed and verbally discussed with Dr. Cravo during and at the closing of the inspection noting that a Hepatitis C test, the basis for exclusion criterion 9 of the protocol, was missed during screening of Subject 2915. A Form FDA 483 was not issued.
- c. **Assessment of data integrity:** The verbal observation is considered an isolated occurrence and does not impact data reliability or subject safety. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indications.

### 4. Dr. Ana Maria Martins, São Paulo, Brazil

- a. **What was inspected:** At this site, for Protocol 2607, a total of 11 subjects were screened and 10 subjects were enrolled and randomized. The audit included review of informed consent documents, study correspondence, source records, and test article handling and accountability. Source documents for all subjects enrolled in study GZGD02607 were reviewed.
- b. **General observations/commentary:** There was no evidence of under-reporting

of adverse events. No discrepancies were noted between the line listings and the source documents and data. One objectionable condition was observed and verbally discussed. Subject no. 2701 signed ICF version 3.0 on September 8, 2010 with (b) (6). The "Signature and Responsibility" log shows that delegation to consent subjects was granted to (b) (6) on April 15, 2011. Subject 2701 had been consented properly under ICF version 2.0 on May 13, 2010. A Form FDA 483 was not issued.

- c. **Assessment of data integrity:** The verbal observation is considered an isolated occurrence and does not impact data reliability or subject safety. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indications.

#### 5. Dr. Heather Lau/Gregory M. Pastores, New York University, New York, NY

- a. **What was inspected:** The inspection assignment indicated Dr. Gregory Pastores as the principal investigator (PI), however, as of July 2013, Dr. Lau took on the role as PI. At this site, for Protocol 2507, a total of four subjects were screened and two subjects were enrolled and randomized. One subject withdrew at week 65 and one subject is ongoing in the study. At this site, for Protocol 2607 a total of five subjects were screened and four subjects were enrolled and randomized. One subject withdrew at week 91, one subject withdrew at week 26 and two subjects are ongoing in the study. An audit of all randomized subjects' records for both studies was conducted. The review included consent form documents, study correspondence, source records, and test article handling and accountability.
- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events, and the source data for the primary efficacy data were able to be verified at the site. No significant regulatory violations were noted, and no Form FDA 483 was issued.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indications.

#### 6. Manisha Balwani, MD, Mount Sinai School of Medicine, New York, NY 10029

- a. **What was inspected:** At this site, Site 19, for Protocol GZGD02607, a total of 15 subjects were screened and 11 subjects were enrolled and randomized. One subject discontinued and ten subjects remain ongoing in the study. An audit of ten randomized subjects' records was conducted. The review included consent form documents, study correspondence, source records, and test article handling and accountability.

- b. **General observations/commentary:** There was no evidence of under-reporting of AEs. The primary endpoint data were verified. No significant regulatory violations were noted, and no Form FDA 483 was issued.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indications.

## 7. Genzyme Corporation, Cambridge, MA 02142

**Note:** Observations below for the sponsor inspection are based on a draft e-mail communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

- a. **What was inspected:** This inspection evaluated compliance with sponsor responsibilities including selection and oversight of contract research organizations, monitoring, financial disclosure, FDA Form 1572s, and quality assurance (QA) for the studies noted above. There was a review of data receipt and handling. In addition to the sites noted above, the monitoring reports for Site 49 of Study 2507 located in Tunis, Tunisia was conducted because FDA was unable to conduct an on-site inspection.
- b. **General observations/commentary:** The monitoring of investigators was adequate and the sponsor maintained adequate oversight of the trials. Data receipt and handling was considered adequate. Oversight of test article was considered adequate. No regulatory violations were noted and a Form FDA 483 was not issued.
- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications.

## III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Six clinical investigator sites and the sponsor were inspected for this NDA. All clinical sites had the classification of NAI with only minor regulatory violations noted. For the sponsor inspection, the preliminary classification is NAI. The studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications.

**Note:** Observations above for the sponsor and the Drelichman site inspections are based on e-mail communications with the FDA field investigator (sponsor) or a draft EIR (Drelichman site). An inspection summary addendum will be issued if conclusions change upon review of the final EIRs.

*{See appended electronic signature page}*

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/s/  
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SUSAN LEIBENHAUT  
05/15/2014

SUSAN D THOMPSON  
05/15/2014

KASSA AYALEW  
05/15/2014

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### **LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** March 5, 2014  
**Requesting Office or Division:** Division of Gastroenterology and Inborn Errors (DGIEP)  
**Application Type and Number:** NDA 205494  
**Product Name and Strength:** Cerdelga (eliglustat) Capsules, 84 mg  
**Product Type:** Single Ingredient Product  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Genzyme Corporation  
**Submission Date:** September 20, 2013  
**OSE RCM #:** 2013-2203  
**DMEPA Primary Reviewer:** Mónica Calderón, PharmD, BCPS  
**DMEPA Team Leader:** Lubna Merchant, MS, PharmD

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### 1. REASON FOR REVIEW

This review responds to the consult from DGIEP. DGIEP requested DMEPA evaluate the Applicant's proposed carton labeling, wallet pack and full prescribing information for areas of vulnerability that could lead to medication errors. DGIEP requested this review as part of their evaluation for NDA 205494.

### 2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
ISMP Newsletters	C (N/A)
Previous DMEPA Reviews	D (N/A)
Human Factors Study (if applicable)	E (N/A)
Other (if applicable)	F (N/A)
Blister card, Carton Labeling, and Instructions for Use or Medication Guide (if applicable)	G

N/A=not applicable for this review

### 3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is proposing a single strength (84 mg) capsule. The product will be packaged inside a cardboard wallet pack and supplied in a carton containing 4 packs, each pack containing 14 capsules (56 capsules total). This packaging configuration is supported by the dosage and administration for this product which is one capsule twice daily. DMEPA performed a risk assessment of the proposed full prescribing information and medication guide to identify any deficiencies that may lead to medication errors. We also reviewed the wallet pack and carton labeling to identify areas of improvement and noted important information was either missing or not prominently displayed on the carton labeling. Additionally, the wallet pack is missing (b) (4) information. We provide recommendations in Section 4.1 to address these deficiencies.

### 4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the full prescribing information and medication guide are acceptable from a medication error perspective. However, the proposed carton labeling, and wallet pack

can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

#### 4.1 RECOMMENDATIONS FOR THE APPLICANT

##### 1) All Proposed Carton (inner and outer) Labeling

a) As currently presented, the (b) (4) is not present on the carton labeling. The established name presentation should include the active ingredient followed by the dosage form. Include the dosage form “capsules” on all labels and labeling immediately following the active ingredient presentation. Ensure the dosage form presentation is commensurate with the prominence of the active ingredient presentation.

b) As currently presented, the net quantity statement is too prominent, and may be misinterpreted as the strength, remove the color block highlighting the net quantity statement, and relocate it to the lower left hand corner.

##### 2) Proposed Outer Carton Labeling

a) Relocate the strength presentation below the established name and dosage form (eliglustat capsules). See e.g. below;

Cerdelga  
Eliglustat Capsules  
84 mg

Present the information as displayed above on each panel where the proprietary name and established name are currently written.

b) Add the statement, “Dispense the enclosed Medication Guide to each patient”, to the principal display panel underneath the strength.

##### 3) Proposed Inner Sleeve Carton Labeling

a) See comment 2a.

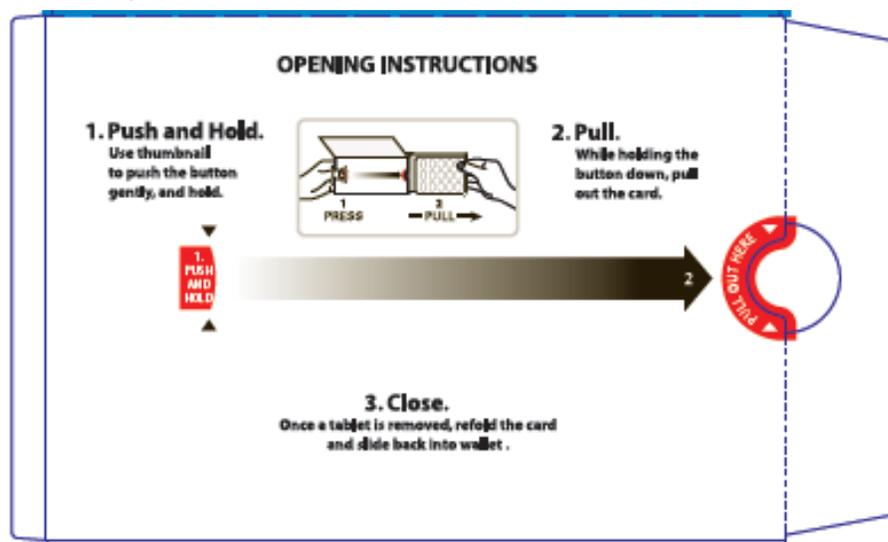
b) Place the NDC code in the upper right hand corner.

c) Include step-by-step instructions with pictures/photographs demonstrating the removal of the wallet pack on the back panel of the inner sleeve carton. The pictorial currently displayed on the principal display panel does not clearly illustrate the removal of the wallet pack. Consider using a graphic with a view from the top versus the side. See example below:

Step 1: Push and hold. Use thumb to push the button gently and hold.

Step 2: Pull. While holding the button down, pull out the wallet pack.

Step 3: Once tablet is removed, refold wallet and slide back into carton.



4) Proposed Wallet Pack

- a) Place the proprietary name, established name, dosage form, strength, lot number, expiration date, and NDC number on the outer flap covering the capsules. If the patient should discard the outer and inner carton this important information is available to the patient up to the point at which the last dose is removed.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Cerdelga that Genzyme Corporation submitted on September 20, 2013.

Table 2. Relevant Product Information for Cerdelga	
Active Ingredient	Eliglustat
Indication	Long-term treatment of adult patients with Gaucher disease Type 1.
Route of Administration	Oral
Dosage Form	Capsules
Strength	84 mg
Dose and Frequency	84 mg twice daily
How Supplied	1 carton containing 4 packs (56 capsules total); Each pack is a blister card of 14 capsules
Storage	Stored at (b) (4) excursions permitted 15°C to (b) (4)

### APPENDIX G. CONTAINER LABEL, CARTON LABELING, INSTRUCTIONS FOR USE, MEDICATION GUIDE

#### G.1 List of Label and Labeling Reviewed

We reviewed the following Cerdelga labels and labeling submitted by Genzyme Corporation on September 20, 2013.

- Wallet pack
- Carton labeling
- Medication guide

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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MONICA M CALDERON  
03/05/2014

LUBNA A MERCHANT  
03/06/2014



# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: February 28, 2014

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.  
Division Director  
Division of Cardiovascular and Renal Products /CDER

To: Jessica Benjamin, RPM  
DGIEP

Subject: QT-IRT Consult to DGIEP (NDA 205494)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated November 13, 2013 regarding labeling. The QT-IRT received and reviewed the following materials:

- Your consult
- Draft Label
- ISS section 9.5.2 (ECGs phase 2 and 3 studies)
- TQT study review ( Feb 5<sup>th</sup> 2009 )

## QT-IRT Comments for DGIEP

QT-IRT conducted further analysis with datasets of the TQT study submitted for eliglustat. Results show no proarrhythmia risk at the predicted steady-state C<sub>max</sub> achieved (44 ng/ml) for the GD1 patients with CYP2D6 phenotype (Table 1).

### Table 1

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However, QT<sub>c</sub>, PR and QRS prolongation are expected at steady-state supratherapeutic scenario C<sub>max</sub> (e.g., more than 10 ms mean change in QT<sub>cF</sub> may be expected when mean C<sub>max</sub> is higher

than 250 ng/mL) (Table 1). The PR effect size is unlikely to be clinically meaningful in healthy subjects. In patients with pre-existing AV nodal disease and/or being co-administered agents that block the AV node, the PR prolongation may become clinically important. QRS effect size is not clinically meaningful in healthy subjects and probably not in patients.

Overall the pooled Eliglustat Safety Set was small (a total of 393 patients). No sudden cardiac deaths, Torsade de pointes or clinically meaningful AV-block cases were reported. One subject (GZGD00304/0302) was withdrawn from study GZGD0034 after the first dose of Eliglustat due to a ventricular tachycardia episode that required hospitalization and was considered by the investigator to be possibly related to Eliglustat.

Data reported from electrocardiogram monitoring during phase 2 and 3 studies showed no clinically relevant changes in QTcF. Seven subjects had PR intervals > 200 ms and increase from baseline  $\geq$  25%. One had a clinically meaningful PR prolongation. Eighteen subjects had a post-baseline QRS  $\geq$  120 ms, two of them had postbaseline increases of 30 and 50%, which are clinically meaningful.

## BACKGROUND

QT-IRT reviewed a TQT study for Genz-112638 (eliglustat). Genz-112638 increased the QTc and PR intervals in a dose- and concentration-dependent manner. For QTcF, the largest upper bounds of the 2-sided 90% CI for the mean difference between GENZ-112638 (200 mg and 800 mg) and placebo were below 10 ms. For PR, the largest upper limits of the 2-sided 90% CI for the mean difference between Genz- 112638 (200 mg and 800 mg) and placebo were 5.8 ms and 16.4 ms, respectively.

### Sponsor's Proposed Label

#### 12.2 Pharmacodynamics

##### Electrocardiographic Evaluation

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] (b) (4)

#### 4 Contraindications<sup>1</sup>

[Redacted text block]

#### Warning and Precautions

##### 5.1 Drug-Drug Interactions

[Redacted text block]

##### 5.2 Patients with Pre-existing Cardiac Conditions

Use of CERDELGA in patients with pre-existing cardiac conditions has not been studied during clinical trials. Because CERDELGA is predicted to cause (b) (4) increases in ECG intervals at substantially elevated eliglustat plasma concentrations, use of CERDELGA (b) (4) patients with (b) (4) (congestive heart failure, recent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmia), long QT syndrome, and in combination with

<sup>1</sup> 2.5 Section 3.2.1, Table 2

Class IA (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications.

### **QT-IRT suggested label**

*The following text is our suggestion for labeling. We defer all labeling decisions to the review division.*

#### 12.2 Pharmacodynamics

QTc interval prolongation was studied in a double-blind, single dose, placebo- and positive-controlled crossover study in 42 healthy subjects. At a dose 4 times the recommended dose, CERDELGA did not prolong the QT interval to any clinically relevant extent.

For PR, the largest upper limits of the 2-sided 90% CI for the mean difference between CERDELGA (169 mg and 675 mg) and placebo were 5.8 ms and 16.4 ms, respectively. Two subjects whose baseline PR was less than 200 ms experienced a maximum change of 18 ms.

#### 5.1 Drug-Drug Interactions

CERDELGA is contraindicated in patients taking a strong (e.g., paroxetine, fluoxetine, quinidine) or moderate (e.g., duloxetine, terbinafine) CYP2D6 inhibitor concomitantly with a strong (e.g., clarithromycin, itraconazole) or moderate (e.g., erythromycin, fluconazole) CYP3A inhibitor. Under these conditions both major metabolic pathways for CERDELGA metabolism are impaired, with predicted substantially elevated eliglustat plasma concentrations [see Contraindications (4), and Pharmacokinetics (12.3)]. (b) (4)

Based on PK/PD modeling, eliglustat plasma concentrations 11-fold those expected at the indicated dose are predicted to (b) (4) increase the PR, QRS, and QTc intervals (by 25% upper bound of (b) (4), 26, (b) (4) 10 and (b) (4) 19 msec, respectively).

### **SAFETY**

#### **From Integrated Electrocardiogram analyses (ISS, section 3.1.2, page 39)**

The ECG data available for this ISS were collected in 5 studies as follows:

- TQT Study, a completed Phase 1 study in healthy subjects;

- Phase 2, a study in treatment-naïve patients with GD1: data from the 52-week Primary Analysis Period, 3 years of Extension Period data, and up to the ISS cut-off date of 31 January 2013;
- ENGAGE, a Phase 3 study in treatment-naïve patients with GD1: data from the 39-week Primary Analysis Period and Long-term Treatment Period data up to the ISS cut-off date (31 January 2013);
- ENCORE, a Phase 3 study in GD1 patients switching from ERT: data from the 52-week Primary Analysis Period and Long-term Treatment Period data up to the ISS cut-off date (31 January 2013);
- EDGE, a Phase 3b study in patients with GD1: available data from the ongoing Lead-in Period up to the ISS cut-off date (31 January 2013).

With the exception of EDGE, all ECG and Holter recordings for the other 4 studies were centrally read by a core laboratory, (b) (4)

## Electrocardiograms

### ECGs Results from Phase 2 and 3 Studies

The effect of eliglustat on ECG parameters was further investigated in the population of adult GD1 patients and after repeated therapeutic dosing at 50, 100 or 150 mg BID during the Phase 2 and 3 studies.

The primary safety database supporting this application contains pooled data from 393 patients with GD1 who received eliglustat in an ongoing Phase 2 study (GZGD00304), and 2 ongoing Phase 3 studies (GZGD02507 [ENGAGE], GZGD02607 [ENCORE], and 1 ongoing Phase 3b study GZGD03109 [EDGE; Lead-In Period only]);

#### **Table 2- Patients With Select Potentially Clinically Significant Abnormalities in Electrocardiogram QTcF and PR Parameters – Phase 2 Study and Phase 3 Studies**

Criterion/ Study	Patient ID#	Duration in Study (last visit evaluated)	Number of Time Points with Liability	Baseline	ECG Highest Values*				PK Conc. at Time of Highest Value (ng/mL)	Highest Conc. Overall Study (ng/mL)
					Raw value	Delta	% Change	Visit/Time		
<b>QTcF Interval &gt;480 msec post Baseline and Baseline ≤480 msec (n=2 patients)</b>										
EDGE	33903	Wk 26	1/19	461.7	502.0	40.3	8.7	Wk 26 T1H	1.70**	10.2
	35704	Wk 26	1/26	463.4	482.7	19.3	4.2	Day 1 T2H	<LLOQ**	50.5
<b>QTcF Interval Increase from Baseline &gt;60 msec (n=6 patients)</b>										
EDGE	30501	Wk 26	5/20	350.9	427.4	76.5	21.8	Wk 2 T4H	0.77**	33.3
	31613	Wk 78	1/29	379.2	441.2	62.0	16.3	Wk 78 T3H	9.68**	18.9
	32804	Wk 26	1/21	362.7	434.6	71.9	19.8	Wk 26 T2H	13.8	14.5
	32806	Wk 26	2/19	362.6	432.0	69.3	19.1	Wk 2 T3H	1.31**	10.5
	38401	Wk 26	2/30	340.0	451.0	111.0	32.6	Wk 2 T1H	21.9	22.58
	38402	Wk 78	1/39	353.6	414.8	61.2	17.3	Wk 8 Pre	6.66	140.09
<b>PR Interval &gt;200 msec and Increase from Baseline ≥ 25% (n=7 patients)</b>										
ENCORE	2103	Wk 91	3/40	397.7	568.0	170.3	42.8	Wk 13 T4H	32.6	62.8
	2703	Wk 130 / Mo 30	2/48	154.0	208.0	54.0	35.1	Wk 52 T1H	29.9	63.2
	5801	Wk 130 / Mo 30	1/50	137.3	206.0	68.7	50.0	Wk 13 Pre	23.7	111
	5957	Wk 52	3/25	155.0	205.0	50.0	32.3	Wk 52 T2H	40.4	84.4
EDGE	31002	Wk 52	6/23	120.0	220.0	100.0	83.3	Wk 13 T1H	4.53	32.3
								Wk 13 T2H	20.8	
								Wk 26 Pre	2.97	
								Wk 52 T1H	4.93	
								Wk 52 T2H	23.0	
	34501	Wk 52	1/24	160.0	240.0	80.0	50.0	Wk 2 T1H	2.41**	28.5
38401	Wk 26	1/30	206.7	260.0	53.3	25.8	Day 1 T3H	5.61	22.58	

Doc ID: m2-7-4-summary-clin-safety-gaucher-dis-type1.doc  
Page 129 of 131

Criterion/ Study	Patient ID#	Duration in Study (last visit evaluated)	Number of Time Points with Liability	Baseline	ECG Highest Values*				PK Conc. at Time of Highest Value (ng/mL)	Highest Conc. Overall Study (ng/mL)
					Raw value	Delta	% Change	Visit/Time		
<b>QRS Interval ≥ 120 msec (n=18 patients)</b>										
ENGAGE	0105	Wk 156 / Mo 36	1/65	104.0	120.0	16.0	15.4	Wk 143 T3H	7.33**	24.7
	2401	Wk 130 / Mo 30	14/57	106.0	127.0	21.0	19.8	Wk 4 T2H	21.7	31.3
ENCORE	5706	Wk 65	2/29	104.7	122.0	17.3	16.6	Day 1 T4H	4.82	81.6
EDGE	30402	Wk 52	2/24	112.7	129.0	16.3	14.5	Wk 52 T1H	24.0**	29.1
								Wk 13 T1H	6.43	
	30406	Wk 26	8/23	113.0	126.0	13.0	11.5	Wk 26 T1H	4.71**	6.43
	30903	Wk 26	1/19	100.7	122.0	21.3	21.2	Wk 13 Pre	2.03	16.8
	32201	Wk 26	3/19	105.7	134.0	28.3	26.8	Wk 26 T1H	7.91**	28.28
	32606	Wk 26	1/16	100.0	124.0a	24.0	24.0	Wk 6 Pre	6.32	31.9
EDGE	32804	Wk 26	4/21	113.3	120.0	6.7	5.9	Day 1 T1H	-	14.5
								Day 1 T2H		
								Day 1 T3H	2.64	
								Day 1 T4H		
	32806	Wk 26	1/19	100.0	120.0	20.0	20.0	Day 1 T4H	0.73**	10.5
	32901	Wk 52	2/24	80.0	120.0	40.0	50.0	Wk 2 T2H	11.6	59.6
								Wk 26 T1H	59.6**	
	32916	Wk 26	1/19	100.0	120.0	20.0	20.0	Wk 26 Pre	-	16.8
	33902	Wk 26	14/18	103.3	134.0	30.7	29.7	Wk 26 T1H	5.97**	34.7
	34801	Wk 26	19/19	133.0	141.0	8.0	6.0	Wk 2 T3H	2.27**	18.0
35706	Wk 26	1/21	106.0	122.0b	16.0	15.1	Wk 2 T4H	4.55**	37.9	
37901	Wk 52	2/25	116.7	120.0	3.3	2.9	Wk 13 Pre	2.55	12.1	

Criterion/ Study	Patient ID#	Duration in Study (last visit evaluated)	Number of Time Points with Liability	Baseline	ECG Highest Values*				PK Conc. at Time of Highest Value (ng/mL)	Highest Conc. Overall Study (ng/mL)
					Raw value	Delta	% Change	Visit/Time		
	38401	Wk 26	6/30	66.7	240.0	173.3	260.0	Wk 13 T1H	12.12	
								Wk 2 Pre	6.42	22.58
EDGE	38402	Wk 78	6/39	120.0	120.0	0.0	0.0	Day 1 T1H	7.84	140.
							Wk 2 Pre			
							Wk 2 T1H			
							Wk 2 T2H			
							Wk 2 T3H			
							Wk 2 T4H			

Source: PGM=DEVOPS/GENZ112638/POOL/ISS\_2013/REPORT/PGM/pool\_pd\_egpca\_s\_t.sas OUT=REPORT/OUTPUT  
/pool\_pd\_egpca\_s\_t\_a\_t\_i.rtf (28JUN2013 - 9:50) (modified)

All data up to cutoff date (31 Jan 2013) are taken into account; for EDGE study, only the lead-in data are considered.

Delta=Change from Baseline; %change=Percent change from Baseline; "pre"=predose value.

The number of time points with liability is calculated using all post-Baseline time points.

a. Reporting error detected by the independent cardiologist expert after the cutoff date: QRS value=100 msec

b. Reporting error detected by the independent cardiologist expert after the cutoff date: QRS value=112 msec

\* The highest values correspond to the highest raw or delta value, depending on the abnormality definition.

\*\* Genz-99067 concentration available at that visit for ECG time point with no concomitant PK sample.

Some values in GZGD03109 study were corrected after the cutoff date (Jan 31 2013) following additional queries; this output takes into account these modifications.

*From ISS, adapted from Table 25 (NDA, module 2.7.4)*

#### *Reviewer's comments*

*With the exception of the EDGE study, all ECGs and Holter recordings were centrally read by a core laboratory. No clinically relevant changes in QTcF were reported in these studies. Seven subjects had PR intervals > 200 ms and increase from baseline  $\geq$  25%. One had a clinically meaningful PR prolongation. Subject 2103, a participant in the ENCORE study had a PR clinically meaningful at baseline (398 ms) and a post-baseline increase of 170 ms (568 ms). Eighteen subjects had a post-baseline QRS  $\geq$  120 ms, two of them had postbaseline increases of 30 and 50%, which are clinically meaningful.*

### **Cardiac Disorders (Section 6.6.3, ISS)**

#### 6.6.3.1 Cardiac Arrhythmias

Table 6-17 and Table 6-18 summarizes the incidence of cardiovascular TEAEs by HLT in the pooled Eliglustat Safety Set by study and overall. A total of 4% of patients (15/393) reported cardiac arrhythmia events by HLT or high level term (HLT).

The most frequent TEAE by HLT were Cardiac conduction disorders (6/393 patients [2%]), Supraventricular arrhythmias (4/393 patients [1%]), and Ventricular arrhythmias and cardiac arrest (4/393 patients [1%]); one patient reported a TEAEs in the HLT Rate and rhythm disorders not elsewhere classified (NEC). The TEAEs considered related to study drug by the investigators were: Atrioventricular block second degree (3/393 patients [1%]); Ventricular tachycardia (2/393 patients [1%]); and Supraventricular tachycardia (2/393 patients [1%]) (Statistical Table 6.1.4.1). One patient temporarily discontinued study drug but remained in the study (GZGD02507/4905; a dose adjustment was made afterward) and 2 patients (GZGD0304/0302 and GZGD0304/0202) withdrew from the study due to a cardiovascular event, and 6 patients (2%) experienced SAEs in the Cardiac disorders SOC (Statistical Table 6.1.5.1 and Statistical Listing 6.1).

**Table 3- Summary of Patients With Treatment-Emergent Cardiac Arrhythmia Adverse Events by MedDRA High Level Term and Preferred Term by Study and Overall - Eliglustat Safety Set**

MedDRA High Level Term MedDRA Preferred Term	GZGD00304 (N = 26)		GZGD02507 (N = 40)		GZGD02607 (N = 157)		GZGD03109 (N = 170)		All Eliglustat (N = 393)	
	Events n/(100py) a	Patients n (%) <sup>b,c</sup>	Events n/(100py) a	Patients n (%) <sup>b,c</sup>						
<b>Total patients with events</b>	3 (3)	2 (8)	4 (7)	3 (8)	7 (3)	6 (4)	4 (3)	4 (2)	18 (3)	15 (4)
<b>Cardiac conduction disorders</b>	0 (0)	0 (0)	3 (5)	2 (5)	5 (2)	4 (3)	0 (0)	0 (0)	8 (1)	6 (2)
Atrioventricular block second degree	0 (0)	0 (0)	2 (3)	2 (5)	3 (1)	2 (1)	0 (0)	0 (0)	5 (1)	4 (1)
Atrioventricular block	0 (0)	0 (0)	1 (2)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (<1)
Atrioventricular block first degree	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (1)	0 (0)	0 (0)	1 (0)	1 (<1)
Sinoatrial block	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (1)	0 (0)	0 (0)	1 (0)	1 (<1)
<b>Supraventricular arrhythmias</b>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (3)	4 (2)	4 (1)	4 (1)
Supraventricular tachycardia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	2 (1)	2 (0)	2 (1)
Arrhythmia supraventricular	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	1 (0)	1 (<1)
Atrial Tachycardia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	1 (0)	1 (<1)
<b>Ventricular arrhythmias and cardiac arrest</b>	3 (3)	2 (8)	0 (0)	0 (0)	2 (1)	2 (1)	0 (0)	0 (0)	5 (1)	4 (1)
Ventricular tachycardia	3 (3)	2 (8)	0 (0)	0 (0)	1 (0)	1 (1)	0 (0)	0 (0)	4 (1)	3 (1)
Ventricular extrasystoles	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (1)	0 (0)	0 (0)	1 (0)	1 (<1)
<b>Rate and rhythm disorders NEC</b>	0 (0)	0 (0)	1 (2)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (<1)
Tachycardia	0 (0)	0 (0)	1 (2)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (<1)

Source: Statistical Table 6.1.7.2

HLGT = High Level Group Term; HLT = High Level Term; NEC = Not elsewhere classified; PT = Preferred Term; py = patient-years

<sup>a</sup> The adverse event counts are accompanied by normalized counts per 100 person years (/100 py).

<sup>b</sup> If a patient had more than one adverse event for a particular HLT/PT, he/she is counted only once for the HLT/PT.

<sup>c</sup> Patient percentages are based on the total number of patients treated with eliglustat for each column in the pooled studies: GZGD00304, GZGD02507, GZGD02607, and GZGD03109 (open-label Lead-in Period only).

Source: ISS, Table 1-18

**Table 4-Summary of Treatment-Emergent Adverse Events Leading to Permanent Study Drug Discontinuation and Study Withdrawal - Eliglustat Safety Set**

Patient ID	Sex/Age (yrs) <sup>a</sup>	Dose <sup>b</sup> (mg)	MedDRA System Organ Class <sup>c</sup> / Preferred Term	Time from 1 <sup>st</sup> Dose (days)	Event Duration (days)	Severity/SAE/ Outcome	Relationship to Study Drug	Other Action Taken
Phase 2 Study: GZGD00304								
GZGD 00304/ 0105	F/31	-- <sup>d</sup>	Musculoskeletal and connective tissue disorders/ Osteonecrosis	365	--	Moderate/No/ Not recovered	Not related	None
GZGD 00304/ 0202	F/56	100 BID	Cardiac disorders/ Ventricular tachycardia	1	1	Mild/No/ Recovered	Remote; unlikely	None
			Cardiac disorders/ Ventricular tachycardia	2	1	Mild/No/ Recovered	Remote; unlikely	None
GZGD 00304/ 0302	M/60	50 QD	Cardiac disorders/ Ventricular tachycardia	1	1	Mild/Yes/ Recovered	Possible	Hospitalization

Source: 2.7.4, table 22 (adapted)

Reviewer's comments:

The pooled Eliglustat Safety Set contained 393 patients, 26 patients from the Phase 2 study, 40 patients from ENGAGE, 157 patients from ENCORE, and 170 patients from EDGE. No sudden cardiac deaths, Torsade de pointes or clinically meaningful AV-block cases were reported.

*Subject GZGD00304/0302 was withdrawn from the study after the first dose of Eliglustat due to a ventricular tachycardia episode that required hospitalization and was considered by the investigator to be possibly related to Eliglustat. Three patients had non-sustained ventricular tachycardia episodes that were asymptomatic. Four patients reported 2<sup>nd</sup>-degree AV block that were asymptomatic and taken from unscheduled Holter monitoring.*

Thank you for requesting our input into the development of this product under NDA 205494. We welcome more discussion with you now and in the future. Please feel free to contact us via email at [cdcrpqt@fda.hhs.gov](mailto:cdcrpqt@fda.hhs.gov)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MONICA L FISZMAN  
02/28/2014

JIANG LIU  
02/28/2014

NORMAN L STOCKBRIDGE  
02/28/2014

# REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 205494

**Application Type:** New NDA

**Name of Drug/Dosage Form:** Cerdelga (eliglustat) /84mg hard capsules

**Applicant:** Genzyme

**Receipt Date:** September 20, 2013

**Goal Date:** May 20, 2013

## 1. Regulatory History and Applicant's Main Proposals

NME "Program" NDA with a Priority Review. Eliglustat is a substrate reduction therapy with a proposed indication of long-term treatment of adult patients with Gaucher disease type 1.

## 2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## 3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by December 16, 2013. The resubmitted PI will be used for further labeling review.

## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

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## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

**HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI**

## Selected Requirements of Prescribing Information

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:**

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

**Comment:**

- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

**Comment:** *There is no horizontal line separating the TOC from the FPI*

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

**Comment:**

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

**Comment:**

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required

## Selected Requirements of Prescribing Information

• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**Comment:**

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

**Comment:**

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

**Comment:**

#### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:**

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

**Comment:**

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

## Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

### Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

### Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

### Comment:

## Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

### Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

### Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

### Comment:

## Indications and Usage in Highlights

- N/A** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

### Comment:

## Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

### Comment:

## Contraindications in Highlights

**YES**

## Selected Requirements of Prescribing Information

21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

### Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
***Comment:***
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
***Comment:***
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
***Comment:***
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
***Comment:***
- NO** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
***Comment:*** The word "use" must be capitalized in the subsection heading, "8.4 Pediatric use" and "8.5 Geriatric use".
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
***Comment:***
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
***Comment:***

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:**

## Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

*Comment:*

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

*Comment:*

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

*Comment:*

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

*Comment:*

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

*Comment:*

#### PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

## Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

**WARNING: [SUBJECT OF WARNING]**

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

### DOSAGE AND ADMINISTRATION

- [text]
- [text]

### DOSAGE FORMS AND STRENGTHS

- [text]

### CONTRAINDICATIONS

- [text]
- [text]

### WARNINGS AND PRECAUTIONS

- [text]
- [text]

### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- [text]
- [text]

### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

#### 6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

#### 7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

#### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

#### 9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JESSICA M BENJAMIN  
12/02/2013

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 205494 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Cerdelga Established/Proper Name: eliglustat Dosage Form: hard capsules Strengths: 84mg		
Applicant: Genzyme Agent for Applicant (if applicable):		
Date of Application: 9/19/2013 Date of Receipt: 9/20/2013 Date clock started after UN:		
PDUFA Goal Date: 5/20/2014		Action Goal Date (if different):
Filing Date: 11/19/13		Date of Filing Meeting: 10/23/13
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): long-term treatment of adult patients with Gaucher disease type 1		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ):				
List referenced IND Number(s): 067589				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, 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.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>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 Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid  <input checked="" type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>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.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>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 is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>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)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>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 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

<b>Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>				
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  If yes, # years requested:  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If yes</b> , 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)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance? <sup>1</sup> <b>If not</b> , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 ( <i>NDAs/NDA efficacy supplements</i> ) or under 21 CFR 601.2 ( <i>BLAs/BLA efficacy supplements</i> ) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>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.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) 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...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>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)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b> Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>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 &amp; deferral requests, pediatric plans, and pediatric assessment studies must be</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>reviewed by PeRC prior to approval of the application/supplement.</i>				
<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If yes, specify consult(s) and date(s) sent: QT/IRT - 11/13/13; Carc stats – 10/22/13; CDRH – pending; Patient Labeling (MG) – 11/13/13</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> 2/5/2009 (clinical) and 5/26/2010 (CMC)	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 5/21/2013	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** October 23, 2013

**BLA/NDA/Supp #:** NDA 205494

**PROPRIETARY NAME:** Cerdelga

**ESTABLISHED/PROPER NAME:** eliglustat

**DOSAGE FORM/STRENGTH:** hard capsules/84mg

**APPLICANT:** Genzyme

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** long term treatment of adult patients with Gaucher disease type 1

**BACKGROUND:** NME “Program” NDA with a Priority Review. Eliglustat is a substrate reduction therapy with a proposed indication of long-term treatment of adult patients with Gaucher disease type 1.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jessica Benjamin	Y
	CPMS/TL:	Brian Strongin	Y
Cross-Discipline Team Leader (CDTL)	Jessica Lee/Lara Dimick		Y
Clinical	Reviewer:	Karyn Berry	Y
	TL:	Jessica Lee/Lara Dimick	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		

Clinical Pharmacology	Reviewer:	Elizabeth Shang/Sandhya Apparaju	Y
	TL:	Sue Chih Lee	Y
Biostatistics	Reviewer:	Behrang Vali	Y
	TL:	Freda Cooner	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Tamal Chakraborti/Sruthi King	Y
	TL:	Sushanta Chakder	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Yichun Sun/Hamid Shafiei/Tarun Mehta	Y
	TL:	Marie Kowblanski	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Lisa Khosla/Monica Calderon	Y
	TL:	Lubna Merchant	N
OSE/DRISK (REMS)	Reviewer:	George Neyarapally	Y
	TL:	Kendra Worthy	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:	Susan Leibenhaut	Y
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Clin Pharm (PKPD): Yuzheo Pan/Ping Zhao Pharmacogenetics: Sarah Dorff/Michael Pacanowski Pharmacometrics: Anshu Marathe/Nitin Mehrotra Biopharmaceuticals: Albert Chen/Tapash Ghosh QT/IRT: Kevin Krudys		
Other attendees	Rebecca Knight – ONDQA RPM Marie Walsh Andrew Mulberg, Julie Beitz		

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues:           <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p> </li> </ul>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable

<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>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</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason: not first in class/no significant safety or efficacy issues at this time
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• 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?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b> carc stats comments for 74-day letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no, was a complete EA submitted?</b></p> <p><b>If EA submitted, consulted to EA officer (OPS)?</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review</u></b></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Julie Beitz</p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): 12/12/2013</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review

ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	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.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• 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)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]
<input type="checkbox"/>	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.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JESSICA M BENJAMIN  
11/19/2013