CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205494Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205494 SUPPL # HFD # 180

Trade Name Cerdelga

Generic Name eliglustat

Applicant Name Genzyme

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Lara Dimick-Santos, MD
Title: Medical Team Leader
Date: 8/18/2014

Name of Office/Division Director signing form: Amy Egan, MD
Title: Deputy Director, ODE 3 (Acting)

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA M BENJAMIN
08/18/2014

AMY G EGAN
08/18/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 205494 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Cerdelga Established/Proper Name: eliglustat tartrate Dosage Form: capsules		Applicant: Genzyme Agent for Applicant (if applicable):
RPM: Jessica Benjamin		Division: DGIEP

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 8/20/2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Breakthrough Therapy designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other - Information Advisory
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Version: 5/14/2014

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval 8/19/14
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	11/21/13 11/21/14
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 12/2/13 DMEPA: ☐ None 7/29/14; 7/16/14; 3/6/14 DMPP/PLT (DRISK): ☐ None 6/3/14 OPDP: ☐ None 6/3/14 SEALD: ☒ None CSS: ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	11/19/13 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: orphan designation	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	8/13/14; 8/12/14; 8/7/14; 8/6/14; 7/29/14; 7/28/14; 7/16/14(2); 7/14/14; 6/20/14; 6/11/14; 6/6/14; 6/4/14; 5/14/14; 5/7/14; 4/22/14; 4/4/14; 3/19/14; 3/7/14; 2/21/14; 2/13/14; 2/12/14; 1/23/14; 1/21/14; 1/16/14; 1/10/14 (2); 1/8/14; 12/20/13; 12/9/13; 12/3/13; 11/27/13; 11/25/13; 11/18/13; 11/13/13; 9/23/13
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 5/21/13
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 5/26/10; 2/5/09
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A 1/9/14
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A 6/19/14
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 8/19/14
Division Director Summary Review *(indicate date for each review)*	☐ None 8/19/14
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 8/18/14
PMR/PMC Development Templates *(indicate total number)*	☐ None 3
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	8/15/14; 10/25/13
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Clinical review dated 8/15/14, pgs 26-28
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None 7/22/14; 7/14/14; 4/24/14
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None 8/19/14
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 5/15/14
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 7/22/14; 116/13
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 8/19/14; 6/16/14; 10/30/13
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review 4/28/14
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 5/5/14; 4/15/14; 10/15/13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc 4/14/14
❖ ECAC/CAC report/memo of meeting	☐ None 4/10/14 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 8/18/14; 8/5/14; 5/21/14; 5/19/14; 11/15/13; 11/13/13
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 1/2/14; 10/25/13
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None 5/23/14; 2/28/14
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	CMC review dated5/21/14, page 126
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: 8/5/14 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☐ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☐ Done

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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.

/s/

JESSICA M BENJAMIN
08/19/2014

From:	Benjamin, Jessica
To:	Sherwin.Sattarzadeh@genzyme.com
Cc:	Benjamin, Jessica
Subject:	Cerdelga labeling
Date:	Thursday, August 07, 2014 7:49:53 PM

Hi Sherwin,

As of May 1, 2014, the sponsor is responsible for performing an end-of-cycle Selective Requirements for Prescribing Information (SRPI) review for NDAs, BLAs, efficacy supplements and PLR conversions. The SRPI is an interactive checklist of 42 important format items from the current labeling regulations and guidances. As we are finishing our labeling negotiations, I wanted to point out a few resources recently added to the FDA website to help guide you thru this process. The following two SRPI videos have been posted on the FDA website at *PLR Requirements for Prescribing Information*:

- SRPI Review of Highlights
- SRPI Review of Table of Contents and Full Prescribing Information

Please ensure that the label you send to us on Monday conforms to these labeling requirements and guidances.

Let me know if you have any questions or need additional information.

Regards,

Jessica

Jessica M. Benjamin, MPH

Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products

Office of New Drugs III

Center for Drug Evaluation and Research

301-796-3924 *office*

301-796-9904 *fax*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA M BENJAMIN
08/13/2014

From:	Benjamin, Jessica
To:	Sherwin.Sattarzadeh@genzyme.com
Cc:	Benjamin, Jessica
Subject:	RE: NDA 205494: Cerdelga labeling comments
Date:	Wednesday, August 13, 2014 12:16:44 PM
Attachments:	Cerdelga MG 13AugFDA.docx Cerdelga PI 13AugFDA.doc

Hi Sherwin,

Attached please find our final revisions to the Cerdalga PI and Medication Guide. If you have any further comments to the label, please respond no later than Friday, August 15th.

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

From: Sherwin.Sattarzadeh@genzyme.com [mailto:Sherwin.Sattarzadeh@genzyme.com]
Sent: Monday, August 11, 2014 6:16 PM
To: Benjamin, Jessica
Subject: RE: NDA 205494: Cerdelga labeling comments

Hi Jessica,

Attached please find the updated Cerdelga USPI and Medication Guide. Genzyme has proposed revisions to the Mechanism of Action section of the USPI, in line with the discussion at the August 7th teleconference. We have removed the (b) (4) from Section 14 and focused Section 12.1 on the factual descriptions of the disease (in line with the VPRIV USPI) and the mechanistic activity of eliglustat on the systemic and skeletal manifestations of Gaucher disease. Please note that this version of the USPI complies with the SRPI formatting checklist. Also attached is the rationale document for the new ENCORE adverse reaction table in Section 6.1.

To ensure the expeditious completion of our label negotiations, Genzyme respectfully request that any further modifications required by the Agency be discussed in a brief teleconference later this week so we may finalize remaining issues in real-time. We are available any time this week.

Kind regards,

Sherwin

Sherwin Sattarzadeh, RAC
Director, Regulatory Affairs
Genzyme, a Sanofi Company
O: 617.768.4345
C: (b) (6)

From: Benjamin, Jessica [mailto:Jessica.Benjamin@fda.hhs.gov]
Sent: Wednesday, August 06, 2014 8:37 PM
To: Sattarzadeh, Sherwin GZ/US
Cc: Benjamin, Jessica
Subject: RE: NDA 205494: Cerdelga labeling comments

Hi Sherwin,

In preparation for our tcon, please see the attached PI and MG with our comments. I've also attached a document which should clarify the values from the PBPK analysis in Section 12.3.

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

From: Sherwin.Sattarzadeh@genzyme.com [mailto:Sherwin.Sattarzadeh@genzyme.com]
Sent: Wednesday, August 06, 2014 3:50 PM
To: Benjamin, Jessica
Subject: RE: NDA 205494: Cerdelga labeling comments

Hi Jessica,

Please use the call-in information below for tomorrow's tcon. In preparation for the discussion, will the Agency have a list of topics for resolution that can be shared with Genzyme in advance of the call?

Dial-in Number – (b) (4)
Passcode – (b) (4)

Thank you,

Sherwin

Sherwin Sattarzadeh, RAC
Director, Regulatory Affairs
Genzyme, a Sanofi Company
O: 617.768.4345
C: (b) (6)

From: Benjamin, Jessica [mailto:Jessica.Benjamin@fda.hhs.gov]
Sent: Monday, July 28, 2014 7:53 PM
To: Sattarzadeh, Sherwin GZ/US
Cc: Benjamin, Jessica
Subject: FW: NDA 205494: Cerdelga labeling comments

Sherwin,

We are available for a labeling tcon on Thursday, August 7th, from 12:15 to 1:00pm. Please let me know your availability and call-in information.

Thanks,
Jessica

From: Benjamin, Jessica
Sent: Monday, July 28, 2014 7:32 PM
To: Sherwin.Sattarzadeh@genzyme.com
Cc: Benjamin, Jessica
Subject: NDA 205494: Cerdelga labeling comments

Hi Sherwin,

Please see the attached Package Insert and Medication Guide with our comments and revisions for Cerdelga. We request a response by Friday, August 1st. I will send you our availability for a tcon shortly.

Let me know if you have any questions.

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*

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/s/

JESSICA M BENJAMIN
08/13/2014

From: Benjamin, Jessica
To: Sherwin.Sattarzadeh@genzyme.com
Cc: Benjamin, Jessica
Subject: RE: NDA 205494: Cerdelga labeling comments
Date: Wednesday, August 06, 2014 8:37:10 PM
Attachments: Cerdelga MG 06Aug.docx
Cerdelga PI 06Aug.doc
PBPK results shared with sponsor on 6August.doc

Hi Sherwin,

In preparation for our tcon, please see the attached PI and MG with our comments. I've also attached a document which should clarify the values from the PBPK analysis in Section 12.3.

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

From: Sherwin.Sattarzadeh@genzyme.com [mailto:Sherwin.Sattarzadeh@genzyme.com]
Sent: Wednesday, August 06, 2014 3:50 PM
To: Benjamin, Jessica
Subject: RE: NDA 205494: Cerdelga labeling comments

Hi Jessica,

Please use the call-in information below for tomorrow's tcon. In preparation for the discussion, will the Agency have a list of topics for resolution that can be shared with Genzyme in advance of the call?

Dial-in Number – (b) (4)
Passcode – (b) (4)

Thank you,

Sherwin

Sherwin Sattarzadeh, RAC

Director, Regulatory Affairs
Genzyme, a Sanofi Company
O: 617.768.4345
C: (b) (6)

From: Benjamin, Jessica [mailto:Jessica.Benjamin@fda.hhs.gov]
Sent: Monday, July 28, 2014 7:53 PM
To: Sattarzadeh, Sherwin GZ/US
Cc: Benjamin, Jessica
Subject: FW: NDA 205494: Cerdelga labeling comments

Sherwin,

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Thanks,
Jessica

From: Benjamin, Jessica
Sent: Monday, July 28, 2014 7:32 PM
To: Sherwin.Sattarzadeh@genzyme.com
Cc: Benjamin, Jessica
Subject: NDA 205494: Cerdelga labeling comments

Hi Sherwin,

Please see the attached Package Insert and Medication Guide with our comments and revisions for Cerdelga. We request a response by Friday, August 1st. I will send you our availability for a tcon shortly.

Let me know if you have any questions.

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
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301-796-9904 *fax*

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/s/

JESSICA M BENJAMIN
08/13/2014

From: Benjamin, Jessica
To: Sherwin.Sattarzadeh@genzyme.com
Cc: Benjamin, Jessica
Subject: RE: NDA 205494: Post Marketing Requirements
Date: Tuesday, July 29, 2014 12:16:40 PM

Hi Sherwin,

We accept your revised language for PMR 2 as well as the milestone dates for both PMRs listed below.

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

From: Sherwin.Sattarzadeh@genzyme.com [mailto:Sherwin.Sattarzadeh@genzyme.com]
Sent: Thursday, July 17, 2014 11:56 AM
To: Benjamin, Jessica
Subject: RE: NDA 205494: Post Marketing Requirements

Hi Jessica,

Below please find the requested dates as well as revisions to PMR 1.

PMR 1 Conduct a clinical study to evaluate the effect ~~s of various degrees~~ of hepatic impairment on eliglustat pharmacokinetics.

Final protocol submission:	June 2015
Study completion date:	January 2017
Final report submission:	July 2017

Genzyme's Response: We propose a revision to the text in PMR 1 so as to allow for future negotiations on the exact study design (see strikethrough text above). As discussed at the Late Cycle Meeting on June 19th, Genzyme seeks to exclude "healthy" (non-GD1) subjects with severe hepatic impairment from this PK study.

The main route of eliglustat metabolism is by CYP450 enzymes, predominantly CYP2D6 and to a lesser extent CYP3A, which are largely expressed in liver. Eliglustat also moderately inhibits CYP2D6, leading to higher than predicted dose-proportional eliglustat exposure levels. Therefore, patients

with hepatic impairment are expected to have higher eliglustat levels than patients without hepatic impairment. While it is unknown to what extent partial hepatic impairment will affect eliglustat levels, patients with severe hepatic impairment are expected to have very little CYP2D6 and CYP3A activity, which would be similar to administering eliglustat with both strong CYP2D6 and CYP3A inhibitors concomitantly; a drug-drug interaction scenario that is contraindicated per the CERDELGA USPI.

Liver failure is a very rare complication of GD1, which itself is an orphan disease. The number of patients with GD1 and liver failure of any cause is still expected to be extremely small, and patients with severe hepatic impairment would be better served by enzyme replacement therapy. Considering the remote likelihood in which a GD1 patient with severe hepatic impairment would use CERDELGA, Genzyme proposes to limit the degrees of hepatic impairment studied in the eliglustat PMR by excluding subjects with severe hepatic impairment.

Genzyme's proposal is to conduct this PMR study initially in "healthy" (non-GD1) subjects with moderate hepatic impairment, with provisions in the study protocol to enroll a cohort of subjects with mild hepatic impairment only if the results in subjects with moderate hepatic impairment show a substantial effect of reduced hepatic function on eliglustat PK compared to the control subjects. This "reduced design" would mimic the renal impairment study design in PMR 2.

PMR 2 Conduct a study to evaluate the effect of renal impairment on eliglustat pharmacokinetics. A reduced design may be used.

Final protocol submission:	June 2015
Study completion date:	January 2017
Final report submission	July 2017

Genzyme's Response: We agree with the text in PMR 2.

Kind regards,

Sherwin

Sherwin Sattarzadeh, RAC
Director, Regulatory Affairs
Genzyme, a Sanofi Company
O: 617.768.4345
C: (b) (6)

From: Benjamin, Jessica [mailto:Jessica.Benjamin@fda.hhs.gov]
Sent: Monday, July 14, 2014 9:06 AM
To: Sattarzadeh, Sherwin GZ/US
Cc: Benjamin, Jessica
Subject: NDA 205494: Post Marketing Requirements

Good morning Sherwin,

Please refer to NDA 205494 for Cerdelga. As a follow-up to our Late Cycle Meeting, we have the following Post Marketing Requirements (PMRs) for your review. Please insert the appropriate dates and let me know if you have any revisions to the language below. We also plan to have a Post Marketing Commitment (PMC) which I will send you as soon as the language has been cleared.

PMR 1 Conduct a clinical study to evaluate the effects of various degrees of hepatic impairment on eliglustat pharmacokinetics.

Final protocol submission *[please insert date]*
Study completion date *[please insert date]*
Final report submission *[please insert date]*

PMR 2 Conduct a study to evaluate the effect of renal impairment on eliglustat pharmacokinetics. A reduced design may be used.

Final protocol submission *[please insert date]*
Study completion date *[please insert date]*
Final report submission *[please insert date]*

We request a response to this email no later than Thursday, July 17th. Let me know if you have any questions.

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

From: Benjamin, Jessica
To: Sherwin.Sattarzadeh@genzyme.com
Cc: Benjamin, Jessica
Subject: RE: NDA 205494: Post Marketing Commitment
Date: Tuesday, July 29, 2014 2:13:54 PM

Sherwin,

We reviewed your response below and propose the following revised PMC 1:

Develop a 21.5-mg and/or 43-mg strength formulation for dosing in CYP2D6 Poor Metabolizers (PMs) and to accommodate dosage adjustment in drug-drug interaction scenarios.

We accept your proposed milestone date for final report submission.

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

From: Sherwin.Sattarzadeh@genzyme.com [mailto:Sherwin.Sattarzadeh@genzyme.com]
Sent: Monday, July 21, 2014 3:00 PM
To: Benjamin, Jessica
Subject: RE: NDA 205494: Post Marketing Commitment

Hi Jessica,

Below please find the requested dates as well as revisions to PMC 1. Can you please also provide an estimate as to when the Agency will provide feedback on the proposed labeling text submitted on June 26th (Sequence 0033)?

PMC 1 Develop 25-mg and/or 50-mg dosage strength(s) to accommodate situations requiring further dosage adjustments. (b) (4)

Final protocol submission *[please insert date]*
~~Study completion date *[please insert date]*~~
Final report submission: *December 2018*

Genzyme's Response: We propose revisions to the PMC 1 text based on the rationale provided below.

- [redacted] (b) (4) .
- As Poor Metabolizers are part of the indicated population at a recommended dose of 100mg QD, the Agency's proposed wording may create confusion among patients and prescribers. Genzyme's proposed revisions more generally cover situations/scenarios that may require further dose adjustments (e.g. drug-drug interactions, renal impairment, hepatic impairment, metabolizer status, etc.).
- Genzyme proposes to modify the conditional statement regarding the bioavailability study and to remove the associated Final Protocol and Study Completion dates from the PMC in the event that a clinical study is not required. If further clinical investigations are needed, Genzyme commits to the timely submission of applicable protocols and study completion to still allow fulfillment of the commitment by December 2018. Furthermore, the resulting PMC structure more closely mimics Quality/Manufacturing PMCs reflected in Agency NDA/BLA approval letters.
- The Final Report Submission date takes into consideration the potential need for new formulation development and associated relative bioavailability evaluations.

Kind regards,

Sherwin

Sherwin Sattarzadeh, RAC
Director, Regulatory Affairs
Genzyme, a Sanofi Company
O: 617.768.4345
C: [redacted] (b) (6)

From: Benjamin, Jessica [mailto:Jessica.Benjamin@fda.hhs.gov]
Sent: Wednesday, July 16, 2014 9:52 AM
To: Sattarzadeh, Sherwin GZ/US
Cc: Benjamin, Jessica
Subject: NDA 205494: Post Marketing Commitment

Sherwin,

Please refer to NDA 205494 for Cerdelga. As a follow-up to our Late Cycle Meeting, we have the following Post Marketing Commitment (PMC) for your review. Please insert the appropriate dates and let me know if you have any revisions to the language below.

PMC 1 Develop a 25-mg and/or 50-mg strength formulation for dosing in Poor Metabolizers (PMs) and to accommodate dosage adjustment in drug-drug interaction scenarios. This should include a relative bioavailability (BA) study comparing to the current strength, if the formulation for the new strength is not proportionally similar.

Final protocol submission *[please insert date]*
Study completion date *[please insert date]*
Final report submission *[please insert date]*

We request a response to this email no later than Monday, July 21st. Let me know if you have any questions.

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

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/s/

JESSICA M BENJAMIN
07/29/2014

From:	Benjamin, Jessica
To:	Sherwin.Sattarzadeh@genzyme.com
Cc:	Benjamin, Jessica
Subject:	NDA 205494: Cerdelga labeling comments
Date:	Monday, July 28, 2014 7:31:48 PM
Attachments:	CerdelgaPI 28JULY.doc DMPP revised_eliglustat MG 21 JUL 2014.docx

Hi Sherwin,

Please see the attached Package Insert and Medication Guide with our comments and revisions for Cerdelga. We request a response by Friday, August 1st. I will send you our availability for a tcon shortly.

Let me know if you have any questions.

Regards,

Jessica

Jessica M. Benjamin, MPH

Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products

Office of New Drugs III

Center for Drug Evaluation and Research

301-796-3924 *office*

301-796-9904 *fax*

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JESSICA M BENJAMIN
07/28/2014

From:	Benjamin, Jessica
To:	Sherwin.Sattarzadeh@genzyme.com
Cc:	Benjamin, Jessica
Subject:	NDA 205494: Post Marketing Commitment
Date:	Wednesday, July 16, 2014 9:51:51 AM

Sherwin,

Please refer to NDA 205494 for Cerdelga. As a follow-up to our Late Cycle Meeting, we have the following Post Marketing Commitment (PMC) for your review. Please insert the appropriate dates and let me know if you have any revisions to the language below.

PMC 1 Develop a 25-mg and/or 50-mg strength formulation for dosing in Poor Metabolizers (PMs) and to accommodate dosage adjustment in drug-drug interaction scenarios. This should include a relative bioavailability (BA) study comparing to the current strength, if the formulation for the new strength is not proportionally similar.

Final protocol submission *[please insert date]*

Study completion date *[please insert date]*

Final report submission *[please insert date]*

We request a response to this email no later than Monday, July 21st. Let me know if you have any questions.

Regards,

Jessica

Jessica M. Benjamin, MPH

Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products

Office of New Drugs III

Center for Drug Evaluation and Research

301-796-3924 *office*

301-796-9904 *fax*

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/s/

JESSICA M BENJAMIN
07/16/2014

From:	Benjamin, Jessica
To:	Sherwin.Sattarzadeh@genzyme.com
Cc:	Benjamin, Jessica
Subject:	NDA 205494: Carton label changes
Date:	Wednesday, July 16, 2014 9:40:14 AM

Sherwin,

Please refer to NDA 205494 for Cerdelga. As a result of our ongoing review of this application, we have the following requests regarding the carton label:

- **Modify the storage condition on the inner and outer carton labels. The storage condition should read as: Store at 20–25°C (68–77°F); excursions permitted to 15–30°C (59–86°F).**

- **For strength expression, add "*" to "84 mg" and it should read as "84 mg*" on the inner and outer carton labels. Add the following statement to the inner and outer carton labels under the dosage strength:**

"*Each capsule contains 84 mg of eliglustat which is equivalent to 100 mg of eliglustat tartrate"

Please let me know if you have any questions.

Regards,

Jessica

Jessica M. Benjamin, MPH

Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products

Office of New Drugs III

Center for Drug Evaluation and Research

301-796-3924 *office*

301-796-9904 *fax*

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/s/

JESSICA M BENJAMIN
07/16/2014

From:	Benjamin, Jessica
To:	Sherwin.Sattarzadeh@genzyme.com
Cc:	Benjamin, Jessica
Subject:	NDA 205494: Post Marketing Requirements
Date:	Monday, July 14, 2014 9:06:23 AM

Good morning Sherwin,

Please refer to NDA 205494 for Cerdelga. As a follow-up to our Late Cycle Meeting, we have the following Post Marketing Requirements (PMRs) for your review. Please insert the appropriate dates and let me know if you have any revisions to the language below. We also plan to have a Post Marketing Commitment (PMC) which I will send you as soon as the language has been cleared.

PMR 1 Conduct a clinical study to evaluate the effects of various degrees of hepatic impairment on eliglustat pharmacokinetics.

Final protocol submission *[please insert date]*

Study completion date *[please insert date]*

Final report submission *[please insert date]*

PMR 2 Conduct a study to evaluate the effect of renal impairment on eliglustat pharmacokinetics. A reduced design may be used.

Final protocol submission *[please insert date]*

Study completion date *[please insert date]*

Final report submission *[please insert date]*

We request a response to this email no later than Thursday, July 17th. Let me know if you have any questions.

Regards,

Jessica

Jessica M. Benjamin, MPH

Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products

Office of New Drugs III

Center for Drug Evaluation and Research

301-796-3924 *office*

301-796-9904 *fax*

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/s/

JESSICA M BENJAMIN
07/14/2014

From:	Benjamin, Jessica
To:	Sherwin.Sattarzadeh@genzyme.com
Cc:	Benjamin, Jessica
Subject:	NDA 205494: Request for Information (clin pharm)
Date:	Friday, June 20, 2014 3:26:06 PM

Hi Sherwin,

Please refer to NDA 205494 for Cerdelga (eliglustat). At the Late Cycle Meeting held on June 19, 2014, you indicated that the CYP2D6 phenotype for several subjects in various studies had been reclassified after the initial submission of the NDA. We request that you provide the following information:

1. Provide the reason for change in phenotype. Indicate whether there was a change in genotype. If so, provide the rationale to change the genotype. If a new testing laboratory was used, provide the information on this new lab and the rationale for adding this lab. If there was no change in genotype, explain why a change in phenotype was necessary.

2. Provide a table showing the study IDs for the affected studies, the subject IDs within each study that had a change in phenotype, the specific changes in lab (from X1 to X2), genotype (if applicable) and phenotype (from Y1 to Y2).

3. Provide corrected PK parameter datasets for the affected studies. It is preferred that you add a column to the original dataset to accommodate the new phenotype. Additionally, provide summary descriptive statistics of the PK parameters by CYP2D6 phenotype for each affected study and describe the impact of the change on the mean and %CV of PK parameters.

4. Provide a justification on having a common set of dosing recommendations for CYP2D6 EMs and IMs in various DDI scenarios. If the justification involves simulations, provide the modeling and simulation results as well.

For data files, submit as SAS transport files (.xpt) with corresponding data definition files. We request a response within 3 business days.

Please let me know if you have any questions.

Regards,

Jessica

Jessica M. Benjamin, MPH

Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products

Office of New Drugs III

Center for Drug Evaluation and Research

301-796-3924 *office*

301-796-9904 *fax*

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/s/

JESSICA M BENJAMIN
06/20/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205494

LABELING PMR/PMC DISCUSSION COMMENTS

Genzyme Corporation
Attention: Sherwin Sattarzadeh
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Sattarzadeh:

Please refer to your New Drug Application (NDA) dated September 20, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cerdelga (eliglustat).

We also refer to our January 10, 2014, letter in which we notified you of our target date of June 30, 2014 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

On December 20, 2013, we received your December 20, 2013 proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by June 18, 2014. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

These revisions have been reviewed and cleared to the level of Cross Discipline Team Leader.

If you have any questions, call me at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE: Package Insert and Medication Guide

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/s/

JESSICA M BENJAMIN
06/11/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205494

INFORMATION REQUEST

Genzyme Corporation
Attention: Sherwin Sattarzadeh
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Sattarzadeh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cerdelga (eliglustat).

We also refer to your NDA dated September 20, 2013.

We are reviewing the carton and container labels of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Modify all proposed carton (inner and outer) labeling with the following changes:
    - As currently presented, the dosage form 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.
    - 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.
    - Delete the sections of (b) (4)
    - Delete the statement: (b) (4)
    - Put a bracket around "eliglustat".
2. Modify the proposed outer carton labeling with the following changes:
    - 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.

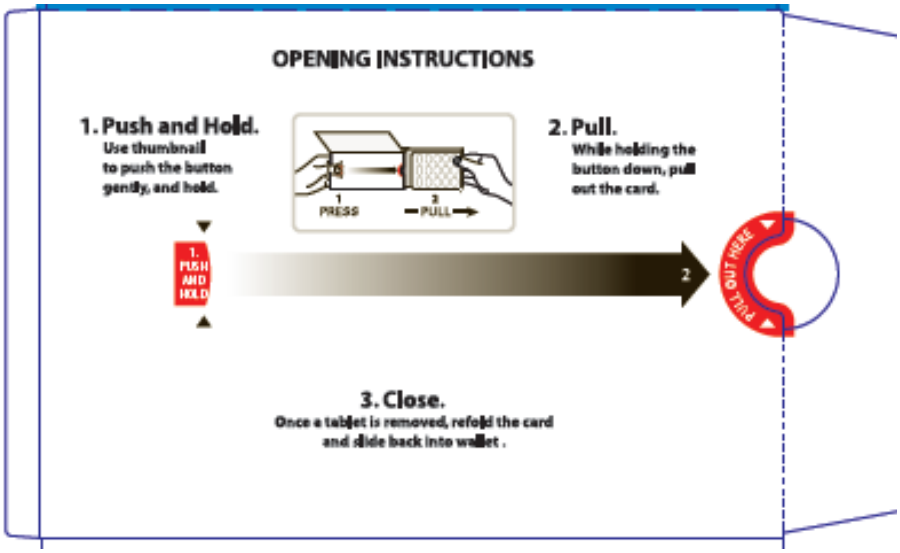
- Add the statement, "Dispense the enclosed Medication Guide to each patient", to the principal display panel underneath the strength.

3. Modify the proposed inner sleeve carton labeling with the following changes:
   - 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.
   - Place the NDC code in the upper right hand corner.
   - Put the bar code on the inner carton.
   - 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. Modify the proposed wallet pack with the following changes:
   - Place the proprietary name, established name, dosage form, strength, "Rx only", lot number, expiration date, bar code, NDC number and name of manufacturer/distributor 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.

If you have any questions, call Jessica Benjamin, Senior Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
06/04/2014

From:	Benjamin, Jessica
To:	Sherwin.Sattarzadeh@genzyme.com
Cc:	Benjamin, Jessica
Subject:	NDA 205494 information request
Date:	Wednesday, May 14, 2014 4:36:56 PM

Hi Sherwin,

Please refer to NDA 205494 for eliglustat tartrate. As a result of our on-going review of this application, we have the following information requests:

1. In your correspondence dated April 29, 2014, you stated that you have additional PK data in 4 poor metabolizers from the EDGE study. Provide a list of each individual's the dosing regimen, steady state AUC0-tau, steady state Cmax, steady state Ctrough for these poor metabolizers and include the list of adverse events observed in these patients. These data need to be submitted in .xpt format. Please submit within 2 business days.

2. Figure 11 and Figure 12 from your PK/PD report (poh0395) shows the observed Cmax and observed AUC0-tau by dose and CYP2D6 phenotype status. Update the graphs to include the observed data from Phase 2 study, ENGAGE trial, and 4 poor metabolizers from the EDGE study. Please note that we are requesting only the observed PK data at the administered dose. Do not stratify the data by responder status in these graphs. Include the dataset and code used for generating the updated graphs. Please submit within 2 business days.

3. For patients with AUC0-tau >400 ng h/ml in the EDGE study, provide their dosing regimen, steady state AUC0-tau, steady state Cmax, steady state Ctrough and include the list of adverse events observed in these patients. These data need to be submitted in .xpt format. Please submit within 3 business days.

Feel free to contact me with any questions.

Regards,

Jessica

Jessica M. Benjamin, MPH

Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products

Office of New Drugs III

Center for Drug Evaluation and Research

301-796-3924 *office*

301-796-9904 *fax*

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/s/

JESSICA M BENJAMIN
05/14/2014

Tran-Zwanetz, Catherine

From: Sherwin.Sattarzadeh@genzyme.com
Sent: Tuesday, May 06, 2014 5:04 PM
To: Tran-Zwanetz, Catherine
Cc: Benjamin, Jessica
Subject: RE: NDA 205494 CMC IR 2

Hi Cathy,

We will reply by May 9th.

Thank you,

Sherwin

Sherwin Sattarzadeh, RAC
Associate Director, Regulatory Affairs
Genzyme, a Sanofi Company
O: 617.768.4345
C: (b) (6)

From: Tran-Zwanetz, Catherine [mailto:Catherine.TranZwanetz@fda.hhs.gov]
Sent: Tuesday, May 06, 2014 4:14 PM
To: Sattarzadeh, Sherwin GZ/US
Cc: Benjamin, Jessica
Subject: NDA 205494 CMC IR 2

Hello Mr. Sattarzadeh,

Please refer to NDA 205494 submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act. We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information request.

1) Update the drug product specification to reflect the change of removing (b) (4) in the amendment dated December 20, 2013.
2) Could you please provide an update on our previous information request: **Since (b) (4) (b) (4) is used in the synthesis of the drug substance, include (b) (4) in your (b) (4) (b) (4) of the drug substance.**

Genzyme Response: In order to address FDA's concerns, work is underway to include (b) (4) in the (b) (4) Once the validation exercise is completed, we will gather the appropriate data on previously manufactured DS batches and propose a release limit for (b) (4)

Of note, (b) (4) would be detected in eliglustat tartrate DS along with other (b) (4) (b) (4) (b) (4)

We request a prompt written response in order to continue our evaluation of your NDA. Please reply by Friday May 9, 2014.

Thanks!
Cathy

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/s/

CATHERINE A TRAN-ZWANETZ
05/07/2014

From:	Benjamin, Jessica
To:	Sherwin.Sattarzadeh@genzyme.com
Cc:	Benjamin, Jessica
Subject:	NDA 205494: Information Request
Date:	Tuesday, April 22, 2014 12:31:39 PM

Hi Sherwin,

Please refer to NDA 205494 for eliglustat. As a result of our on-going review of this application, we have the following information request:

1. Provide the location or resubmit the in-study bioanalytical report for eliglustat plasma concentrations measured in Study GZGD01907. The hyperlink provided in the clinical study report linked to the validation report (b) (4) 141364 and not to the in-study bioanalytical report.

2. Provide the location or resubmit the in-study bioanalytical report for eliglustat and its metabolite plasma concentrations measured in Study GZGD02407. We are unable to locate the report.

3. Provide the location or resubmit the in-study bioanalytical report for eliglustat plasma concentrations measured in the Phase 3 ENCORE trial. We were unable to locate the report in Appendix 16.1.9.

We request a response to this email no later than April 28, 2014. Please let me know if you have any questions.

Regards,

Jessica

Jessica M. Benjamin, MPH

Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products

Office of New Drugs III

Center for Drug Evaluation and Research

301-796-3924 *office*

301-796-9904 *fax*

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/s/

JESSICA M BENJAMIN
04/22/2014

Executive CAC
Date of Meeting: April 8, 2014

Committee: Abigail Jacobs, Ph.D., OND-IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Tim McGovern, Ph.D., OND IO, Alternate Member
Sushanta Chakder, Ph.D. , Supervisor
Sruthi Tallapragada King, Ph.D., Presenting Reviewer

Author of Draft: Sruthi Tallapragada King, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 205494
Drug Name: Eliglustat
Sponsor: Genzyme Corporation, Cambridge MA

Background:

Gaucher Disease is a rare lysosomal storage disorder resulting from a deficiency of the enzyme glucocerebrocidase, which is the rate-limiting enzyme in the hydrolysis of glucosylceramide (GL-1) to glucose and ceramide. The Applicant is seeking marketing approval of eliglustat tartrate as a substrate reduction therapy (SRT) for adult patients with type 1 Gaucher disease who are CYP2D6 Intermediate and Extensive Metabolizers. Eliglustat tartrate was shown to be a potent inhibitor of GL-1 synthesis in vitro and in vivo. The goal of treatment with this SRT is to reduce GL-1 accumulation in multiple organs, thereby alleviating the clinical manifestations of Gaucher disease. The applicant conducted 2-year carcinogenicity studies in CD-1 mice and Sprague-Dawley rats with eliglustat tartrate to assess its carcinogenic potential.

Mouse Carcinogenicity Study

In the 2-year carcinogenicity study in CD-1 mice (60/sex/dose), eliglustat tartrate was administered to mice (60/sex/dose) at 10, 25, and 75 mg/kg/day, by dietary admixture for 105/106 weeks. Control animals (2 groups of 60/sex each) were fed the powdered, maintenance diet. The high dose used in the mouse carcinogenicity study was based on the MTD derived from a 13-week dietary toxicity study in mice, and the protocol was based on previous concurrence with the CDER Exec CAC. No neoplasms occurred at statistically significant increased incidences by CDER criteria.

Rat Carcinogenicity Study

In the 2-year rat carcinogenicity study, eliglustat tartrate was administered by oral gavage to SD rats (50/sex/dose) at 10, 25, and 75 mg/kg/day in males for 105 weeks and at 5, 15, and 50 mg/kg/day in females for 103 weeks. Two groups of 50 rats/sex were assigned as Controls and received the vehicle (drinking water, treated by reverse osmosis) via oral gavage. The dose levels for the the 2-year rat carcinogenicity study were based on the MTD in males and AUC in females, and the protocol was based on previous concurrence with the CDER Exec CAC. No neoplasms occurred at statistically significant increased incidences by CDER criteria.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol.

- The Committee concurred that there were no drug-related neoplastic findings in male and female mice at any of the doses tested.

Rat:

- The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol.

- The Committee concurred that there were no drug-related neoplasms in in male and female rats at any of the doses tested.

Abigail Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\

Division of Gastroenterology and Inborn Error Products/Division File, [DGIEP]
Sushanta Chakder, Ph.D./Supervisory Pharmacologist, [DGIEP]
Sruthi Tallapragada King, Ph.D./Reviewer, [DGIEP]
Jessica Benjamin, MPH/RPM, [DGIEP]
/ASeifried, OND-IO

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/s/

ADELE S SEIFRIED
04/10/2014

ABIGAIL C JACOBS
04/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205494

GENERAL ADVICE

Genzyme Corporation
Attention: Sherwin Sattarzadeh
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Sattarzadeh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for eliglustat tartrate.

We also refer to your February 25, 2014, submission, containing a background package relating to dosing regimens in CYP2D6 intermediate, extensive, poor, (b) (4) metabolizer patients.

We have reviewed the referenced material and have the following comments:

1. With respect to dosing in extensive metabolizers, we agree with your assessment that in ENGAGE and Phase 2 trials, treatment naïve patients that had trough concentrations <5 ng/ml showed clinically meaningful response. However, trends for increase in response with increasing exposure is observed in both ENGAGE and Phase 2 studies. Thus, we are still evaluating and having internal discussions about dose optimization in this population.
2. With respect to dosing in poor metabolizers (PMs), with the current data (20 subjects in Phase 1, Phase 2 and Phase 3 studies combined) and the PBPK model, we believe that recommendations for dosing in PMs can be provided.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, M.D., FAAP, CPI
Deputy Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ANDREW E MULBERG
04/04/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205494 **INFORMATION REQUEST**

Genzyme Corporation
Attention: Sherwin Sattarzadeh
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Sattarzadeh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for eliglustat tartrate.

We are reviewing the clinical pharmacology section of your submission and have the following comments and information request. We request a written response by March 24, 2014, in order to continue our evaluation of your NDA.

Please use your PBPK models to simulate eliglustat plasma PK at steady state in the following scenarios:

In CYP2D6 extensive metabolizers
a. 100 mg twice daily (b.i.d) co-administered with paroxetine
b. 100 mg b.i.d co-administered with ketoconazole
c. 100 mg once daily (q.d.) co-administered with ketoconazole
d. 100 mg b.i.d. co-administered with paroxetine and ketoconazole
e. 100 mg q.d. co-administered with paroxetine and ketoconazole
f. 100 mg q.d. co-administered with fluconazole
g. 100 mg q.d. co-administered with terbinafine
h. 100 mg q.d. co-administered with terbinafine and fluconazole

In CYP2D6 intermediate metabolizers
a. 100 mg twice daily (b.i.d.) co-administered with paroxetine
b. 100 mg b.i.d. co-administered with ketoconazole
c. 100 mg q.d. co-administered with ketoconazole
d. 100 mg b.i.d. co-administered with paroxetine and ketoconazole
e. 100 mg q.d. co-administered with paroxetine and ketoconazole
f. 100 mg q.d. co-administered with fluconazole
g. 100 mg q.d. co-administered with terbinafine
h. 100 mg q.d. co-administered with terbinafine and fluconazole

In CYP2D6 poor metabolizers
a. 100 mg b.i.d. co-administered with ketoconazole
b. 100 mg q.d. co-administered with ketoconazole

In CYP2D6 ultra rapid metabolizers
a. 100 mg b.i.d. co-administered with quinidine
b. 200 mg b.i.d. co-administered with quinidine
c. 100 mg b.i.d. co-administered with ketoconazole
d. 200 mg b.i.d. co-administered with ketoconazole

All simulations should be conducted in SimCYP V11.1, as described in your clinical pharmacology information amendments submitted on Dec 12, 2013 and Jan 16, 2014. You can use the simulation design presented in these two amendments. For situations of co-administration of ketoconazole and co-administration of combined paroxetine and ketoconazole, simulation designs in study sim0105 can be used.

Please summarize simulated population mean eliglustat exposure values (AUC_0-last, Cmax, and Cmin) for these scenarios, and calculate exposure ratios using simulation results of 100 mg BID in CYP2D6 extensive metabolizers alone as reference.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
03/19/2014

Tran-Zwanetz, Catherine

From: Sherwin.Sattarzadeh@genzyme.com
Sent: Friday, March 07, 2014 10:05 AM
To: Tran-Zwanetz, Catherine
Cc: Benjamin, Jessica
Subject: RE: NDA 205494 CMC IR

Hi Cathy,

We are in receipt of this IR and will submit a response by Friday, March 14th.

Kind regards,

Sherwin

Sherwin Sattarzadeh, RAC
Associate Director, Regulatory Affairs
Genzyme, a Sanofi Company
O: 617.768.4345
C: (b) (6)

From: Tran-Zwanetz, Catherine [mailto:Catherine.TranZwanetz@fda.hhs.gov]
Sent: Tuesday, March 04, 2014 2:54 PM
To: Sattarzadeh, Sherwin GZ/US; Haque-Ahmed, Rumana GZ/US; Alexander, Kate GZ/US
Cc: Benjamin, Jessica
Subject: NDA 205494 CMC IR

Dear Mr. Sattarzadeh,

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- To justify the proposed (b) (4) holding time, please provide stability data for the product that was packaged from bulk capsules that had a (b) (4) holding time. If such supportive stability data are not available, the holding time should be set for (b) (4)

- During the teleconference on December 5, 2013, the agency requested that Genzyme make the following changes to the in-process specifications:

1) (b) (4) the acceptance criterion for the weight of the dispensed drug substance from (b) (4)% to (b) (4)%.
2) (b) (4) the acceptance criterion for the capsule fill-weight from (b) (4)% to (b) (4)%.

Please submit an updated master batch record reflecting all changes that have been made to the in-process specifications.

Please reply by March 15, 2014.

Thanks,

Cathy Tran-Zwanetz
Regulatory Project Manager
(301) 796-3877

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/s/

CATHERINE A TRAN-ZWANETZ
03/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205494 **INFORMATION REQUEST**

Genzyme Corporation
Attention: Sherwin Sattarzadeh
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Sattarzadeh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for eliglustat tartrate.

We are reviewing the clinical section of your submission and have the following comments and information request. We request a written response by March 7, 2014, in order to continue our evaluation of your NDA.

1. Clarify whether bone mineral density interpretation occurred at the local radiologist (as recorded in the dataset) or central radiologist for study GZGD00304.

2. Explain the terms used in the study reports "Lumbar Spine", "Total Lumbar Spine" and "Total Spine". These terms appear to be used interchangeably in reporting BMD data. Define the terms and any differences between the groups.

3. Provide documentation of any central calibration of DXA scanners used in these studies.

4. In GZGD00304, there are 22 patients with baseline and Week 52 lumbar spine BMD data (g/cm2) recorded in study 0304 dataset ADXS. Study report GZGD00304 body Page 99 states "Excluded from the BMD analyses were 2 patients (0102 and 0103) who were assessed with different scanner types at Baseline and follow-up, and a patient (0111) with local bone abnormalities that precluded DXA measurements (Listing 16.2.6.10). Also excluded, as previously described in Section 9.5, was patient 0205, who was re-instated on bisphosphonate therapy." Based on this information, it would appear that 18 subjects should be included in the Week 52 lumbar spine BMD analyses. Clarify which subjects (n=20) were included in the analyses presented on page 759 of Study report GZGD00304 body, Table 14.2.2.6.3.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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BRIAN K STRONGIN
02/21/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205494 **INFORMATION REQUEST**

Genzyme Corporation
Attention: Sherwin Sattarzadeh
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Sattarzadeh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for eliglustat tartrate.

We are reviewing the clinical pharmacology section of your submission and have the following comments and information request. We request a written response by February 21, 2014, in order to continue our evaluation of your NDA.

We noted that the *in vitro* study DMPK11-R015 (Genz-99067 Human Cytochrome P450 Reaction Phenotyping Studies) suggested a potential involvement of (b) (4) in the metabolic clearance of eliglustat. This study suggested that the relative contributions of CYP2D6, (b) (4) and CYP3A4 to the metabolism of Genz-99067 in HLM were approximately 54%, (b) (4)% and 15% at 0.01 µM, and 54%, (b) (4)% and 30% at 0.05 µM, respectively.

A subsequent *in vitro* study DMPK08-R035 using higher concentrations of the drug (Human CYP450 reaction phenotyping of Genz-99067 using recombinant CYP450s, CYP450 isozyme selective chemical inhibitors and CYP450 isozyme activity correlation analysis in liver microsomes), did not suggest (b) (4) involvement. The study concluded relative contributions of CYP2D6 and CYP3A4 to the NADPH-dependent clearance of Genz-99067 as approximately 60% and 38% at 0.100 µM, 48% and 52% at 1.00 µM 99067, and 35% and 50% at 10.0 µM respectively.

Given the findings from these studies, particularly study DMPK11-R015, clarify the significance of (b) (4) mediated metabolism for eliglustat clearance at clinically relevant doses/ concentrations.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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BRIAN K STRONGIN
02/13/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205494 **INFORMATION REQUEST**

Genzyme Corporation
Attention: Sherwin Sattarzadeh
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Sattarzadeh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for eliglustat tartrate.

We are reviewing the clinical pharmacology section of your submission and have the following comments and information requests. We request a written response by February 18, 2014, in order to continue our evaluation of your NDA.

1. It appears that the format of DATE field (DAT2) in datasetd.xpt is incorrect. Please confirm that you have submitted the correct dataset and control stream for the final and base model for objective 2 and objective 1. If not, submit the correct dataset and control streams.

2. Provide the additional diagnostic plots/information from your final population PK model (objective 2) within 3 business days. If these are already provided in the submission, direct us to the correct sections and page numbers in your report.

    a. Observed versus population predicted and observed versus individual predicted goodness of fit plots by CYP2D6 phenotype status for occasion 1 and occasion 2.

    b. Observed versus population predicted and observed versus individual predicted goodness of fit plots by study. We are specifically interested to see the goodness of fit plots for all the drug-drug interaction studies that were included in pop PK model. The data for various CYP2D6 patients should be presented in different colors in the diagnostic plots.

    c. Provide the predicted AUC and Cmax from the model in subjects when eliglustat is administered alone versus when administered with a) paroxetine, b) ketoconazole and c) rifampin. How do the model predictions compare with the NCA results from the dedicated studies?

d. Your eta plot for bioavailability (Figure 125: Effect of study, CYP2D6 and Race on F –Objective 2) from the final model shows significant deviation from 0 for poor metabolizers. The reason for such a large deviation is unclear when PM status is included as a covariate in your model.

e. Individual plots of observed, population predicted and individual predicted concentration versus time by CYP2D6 status.

f. Provide information regarding the decrease in inter-individual variability on F after inclusion of CYP2D6 status as covariate on F.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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BRIAN K STRONGIN
02/12/2014

From:	Benjamin, Jessica
To:	Sherwin.Sattarzadeh@genzyme.com
Cc:	Benjamin, Jessica
Subject:	NDA 205494 - sample carton/container request
Date:	Thursday, January 23, 2014 11:31:13 AM

Hi Sherwin,

Please refer to NDA 205494 for eliglustat. To continue our review of this application, we are requesting an actual sample of the carton (outer and inner) as well as the blister (wallet) pack. Please send these to my attention at the following address:

Jessica Benjamin
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 5236
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

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/s/

JESSICA M BENJAMIN
01/23/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205494

MID-CYCLE COMMUNICATION

Genzyme Corporation
Attention: Sherwin Sattarzadeh
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Sattarzadeh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for eliglustat tartrate.

We also refer to the teleconference between representatives of your firm and the FDA on January 9, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: January 9, 2014 from 3:00 PM to 4:00 PM EST

Application Number: NDA 205494
Product Name: eliglustat
Indication: long-term treatment of adult patients with Gaucher disease type 1
Applicant Name: Genzyme Corporation

Meeting Chair: Lara Dimick, MD
Meeting Recorder: Jessica M. Benjamin, MPH

FDA ATTENDEES
Julie Beitz, MD, Director, ODE III
Amy Egan, MD, Deputy Director, ODE III
Andrew Mulberg, MD, Deputy Director, DGIEP
Lara Dimick, MD, Acting Clinical Team Leader, DGIEP
Karyn Berry, MD, Medical Reviewer, DGIEP
John Stinson, MD, Medical Reviewer, DBRUP
Elizabeth Shang, PhD, Clinical Pharmacology Reviewer
Sandhya Apparaju, PhD, Clinical Pharmacology Reviewer
Ping Zhao, PKPB Team Leader
Yuzhuo Pan, PKPB Reviewer
Sruthi King, PhD, Nonclinical Reviewer, DGIEP
Tamal Chakraborti, PhD, Nonclinical Reviewer, DGIEP
Sushanta Chakder, PhD, Nonclinical Team Leader, DGIEP
Anshu Marathe, PhD, Pharmacometrics Reviewer
Nitin Mehrotra, PhD, Pharmacometrics Team Leader
Marie Kowblansky, PhD, CMC Lead, ONDQA
Yichun Sun, PhD, CMC Reviewer, ONDQA
Tarun Mehta, PhD, CMC Reviewer, ONDQA
Behrang Vali, MS, Biostatistcs Reviewer
Freda Cooner, PhD, Acting Biostatistics Team Leader
Sarah Dorff, PhD, Pharmacogenomics Reviewer
Michael Pacanowski, PhD, Pharmacogenomics Team Leader
Wu, Ling-Yu, Team Leader, OSE
Lynn Pouliot, PhD, Microbiologist, CDRH
Susan Leibenhaut, MD, Office of Compliance
Monica Claderon, PhD, Reviewer, DMEPA, OSE
Reema Mehta, Team Leader, DRISK, OSE
Jessica Benjamin, MPH, Senior Regulatory Project Manager, DGIEP

Maria Walsh, Associate Director for Regulatory Affairs, ODE III
Brian Strongin, RPh, Chief Project Management Staff, DGIEP
So Hyun Kim, Eastern Research Group, Independent Assessor for PDUFA V

APPLICANT ATTENDEES
Pamela Williamson, Senior Vice President, Regulatory Affairs and Compliance
Rumana Haque-Ahmed, Senior Director, Regulatory Affairs
Sherwin Sattarzadeh, Associate Director, Regulatory Affairs
Lisa von Moltke, MD PhD, Vice President, Clinical Pharmacology
Gerald Cox, MD, Vice President, Clinical Research
Judith Peterschmitt, MD, Director, Clinical Research
Kimberlee Raymer, Principal Associate, Regulatory Affairs, CMC
David Harris, PhD, Group Vice President, Science Administration, CMC
Craig Siegel, PhD, Scientific Director, Process Development, CMC
Christopher Willis, Senior Scientist, Analytical R&D, CMC
Sandrine Turpault, PhD, Assistant Director, Pharmacokinetics Modeling & Simulation
Catherine Orteman-Renon, PhD Director, Clinical Pharmacology
Stephen Lake, PhD, Senior Director, Biostatistcs
Laura Andrews, PhD, Vice President, Pharmacology and Toxicology
Tom O'Shea, PhD, Vice President, DMPK and Pharmaceutics
Rafif Dagher, PhD, Scientific Director, Pharmacology and Toxicology
Kate Alexander, Principal Associate, Regulatory Affairs
Tanya Green, Principal Associate, Regulatory Affairs
Cordula Schwarz, Principal Associate, Regulatory Affairs
Christopher Kripas, MD, Senior Director, Global Pharmacovigilance and Epidemiology
Asif Mahmood, MD, Senior Medical Director, Global Pharmacovigilance and Epidemiology
Susan Bouchard, Manager Global Patient Safety, Pharmacovigilance and Epidemiology

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Non-Clinical:
The specification of NMT (b) (4)% for the impurity (b) (4) in the drug substance is not acceptable as the specification for this impurity is above the ICH qualification threshold of (b) (4)%. Reduce the level of this impurity at or below (b) (4)% or provide toxicological qualification of this impurity at NMT (b) (4)%.

Clinical Pharmacology:

1. We are concerned about the proposed fixed dosing regimen of 100 mg BID for extensive CYP2D6 metabolizers, as exposure-response relationship for percentage change in spleen volume showed low response in patients with trough concentration lower than 5 ng/mL. We are considering whether dose adjustments for efficacy should be made if patients' trough concentrations are lower than 5 ng/mL. Modeling for a dose of 100 mg TID for extensive metabolizers should be performed.
2. We would like to discuss the availability of an assay to assess drug levels if the drug were approved, to optimize safety and efficacy.
3. We are concerned that there are (b) (4) for CYP2D6 poor metabolizers in your proposed label. (b) (4) the drug-drug interaction risk should be addressed . Modeling for a dose of 100mg daily in poor metabolizers should be performed.
4. Your submitted PBPK models are under review. Information requests will be sent to you for (a) further clarifications of the models, and (b) additional simulations to support dose recommendations.

CMC:

1. You have not provided sufficient information to support your claim that the (b) (4) that you introduce into your reaction is effectively removed from the final drug substance. You have not provided sufficient detail about the (b) (4) on which you base your conclusion. Since (b) (4) identify what is being determined in the assay (b) (4) Also, identify what is being used as the reference standard in this procedure, and how you determined the limit of detection (LOD) to be (b) (4) ppm.
2. In view of the (b) (4) ppm LOD, the toxicologic safety of the (b) (4) needs to be established.
3. Since (b) (4) is used in the synthesis of the drug substance, include (b) (4) in your (b) (4) of the drug substance.
4. Revise the specification and Analytical Methods table (3.2.S.4.2, table1) to include numerical identifiers for each of the analytical methods (document number) and the dates they went into effect, including for stability testing.
5. Clarify if the blister packaging used for your product is (b) (4) (b) (4) (b) (4) is required for prescription drugs by the (b) (4) .
6. In the commercial process, the holding time for bulk capsules prior to packaging should not exceed the holding times that were used in preparation of the registration batches. Provide a tabulation of the bulk capsule holding times for each of the registration batches.

3.0 INFORMATION REQUESTS

1. Clarify how the AUC_{0-12} (i.e. AUCtau) on Days 10, 20, Weeks 13, 39, 52, 65, 78, 91, and 104 reported in your Phase 2 study GZGD00304 Clinical Study Report (Table 12-2) were derived when the sampling time point during these PK assessment periods was up to Hour 6 according to your Final Study protocol dated on January 31, 2013. It appears that PK concentration dataset for this study (PC.xpt and ADPC.xpt under Section 5.3.5.2 submitted on September 20, 2013) does not contain Hour 12 eliglustat plasma

concentration values from Week 39 and beyond while the AUCtau in these PK assessment periods were reported. Provide the location of the complete PK concentration dataset.

2. Provide an update on the EDGE trial and what data may be available for review at this time.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

FDA is evaluating the potential need for a REMS to manage the risk of QT prolongation and other potential serious safety issues in at-risk patients (poor metabolizers, liver impairment or concomitant meds that inhibit CYP2D6 and 3A4).

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an Advisory Committee meeting.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

Your submissions dated November 27, 2013 and December 6, 9, 12, 13, and 16, 2013 constitute a Major Amendment to your NDA. The new PDUFA date is August 20, 2014. The late cycle meeting will tentatively occur at the end of June 2014.

7.0 ACTION ITEMS

1. Genzyme will provide the appropriate nonclinical information qualifying the impurity as mentioned in nonclinical significant issues above.
2. Genzyme will provide a clarification on how the AUC_{0-12} hours were derived for the Phase 2 study.
3. Genzyme will provide responses to the CMC significant issues listed above and schedule a teleconference with ONDQA to discuss further.

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/s/

JESSICA M BENJAMIN
01/21/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205494

INFORMATION REQUEST

Genzyme Corporation
Attention: Sherwin Sattarzadeh
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Sattarzadeh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eliglustat Tartrate Capsules.

We are reviewing the Chemistry Manufacturing and Controls section of your NDA, and have the following questions:

1. You have not provided sufficient information to support your claim that the (b) (4) that you introduce into your reaction is effectively removed from the final drug substance. You have not provided sufficient detail about the (b) (4) on which you base your conclusion. Since (b) (4) please identify what is being determined in the assay (b) (4) Also, identify what is being used as the reference standard in this procedure, and how you determined the limit of detection (LOD) to be (b) (4) ppm.

2. In view of the (b) (4) ppm LOD, the safety of the (b) (4) needs to be established.

3. Since (b) (4) is used in the synthesis of the drug substance, please include (b) (4) in your (b) (4) of the drug substance.

4. Please revise the specification and Analytical Methods table (3.2.S.4.2, table1) to include numerical identifiers for each of the analytical methods (Document number) and the dates they went into effect, including for stability testing.

5. Please clarify if the blister packaging used for your product is (b) (4). (b) (4) is required for prescription drugs by the (b) (4)

6. In the commercial process, the holding time for bulk capsules prior to packaging should not exceed the holding times that were used in preparation of the registration batches. Please provide a tabulation of the bulk capsule holding times for each of the registration batches.

If you have any questions, please contact Rebecca McKnight, Regulatory Project Manager, at (301) 796-1765.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

MOO JHONG RHEE
01/16/2014
Chief, Branch IV

From:	Benjamin, Jessica
To:	Sherwin.Sattarzadeh@genzyme.com
Cc:	Benjamin, Jessica
Subject:	NDA 205494 - information request
Date:	Friday, January 10, 2014 2:59:15 PM

Sherwin,

Please refer to NDA 205494 for eliglustat. As a result of our on-going review of this application, we have the following clinical pharmacology information requests. Please note that #2 is a modified request based on our mid-cycle communication tcon on January 9, 2014.

1. **Use your PBPK models to simulate eliglustat plasma PK at steady state in the following scenarios:**

a. 50 mg twice daily (BID) in CYP2D6 poor metabolizers (PMs)

b. 50 mg BID in CYP2D6 PMs co-administered with a moderate CYP3A4 inhibitor fluconazole

c. 50 mg once daily (QD) in CYP2D6 PMs

d. 100 mg QD in CYP2D6 PMs

e. 100 mg QD in CYP2D6 PMs co-administered with a moderate CYP3A4 inhibitor fluconazole

f. 100 mg three times a day (TID) in CYP2D6 ultra-rapid metabolizers (URMs)

g. 200 mg BID in CYP2D6 URMs

h. 100 mg BID in extensive metabolizers (EMs) taking a moderate CYP3A4 inhibitor fluconazole or a CYP2D6 inhibitor terfinabine

Summarize simulated population mean eliglustat exposure values (AUC_0-last, Cmax, and Cmin) for these scenarios, and calculate exposure ratios using simulation results of 100 mg BID in CYP2D6 EMs alone as reference. You can use simulation design presented in your Efficacy Information Amendment submitted on Dec 12, 2013.

Please also provide simulated Cmin values (mean [minimum, maximum]) for scenarios presented in Tables 6, 7, 9, 10, 11, 12, and 13 in your Efficacy Information Amendment submitted on Dec 12, 2013.

These simulations will support further review of eliglustat dose stratification in different patient groups.

2. Clarify how the $AUC_{0\text{-}12h}$ (i.e. AUCtau) on Days 10, 20, Weeks 13, 39, 52, 65, 78, 91, and 104 reported in your Phase 2 study GZGD00304 Clinical Study Report (Table 12-2) were derived when the sampling time point during these PK assessment periods was up to Hour 6 according to your Final Study protocol dated on January 31, 2013. Similarly, please clarify how the reported $AUC_{0\text{-}12h}$ for ENGAGE and ENCORE was derived.

3. You defined Cmin as minimum plasma concentration during a dosing interval and Ctrough as plasma concentration before treatment administration

during repeated dosing. Clarify whether if you used the Cmin and Ctrough interchangeably for the following study results:

a. For ENCORE study, you plotted Ctrough in Week 52 (See Figure 12-6 and Table in CSR) while your supporting dataset (ADPPAV.XPT) submitted on Dec. 20 for this study indicated that Cmin values were for Week 13 and Week 52 and Ctrough values were for other time periods. Clarify if the Cmin for Week13 and Week 52 were same as Ctrough by definition. Similarly, situation occurred for ENGAGE. Clarify if the Cmin for Week 4 and Week 39 were the same as Ctrough by definition. If not, provide each individual's trough concentrations for the period specified above and descriptive statistics stratified by CYP2D6 phenotypes. The individual data should be submitted in .xpt format.

b. For your Phase 2 study, you reported Cmin. Clarify if they were the same as Ctrough by the definition you provided in your Clinical Study Report (Table 8-5). If not, provide the listing of Ctrough concentrations and descriptive statistics stratified by CYP2D6 phenotypes. The individual data should be submitted in .xpt format.

We request a response to this email by COB, Jan 16, 2014. Please let me know if you have any questions.

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

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/s/

JESSICA M BENJAMIN
01/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205494

REVIEW EXTENSION – MAJOR AMENDMENT

Genzyme Corporation
Attention: Sherwin Sattarzadeh
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Sattarzadeh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for eliglustat tartrate.

Your submissions dated and received on November 27, 2013 and December 6, 9, 12, 13, and 16, 2013, are considered major amendments to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is August 20, 2014.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by June 30, 2014.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
01/10/2014

From: Benjamin, Jessica
To: Sherwin.Sattarzadeh@genzyme.com
Cc: Benjamin, Jessica
Subject: Mid Cycle communication tcon - Discussion topics
Date: Wednesday, January 08, 2014 3:44:51 PM

Hi Sherwin,

Please see below for the discussion topics/agenda for tomorrow's tcon.

SIGNIFICANT ISSUES

Non-Clinical:

The specification of NMT (b) (4)% for the impurity (b) (4) in the drug substance is not acceptable as the specification for this impurity is above the ICH qualification threshold of (b) (4)%. Reduce the level of this impurity at or below (b) (4)% or provide toxicological qualification of this impurity at NMT (b) (4)%.

Clinical Pharmacology:

1. We are concerned about the proposed fixed dosing regimen of 100 mg BID for extensive CYP2D6 metabolizers, as exposure-response relationship for percentage change in spleen volume showed low response in patients with trough concentration lower than 5 ng/mL. We are considering whether dose adjustments for efficacy should be made if patients' trough concentrations are lower than 5 ng/mL. Modeling for a dose of 100 mg TID for extensive metabolizers should be performed.

2. We would like to discuss the availability of an assay to assess drug levels if the drug were approved, to optimize safety and efficacy.

3. We are concerned that there are (b) (4) for CYP2D6 poor metabolizers in your proposed label. (b) (4) the drug-drug interaction risk should be addressed (open to discussions). Modeling for a dose of 100mg daily in poor metabolizers should be performed.

4. Your submitted PBPK models are under review. Information requests will be sent to you for (a) further clarifications of the models, and (b) additional simulations to support dose recommendations.

CMC:

1. You have not provided sufficient information to support your claim that the (b) (4) that you introduce into your reaction is effectively removed from the final drug substance. You have not provided sufficient detail about the (b) (4) on which you base your conclusion. Since (b) (4) identify what is being determined in the assay (b) (4). Also, identify what is being used as the reference standard in this procedure, and how you determined the limit of detection (LOD) to be (b) (4) ppm.

2. In view of the [redacted] ppm LOD, the toxicologic safety of the [redacted] needs to be established.
3. Since [redacted] is used in the synthesis of the drug substance, include [redacted] in your [redacted] of the drug substance.

4. Revise the specification and Analytical Methods table (3.2.S.4.2, table1) to include numerical identifiers for each of the analytical methods (document number) and the dates they went into effect, including for stability testing.

5. Clarify if the blister packaging used for your product is [redacted] is required for prescription drugs by the [redacted]

6. In the commercial process, the holding time for bulk capsules prior to packaging should not exceed the holding times that were used in preparation of the registration batches. Provide a tabulation of the bulk capsule holding times for each of the registration batches.

INFORMATION REQUESTS

1. Clarify how the AUC_{0-12} (i.e. AUCtau) on Days 10, 20, Weeks 13, 39, 52, 65, 78, 91, and 104 reported in your Phase 2 study GZGD00304 Clinical Study Report (Table 12-2) were derived when the sampling time point during these PK assessment periods was up to Hour 6 according to your Final Study protocol dated on January 31, 2013. It appears that PK concentration dataset for this study (PC.xpt and ADPC.xpt under Section 5.3.5.2 submitted on September 20, 2013) does not contain Hour 12 eliglustat plasma concentration values from Week 39 and beyond while the AUCtau in these PK assessment periods were reported. Provide the location of the complete PK concentration dataset.

2. Provide an update on the EDGE trial and what data may be available for review at this time.

MAJOR SAFETY CONCERNS/RISK MANAGEMENT
FDA is evaluating the potential need for a REMS to manage the risk of QT prolongation and other potential serious safety issues in at-risk patients (poor metabolizers, liver impairment or concomitant meds that inhibit CYP2D6 and 3A4).

ADVISORY COMMITTEE MEETING
there are no plans at this time for an Advisory Committee meeting.

LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES
Your submissions dated November 27, 2013 and December 6, 9, 12, 13, and 16, 2013 constitute a Major Amendment to your NDA. The new PDUFA date is August 20, 2014. The late cycle meeting will tentatively occur at the end of June 2014.

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

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/s/

JESSICA M BENJAMIN
01/08/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205494 **INFORMATION REQUEST**

Genzyme Corporation
Attention: Sherwin Sattarzadeh
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Sattarzadeh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for eliglustat tartrate.

We are reviewing the clinical and statistical sections of your submission and have the following comments and information requests. We request a written response by January 10, 2013, in order to continue our evaluation of your NDA.

1. Specify the date of study data unblinding for the ENGAGE study.

2. For all patients enrolled in the ENGAGE study that also rolled over into the ongoing open-label period, provide a separate figure for each of the following items. For each figure, time should range from the beginning of the ENGAGE study (i.e., randomization day) through the time point with the latest available data from the ongoing open-label period. Patients should be presented by their originally randomized treatment groups in the double-blind primary analysis period of the ENGAGE study.

    a. Plot the mean (± standard deviation) spleen volume in multiples of Normal (MN) over time for each group.
    b. Plot the mean (± standard deviation) spleen volume in milliliters (mL) over time for each group.
    c. Plot the mean (± standard deviation) liver volume in multiples of Normal (MN) over time for each group.
    d. Plot the mean (± standard deviation) liver volume in milliliters (mL) over time for each group.
    e. Plot the mean (± standard deviation) hemoglobin concentration in grams per deciliter (g/dL) over time for each group.
    f. Plot the mean (± standard deviation) platelet count in billions per liter (10^9/L) over time for each group.

3. For all patients enrolled in the ENCORE study that continued their study treatments beyond the 52-week primary analysis treatment period, provide a separate figure for each

of the following items. For each figure, time should range from the beginning of the ENCORE study (i.e., randomization day) through the time point with the latest available data from the ongoing long-term treatment period. Patients should be presented by their originally randomized treatment groups in the primary analysis treatment period of the ENCORE study.

a. Plot the mean (± standard deviation) spleen volume in multiples of Normal (MN) over time for each group.
b. Plot the mean (± standard deviation) spleen volume in milliliters (mL) over time for each group.
c. Plot the mean (± standard deviation) liver volume in multiples of Normal (MN) over time for each group.
d. Plot the mean (± standard deviation) liver volume in milliliters (mL) over time for each group.
e. Plot the mean (± standard deviation) hemoglobin concentration in grams per deciliter (g/dL) over time for each group.
f. Plot the mean (± standard deviation) platelet count in billions per liter (10^9/L) over time for each group.

4. Reproduce Tables 14.2.1.1.1, 14.2.1.1.2, 14.2.2.3.1, and 14.2.2.3.2, in section 14.2 of the ENCORE Clinical Study Report, excluding all patients from the Martins (Site 27), Drelichman (Site 28), and Cravo (Site 29) clinical sites.

5. Reproduce Tables 14.2.1.1.1, 14.2.1.1.2, 14.2.2.3.1, and 14.2.2.3.2, in section 14.2 of the ENCORE Clinical Study Report, by the actual eliglustat dose received (i.e., by 50 mg BID, 100 mg BID, and 150 mg BID).

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
12/20/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205494 **INFORMATION REQUEST**

Genzyme Corporation
Attention: Sherwin Sattarzadeh
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Sattarzadeh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for eliglustat tartrate.

We are reviewing the clinical pharmacology section of your submission and have the following comments and information requests. We request a written response within 5 business days in order to continue our evaluation of your NDA.

1. The systemic exposure of eliglustat increases substantially when it is coadministered with drugs that are CYP2D6 inhibitors and/or CYP3A4 inhibitors. Tabulate individual patients in your Phase 2 and Phase 3 trials who were taking concomitant drugs that are CYP2D6 or CYP3A4 inhibitors. Group these by weak, moderate and strong inhibitors and have separate tables for CYP2D6 and CYP3A4 inhibitors. For each of these patients, indicate drug name and dose of the concomitant medication, adverse events experienced, and when the event(s) occurred in relation to the dosing days of the concomitant medication.

2. The dataset adppp1.xpt submitted on November 27, 2013 only included Cmax and AUC for the Phase 1 studies. In our information request letter dated November 13, 2013 (Parts 1a and 1b), we requested that pharmacokinetic parameters for eliglustat, not just the exposure parameters, i.e. Cmax and AUC, to be merged with subjects' CYP2D6 phenotypes. The pharmacokinetic parameters for elimination (e.g. t1/2 and/or CL), volume of distribution (V) and Tmax should also be merged with subjects' CYP2D6 phenotying results. Provide a dataset that includes all the derived pharmacokinetic parameters in 10 Phase 1 studies by noncompartmental analysis and each subject's CYP2D6 phenotype.

3. For the Phase 3 ENGAGE trial, add dosing information to the ppcyp.xpt file that was submitted on November 27, 2013. Include PK parameters estimated on Day 1 and Week 4. In addition, include trough concentrations at Weeks 2, 4, 13, 26, and 39. Currently,

the dataset only has PK parameters estimated at Week 39. Again, the data file should be formatted as SAS transport files (.xpt) with a corresponding data definition file.

4. For the Phase 3 ENCORE trial, add dosing information to the ppcyp.xpt file that was submitted on November 27, 2013. Include PK parameters estimated on Day 1, Week 13. In addition, include trough concentrations at Weeks 2, 6, 13, 26, 39, and 52. Currently, the dataset only has PK parameters estimated at Week 52. The data file should be formatted as SAS transport files (.xpt) with a corresponding data definition file.

5. For the Phase 2 study GZGD00304, add to the ppcyp.xpt file submitted on November 27, 2013 dosing information for each visit where the PK parameters were calculated. The data file should be formatted as SAS transport files (.xpt) with a corresponding data definition file.

6. For the Phase 2 study GZGD00304, the summary data in Tables 6 to 11 in Appendix 16.2.8 of the clinical study report were not stratified by CYP2D6 phenotypes for all visits. Your clinical study report only presented eliglustat PK versus CYP2D6 metabolizer status on Day 1 (Table 12-3). Considering eliglustat PK is affected by CYP2D6 phenotypes, you need to stratify the summary data in Tables 6 to 11 by patient's CYP2D6 phenotypes.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
12/09/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205494

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Genzyme Corporation
Attention: Sherwin Sattarzadeh
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Sattarzadeh:

Please refer to your New Drug Application (NDA) dated September 19, 2013, received September 20, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Cerdelga (eliglustat tartrate).

We also refer to your amendments dated October 25 and November 20. 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm. Therefore, the user fee goal date is May 20, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by March 31, 2014. In addition, the planned date for our internal mid-cycle review meeting is December 12, 2013. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. For both studies GZGD02507 (ENGAGE) and GZGD02607 (ENCORE), provide the subgroup efficacy analysis by gender for the primary and key secondary endpoints.

2. (b) (4)
Since you have demonstrated adequate upstream microbial controls within your manufacturing process, you are advised to amend your Release Specifications Table 1 (Section 3.2.P.5.1) to delete (b) (4) (b) (4) Since you are conducting microbial limits testing within your long-term stability program, Table 1, *Evolution of Eliglustat Hard Capsule Stability Specification"* (Section 3.2.P.8.1, page 3/12) adequately establishes the microbial limit specification within the on-going, commercial stability program.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. A horizontal line must separate the Table of Contents (TOC) from the FPI.

2. The word "use" must be capitalized in the subsection heading," 8.4 Pediatric use" and "8.5 Geriatric use".

We request that you resubmit labeling that addresses these issues by December 20, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

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

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JOYCE A KORVICK
12/03/2013

From:	Benjamin, Jessica
To:	Sherwin.Sattarzadeh@genzyme.com
Cc:	Benjamin, Jessica
Subject:	NDA 205494 - information request
Date:	Wednesday, November 27, 2013 10:22:26 AM
Importance:	High

Sherwin,

Please refer to NDA 205494 for eliglustat. As a result of our on-going review of this application, we have the following information requests. If you cannot meet the specified timelines, let us know as soon as you receive this information request. If you have already submitted any of the following, please direct us to the appropriate location.

1. Conduct exposure-response relationship analyses for the ENCORE trial using steady state trough concentration as the exposure metric for the following efficacy endpoints:

   A. primary composite endpoint

   B. secondary endpoints (% of patients meeting the criteria of stability in the individual components)

   C. percentage change in liver volume

   D. percentage change in spleen volume

   E. percentage change in platelet count

   F. change in hemoglobin

Both univariate and multivariate analysis should be conducted. For multivariate analysis, you should include all possible covariates that are likely to influence response. Both predicted steady state Ctrough from population PK analysis and observed Ctrough should be used for analysis.

Please submit the analysis including the report, datasets, define file and program codes by **COB December 5.**

2. Conduct exposure-response relationship analyses for safety endpoints using pooled data from ENGAGE and ENCORE trial with steady state trough concentration as the exposure metric. The safety endpoints should include the following:

Pooled toxicities

Grade ¾ Infections and infestations and all grade Infections and infestations

Grade ¾ Gastrointestinal Disorders and all grade Gastrointestinal Disorders

Grade ¾ Nervous system disorders and all grade Nervous system disorders

Grade ¾ Muscoskeletal and connective tissue disorders and all grade Muscoskeletal and connective tissue disorders

Individual toxicities

Grade ¾ nasophranytis and all grade nasophranytis
Grade ¾ urinary tract infection and all grade urinary tract infection
Grade ¾ sinusitis and all grade sinusitis
Grade ¾ diarrhea and all grade diarrhea
Grade ¾ nausea and all grade nausea
Grade ¾ abdominal upper pain and all grade abdominal upper pain
Grade ¾ arthralgia and all grade arthralgia
Grade ¾ Back pain and all grade Back pain
Grade ¾ Pain in extremity and all grade Pain in extremity
Grade ¾ Headache and all grade Headache
Grade ¾ fatigue and all grade Fatigue

Both univariate and multivariate analysis should be conducted. For multivariate analysis, you should include all possible covariates that are likely to influence the incidence of the above mentioned AEs. . Both predicted steady state Ctrough from population PK analysis and observed Ctrough should be used for analysis.

Please submit the analysis for Grade ¾ events including the report, datasets, define file and program codes by **COB December 5.**

Please submit the analysis for all grade events including the report, datasets, define file and program codes by **COB December 9.**

3. Conduct a subgroup analysis for the following efficacy endpoints by CYP2D6 phenotype and dose for both ENCORE and ENGAGE trials. An example regarding the format of result submission is presented for your convenience. Please submit the analysis **by COB December 2.**

ENCORE

primary composite endpoint

secondary endpoints (% of patients meeting the criteria of stability in the individual components)

percentage change in liver volume

percentage change in spleen volume

percentage change in platelet count

change in hemoglobin

ENGAGE

percentage change in liver volume

percentage change in spleen volume

percentage change in platelet count

change in hemoglobin

Table 1: Percentage change in Spleen Volume by Dose and CYP2D6 phenotype in

ENCORE

CYP2D6 phenotype 50 mg BID
100 mg BID
150 mg BID

PM
IM
EM
UM
Indeterminate
Total

Let me know if you have any questions.

Regards,

Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

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/s/

JESSICA M BENJAMIN
11/27/2013

From:	Benjamin, Jessica
To:	Sherwin.Sattarzadeh@genzyme.com
Cc:	Benjamin, Jessica
Subject:	NDA 205494 - Request for information
Date:	Monday, November 25, 2013 2:25:09 PM
Importance:	High

Sherwin,

Please refer to NDA 205494 for eliglustat. As a result of our on-going review of this application, we have the following information request:

We are unable to locate the dataset and programs for the results generated in your study report of Pharmacokinetic/Efficacy Modeling of CYP2D6 Phenotype Guided Eliglustat Dosing [poh0395- Module 5.3.3.5]. Please direct us to the dataset and programs, if already submitted, or else submit them within 2 business days.

Let me know if you have any questions.
Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

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/s/

JESSICA M BENJAMIN
11/25/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205494

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142

Attention: Sherwin Sattarzadeh
Associate Director, Regulatory Affairs

Dear Mr. Sattarzadeh:

Please refer to your New Drug Application (NDA) dated September 19, 2013, received September 20, 2013, submitted under section 505(b)(1) the Federal Food, Drug, and Cosmetic Act for Eliglustat Capsules, 84 mg.

We also refer to your correspondence, dated and received September 27, 2013, requesting review of your proposed proprietary name, Cerdelga. We have completed our review of the proposed proprietary name, Cerdelga and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your September 27, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Phong Do, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4795. For any other information regarding this application contact Jessica Benjamin, the Office of New Drugs (OND) Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
11/21/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205494

REQUEST FOR METHODS VALIDATION MATERIALS

Genzyme Corporation
Attention: Sherwin Sattarzadeh
500 Kendall Street
Cambridge, MA 02142

Dear Sherwin Sattarzadeh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cerdelga (eliglustat) capsules 84 mg.

We will be performing methods validation studies on Cerdelga (eliglustat) capsules 84 mg, as described in NDA 205494.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

AP-LSD-0003-08 HPLC method – Impurities by RP-HPLC
Chiral Analysis by HPLC
Degradation Products by HPLC

Samples and Reference Standards

(b) (4)

(b) (4)

Equipment

(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
11/19/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205494

PRIORITY REVIEW DESIGNATION

Genzyme Corporation
Attention: Sherwin Sattarzadeh
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Sattarzadeh:

Please refer to your New Drug Application (NDA) dated September 19, 2013, received September 20, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Cerdelga (eliglustat tartrate).

We also refer to your submission dated October 25, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is May 20, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by March 5, 2014.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before December 3, 2013.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, M.D., FAAP, CPI
Deputy Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ANDREW E MULBERG
11/18/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205494 **INFORMATION REQUEST**

Genzyme Corporation
Attention: Sherwin Sattarzadeh
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Sattarzadeh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for eliglustat tartrate.

We are reviewing the clinical pharmacology and nonclinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Submit the following data files within 10 business days:

    a. For your 11 phase 1 studies excluding Study GZGD00103 and GZGD00404, phase 2 study, and phase 3 studies (ENGAGE and ENCORE), merge each individual's CYP2D6 phenotype status with the pharmacokinetic parameters estimated by non-compartmental analysis (NCA) currently contained in the pp.xpt files. Indicate in the data files which lab (b) (4) (b) (4) conducted the CYP2D6 genotyping. The data file should be formatted as SAS transport files (.xpt) with an associated data definition file.

    b. For study GZGD02107, merge the ex.xpt file containing dosing information with the pp.xpt file along with each subject's CYP2D6 phenotype status. The data file should be formatted as SAS transport files (.xpt) with an associated data definition file.

2. Provide a response to the following requests related to PBPK modeling and simulation study reports SIM0105 and SIM0106 within 15 business days:

    a. Conduct simulations according to the designs of additional human PK studies and determine the need to optimize your Genz-99067 model with regard to its nonlinear PK and its effect on other CYP2D6 substrates. These studies include GZGD00204 (50 mg, 200 mg, and 300 mg twice daily in healthy, non-CYP2D6 PM subjects, with PK data available on day 1, day 10 and day 12 for each dose

level), GZGD02007 (specifically the effect of Genz-99067 on pharmacokinetics of paroxetine), and GZGD04112 (the effect of Genz-99067 on pharmacokinetics of metoprolol).

b. Develop virtual CYP2D6 intermediate metabolizer population (IMs) and ultra-rapid metabolizer population (URM) and specifically simulate the pharmacokinetics of Genz-99067 in these groups. The effect of a moderate CYP3A4 inhibitor and/or a moderate CYP2D6 inhibitor (such as fluconazole and terbinafine) on Genz-99067 should be simulated in CYP2D6 IMs. The dose regimens of eliglustat in these simulations should be 50, 100, and 150 mg twice daily. The simulated exposure of Genz-99067 under these conditions should be compared to that from CYP2D6 extensive metabolizers taking eliglustat alone.

c. Conduct simulations according to Study GZGD02407 (effect of rifampin on Genz-099067).

d. For the simulation of the effect of ketoconazole and the effect of rifampin, consider the inhibition and induction effect of active renal secretion of Genz-99067 using your PBPK model.

e. Justify the calculation of exposure ratios for the effect of paroxetine and the effect of ketoconazole on the exposure of Genz-99067 in report SIM0105.

f. Provide simulation results of the effect of terbinafine on the pharmacokinetics of another CYP2D6 substrate.

g. Provide the updated files used to generate PBPK simulations (drug model files, population files, and workspace files: .cmp, .lbr, and .wks) and respective output files.

3. Provide the tumor data in conformance to the electronic format specified in the April 2006 guidance document entitled "*Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications*". Specifically, the tumor datasets should conform to the format described on pages 9 and 10 of the associated document titled "*Study Data Specifications*". This associated document can be found at the following website:
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163561.pdf

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
11/13/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205494

NDA ACKNOWLEDGMENT

Genzyme Corporation
Attention: Sherwin Sattarzadeh
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Sattarzadeh:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: eliglustat tartrate

Date of Application: September 19, 2013

Date of Receipt: September 20, 2013

Our Reference Number: NDA 205494

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 19, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JESSICA M BENJAMIN
09/23/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 067589

MEETING MINUTES

Genzyme Corporation
Attention: Sherwin Sattarzadeh, RAC
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Sattarzadeh:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for eliglustat tartrate.

We also refer to the meeting between representatives of your firm and the FDA on May 21, 2013. The purpose of the meeting was to discuss the format and presentation of a future NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Jessica M. Benjamin
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: May 21, 2013 from 10:00 AM to 11:00 AM EDT
Meeting Location: White Oak Building 22, Room 1309

Application Number: IND 067589
Product Name: eliglustat tartrate
Indication: Gaucher disease
Sponsor/Applicant Name: Genzyme Corporation

Meeting Chair: Lara Dimick, MD
Meeting Recorder: Jessica Benjamin, MPH

FDA ATTENDEES

Victoria Kusiak, MD, Deputy Director, Office of Drug Evaluation III
Donna Griebel, MD, Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Andrew Mulberg, MD, FAAP, CPI, Deputy Director, DGIEP
Lara Dimick, MD, Clinical Team Leader, DGIEP
Carla Epps, MD, Medical Officer, DGIEP
Sushanta Chakder, PhD, Lead Interdisciplinary Scientist, DGIEP
Tamal Chakraborti, PhD, Pharmacologist, DGIEP
Sue Chih Lee, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology
Dilara Jappar, PhD, Clinical Pharmacology Reviewer, OCP
Behrang Vali, Biostatistician, Office of Biostatistics
Freda Cooner, PhD, Biostatistician, Office of Biostatistics
Jessica Benjamin, MPH, Senior Regulatory Project Manager, DGIEP
Maria Walsh, RN, MS, Associate Director for Regulatory Affairs, ODE III
David Shih, MD, Medical Team Leader, Division of Epidemiology II, Office of Surveillance and Epidemiology (OSE)
Lubna Merchant, Lead Pharmacist, Division of Medication Error Prevention and Analysis, OSE
Thang La, Senior Regulatory Project Manager, OSE
George Neyarapally, Health Scientist, Division of Risk Management, OSE
Phong Do, Senior Regulatory Project Manager, OSE

EASTERN RESEARCH GROUP ATTENDEES

(b) (6)

SPONSOR ATTENDEES

Pamela Williamson, Senior Vice President and Global Head, Regulatory Affairs and Compliance

Rumana Haque-Ahmed, Senior Director, Regulatory Affairs
Sherwin Sattarzadeh, Associate Director, Regulatory Affairs
Gerald Cox, MD, PhD, Vice President, Clinical Research
Judith Peterschmitt, MD, Medical Director, Clinical Research
Lisa Von Moltke, MD, PhD, Vice President, Clinical Pharmacology
Leorah Ross, MD, PhD, Medical Director, Global Pharmacovigilance and Epidemiology
Stephen Lake, ScD, Senior Director, Biostatistics
Jennifer Angell, ScM, Director, Biostatistics
Kate Alexander, Principal Associate, Regulatory Affairs
Tanya Green, MS, Principal Associate, Regulatory Affairs
Kimberlee Raymer, Principal Associate, Regulatory Affairs CMC
Cordula Schwarz, MS, Principal Associate, Regulatory Affairs
Bas Wullems, Associate Director, Regulatory Affairs

1.0 BACKGROUND

Gaucher disease is a rare, autosomal, recessive, lysosomal, glycolipid storage disease that results from a deficiency of acid beta (β)-glucosidase (also known as glucocerebrosidase). The major natural substrate for this enzyme is glucosylceramide (GL-1), an intermediate metabolite in the synthesis and catabolism of more complex glycosphingolipids. Eliglusat is being developed for the treatment of adult patients with Gaucher disease. It is a member of a class of glucosylceramide synthase inhibitors that resembles the substrate (ceramide) of the enzyme, thereby inhibiting enzymatic activity of GL-1 synthase in a concentration-dependent manner.

Genzyme's clinical development program consists of thirteen Phase 1 studies, one Phase 2 study (GZGD00304), two adequate and well-controlled Phase 3 registration studies (ENGAGE Study GZGD02507 and ENCORE Study GZGD02607), and one ongoing Phase 3b study (EDGE Study GZGD03109). The Phase 2 and 3 studies will provide efficacy and safety data in support of the NDA application, while the ongoing Phase 3b study will provide additional safety data for inclusion in the Integrated Summary of Safety (ISS).

The purpose of this meeting was to gain agreement on the adequacy of the current clinical and nonclinical data packages to support an NDA filing of eliglustat for the proposed indication in Gaucher disease.

Each of the sponsor's questions is presented below in italics, followed by the Division's response in bold. A record of the discussion that occurred during the meeting is presented in normal font. The Division provided preliminary written responses to the sponsor on May 20, 2013.

2.0 DISCUSSION

Question 1. *Does the Agency agree that Genzyme will request an Applicant Orientation Presentation Meeting, to be held within 14 days following receipt of the NDA submission?*

FDA Response:
An Application Orientation Presentation Meeting may be held within 45 days upon receipt of the application.

Discussion:
No further discussion.

Question 2. *Does the Agency agree that the data to be provided in the NDA will be sufficient to support the proposed indication for eliglustat?*

FDA Response:
We agree with your plan to submit data from both trials and the overall organization your NDA application. It appears that you conducted the ENGAGE trial using a trial design and primary endpoint agreed upon with the Division. However, we have concerns about the adequacy of the data from the ENCORE to demonstrate efficacy since the trial was conducted using a non-agreed upon primary efficacy endpoint (spleen volume, liver volume, hemoglobin, and platelet count). During the April 12, 2011 Type C meeting, the Division stated concerns about the proposed primary efficacy endpoint for the ENCORE trial, namely:

- **The use of a composite endpoint may result in efficacy data that are difficult to interpret**
- **The proposed non-inferiority margin of 25% compared to treatment with enzyme replacement therapy was not clinically acceptable**

In your briefing materials, you note that your efficacy analyses for ENCORE included the percentage change in spleen volume, the primary endpoint recommended by the Division, and that the results appear to support efficacy. The adequacy of the totality of data to support your proposed indication will be determined during the review.

Discussion:
No further discussion.

Question 3. *Does the Agency agree that an optimized dosing regimen based on CYP2D6 phenotype is most appropriate?*

FDA Response:
You have not provided sufficient information to determine if dosing based on trough levels or CYP2D6 genotyping is the most appropriate method. Whether your proposal to dose based on CYP2D6 phenotype or measurement of trough concentrations is appropriate will depend on review of efficacy and safety, particularly the PK/safety relationships. The acceptability of genotyping will depend in part on how predictive testing is for identifying those patients who require an alternative dose, the ability to achieve concentrations that, on

average, are similar to the effective and safe concentrations observed in clinical trials, and the residual variability.

We have the following comments regarding your proposed dosing based on the CYP2D6 genotyping:

- **We are concerned that you do not have sufficient number of patients in each genotype group in treatment naive group (table 30) to make a meaningful interpretation of the data at this point to support your proposed dosing.**
- **It appears that for EM, regardless of the dose, the exposure appears to be very similar across different doses, 50 mg, 100 mg, and 150 mg based on the observed data (table 6-7, Figure 5-6). However, your predicted data predicts that EM (b) (4) (b) (4) (table 31). Explain this difference.**
- **Based on both observed (table 6-7) and predicted data (table 32), it appears that IM with 100 mg BID dosing have almost 2-fold higher exposure than EM with 100 mg BID dosing (b) (4) have more comparable exposure to EM with 100 mg BID. Explain your rationale for proposing 100 mg BID dosing for both IM and EM.**
- **Based on both observed (table 6-7) and predicted data (table 32), the exposure of PM with (b) (4) dose was 2.5 to 5 fold higher than the exposure of EM with 100 mg BID dosing. Explain your rationale for (b) (4)**
- **For the previously-treated population, although dosing based on CYP2D6 genotyping matches the actual dosing based on titration for PM and URM group, for IM/EM group, more than half of the patients (57/91) would be reassigned to 100 mg BID dosing either from (b) (4) You have not provided sufficient evidence that patient who received (b) (4) under titration method still would retain its efficacy if they were dosed at 100 mg BID dosing based on CYP2D6 genotype, especially while no apparent exposure –response relationship has been established.**
- **Submit individual CYP2D6 genotype data in addition to the inferred phenotypes. Also, submit a summary of the genotyping methods, tested alleles, quality control procedures, and phenotype parameterization.**

Discussion:
See attached slide presentation.
The PK profile of the drug and proposed dosing algorithm by genotype will require a full review of data during the NDA review period. FDA accepts path forward for filing to propose genotype based dosing. If an FDA approved reliable test is available for genotyping, it would not require the development of a separate companion diagnostic device.

Question 4. *Does the Agency agree with Genzyme's plan to summarize clinical efficacy data from the Phase 2 and two Phase 3 studies (ENGAGE and ENCORE), and to address the requirements for an ISE within Module 2.7.3?*

FDA Response:
Yes, your plan to summarize the two studies individually is acceptable.

Discussion:
No further discussion.

Question 5. *Does the Agency agree with the statistical approach proposed in the analysis plan for the ISS, including the pooling strategy and data cutoff?*

FDA Response:
No, we do not agree. In addition to a pooled analysis of safety data for patients treated with eliglustat, you should provide the following pooled analyses: safety data for healthy volunteers who received eliglustat and safety data for the total population (i.e., healthy volunteers and patients with Gaucher disease) exposed to eliglustat. Please clarify how many patients will have at least 12 months of safety data available at the time of your proposed data cut-off date of January 13, 2013.

Discussion:
Genzyme agrees to pool and summarize the adverse event data from the Phase 1 studies, and to provide the corresponding pooled datasets in the NDA.

Question 6. *Does the Agency agree with the statistical approach proposed for the ISS analysis of electrocardiogram data?*

FDA Response:
Yes, we agree.

Discussion:
No further discussion.

Question 7. *Does the Agency agree with Genzyme's proposal for the handling of the safety data from ongoing Phase 3b clinical study EDGE (GZGD03109)?*

FDA Response:
Yes, we agree with your proposal to included safety data from the study lead-in period for EDGE.

Discussion:
No further discussion.

Question 8. *Does the Agency agree with the proposal for inclusion of narratives and CRFs?*

FDA Response:
Yes, we agree.

Discussion:
No further discussion.

Question 9. *Does the Agency agree that issuance of a Medication Guide pursuant to 21 CFR 208, used in conjunction with the approved PI, is appropriate to ensure the safe and effective use of eliglustat without requiring a REMS in the initial NDA filing?*

FDA Response:
It is premature to answer this question. We are concerned with the risk of QT prolongation in the setting of DDI and/or poor metabolizers. You may need a Medication Guide and a REMS to address this issue.

Discussion:
No further discussion.

Question 10. *Does the Agency agree with this proposal for the submission of datasets?*

FDA Response:
We request that you submit datasets for single dose study (GZGD00103), multiple doses PK study (GZGD00204), relative Bioavailability study (GZGD03811), as well as the radiolabeled study (GZGD02107) in addition to what you have proposed to submit for clinical pharmacology studies.

You proposal for PopPK and PopPK/PD analysis appears to be reasonable. You can also refer to http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for our general expectations of submitting pharmacometric data/models.

Regarding your PBPK modeling data submission, we have the two following comments:

1. **Provide the files used to generate the final PBPK simulations for study reports SIM0105 and SIM0106. These files are drug model files (SimCYP® .cmp file), population files (SimCYP® .lbr file), workspace files (SimCYP® .wks file), and output files (Microsoft excel files). These files may be submitted via CD.**
2. **In addition, because eliglustat causes time-dependent inhibition of CYP2D6 in vitro and may have been responsible for potential time- and dose-dependent PK of eliglustat, we recommend you adequately integrate this mechanism for the development of eliglustat PBPK model. The performance of eliglustat PBPK model for eliglustat as a CYP2D6 inhibitor should be presented by comparing the simulations with clinical observations using metoprolol as substrate (GZGD0411).**

Discussion:
Genzyme agrees to submit datasets for all of the clinical pharmacology studies including the requested single dose study (GZGD00103), multiple doses PK study (GZGD00204), relative Bioavailability study (GZGD03811), and radiolabeled study (GZGD02107), and to comply with FDA's request regarding PBPK modeling data submission.

Post-Meeting Note:
The Agency agrees with Genzyme's dataset submission plan for the Phase 1 (including the four studies above), Phase 2, and Phase 3 studies, and the ISS, as outlined in the briefing package.

Question 11. Does the Agency agree with the proposed content and format of the Day 120 safety update report?

FDA Response:
No, we do not agree. The 120 Day update should include a summary of adverse events in addition to the proposed content (deaths, serious adverse events, discontinuations, and other "selected events of interest" [i.e., cardiac arrhythmias, electrocardiogram abnormalities, seizures]) listed in your briefing package.

Discussion:
Genzyme agrees to include a summary of adverse events in the Day 120 update. Specifically, Genzyme will include the content listed in the briefing package as well as cumulative and interval (for the period of February 1, 2013 through the Day 120 cut off) summaries of adverse events.

Question 12. Does the Agency agree that the two proposed studies in subjects with renal impairment and hepatic impairment will be conducted as post-marketing commitments for eliglustat?

FDA Response:
If the NDA will propose to dose patients at fixed dose based on CYP2D6 genotyping rather than titration, then you would need to conduct the PK studies in hepatic/renal impairment patients prior to the NDA submission.

Discussion:
See attached slide presentation.
The Agency agrees that the referenced studies could be conducted as PMRs; however, labeling will reflect appropriate dosing approach for hepatic and renally impaired sub-populations.

Question 13. Does the Agency agree that the nonclinical data package to be included in the NDA for eliglustat is adequate to support a filing for the proposed indication in GD1?

FDA Response:
Yes, we agree.

Discussion:
No further discussion.

Question 14. Does the Agency agree with the proposed approach for the eliglustat shelf-life determination?

FDA Response:
Your approach is consistent with recommendations of ICH Q1E and, therefore, acceptable. The acceptability of the proposed expiration dating period will be based on the submitted data.

Discussion:
No further discussion.

Additional Comments:
The Division is concerned that your thorough Q-T study did not adequately address the risk of Q-T interval prolongation in special populations and that further investigation will be necessary to address this issue. 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, the threshold for regulatory concern as described in ICH E14 guidance. However, even though the supratherapeutic dose (800 mg) produced a geometric mean Cmax value 14-fold higher than the geometric mean Cmax for the therapeutic dose (200 mg), these concentrations may not be sufficient to cover the high clinical exposure scenario (e.g., drug interaction with CYP2D6 inhibitor, elderly, and hepatic impairment).

In a December 2012 update to this IND, you refer to a Phase 2 & 3 formulation and a Late Phase 3 formulation. The Late Phase 3 formulation is also described as the proposed commercial formulation. You will need to clarify how the late phase and early phase 3 formulations differ and specify which patients were exposed to which formulation. You should be aware that the commercial formulation should be the same as the formulation used in the pivotal clinical trials. Otherwise, additional experimental data to bridge the two formulations will be required.

Your drug product will need to conform to USP <232> Elemental Impurities.

Discussion:
No further discussion.

3.0 OTHER IMPORTANT INFORMATION

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application
- A preliminary discussion on the need for a REMS was held and it was concluded that a REMS or Medication Guide may be needed to address the risk of QT prolongation in the setting of DDI and/or poor metabolizers.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Further, under the Food and Drug Administration Safety and Innovation ACT (FDASIA), sponsors must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.
- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[*see Warnings and Precautions (5.2)*]".

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes

of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items from this meeting.

6.0 ATTACHMENTS AND HANDOUTS

Slides presented at the meeting are attached to the meeting minutes.

20 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JESSICA M BENJAMIN
06/20/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 67,589

MEETING MINUTES

Genzyme Corporation
Attention Carly Evans
Principle Associate, Regulatory Affairs
15 Pleasant Street Connector
Framingham, MA 01701-9322

Dear Ms. Evans:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Genz-112638 eliflustat tartrate.

We also refer to the telecon between representatives of your firm and the FDA on May 26, 2010. The purpose of the meeting was to discuss the Sponsor CMC plans for the development of the drug product.

A copy of the official minutes of the telecon is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

Cathy Tran-Zwanetz
Regulatory Project Manager
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES ATTACHED

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B End of Phase 2
Meeting Category:	End of Phase 2
Meeting Date and Time:	May 26, 2010 at 10:00 AM
Application Number:	IND 67,589
Product Name:	Genz-112638
Indication:	Type 1 Gaucher Disease
Sponsor/Applicant Name:	Genzyme
Meeting Chair:	Terrance Ocheltree, Ph.D., Rh.D.
Meeting Recorder:	Cathy Tran-Zwanetz

FDA ATTENDEES
Terrance Ocheltree, Ph.D., R.Ph., Division Director
Marie Kowblansky, Ph.D., CMC Lead
Angelica Dorantes, Ph.D, Biopharmaceutics Team Leader
Sharmista Chatterjee, PhD., Product Quality Reviewer
Ali, Niak, M.D., Medical Officer
Don Henry, Regulatory Project Manager
Cathy Tran-Zwanetz, Regulatory Project Manager

SPONSOR ATTENDEES
David Harris, Ph.D., Group Vice President, Pharmaceutical Development Sciences
Craig Siegel, Ph.D., Principal Scientist, Process Chemistry
Andrew Matthews, Ph.D., Project Manager, API Operations in Liestal, Switzerland
Hitesh Bhagat, Ph.D., Vice President, Formulation Development
Jianmei Kochling, Ph.D., Associate Scientific Director, Analytical Development
Dolly A. Parasrampuria, Ph.D., Senior Director, Pharmacokinetics
Thomas O'Shea, Ph.D., Vice President, Pharmaceutics
Maria Iacovelli, Manager, Regulatory Affairs
Carly Evans, Principle Associate, Regulatory Affairs
Lauren Sykes, Senior Associate, Regulatory Affairs
Tim Olson, Director, Program Management

1.0 BACKGROUND

Genzyme Corporation (Genzyme) requested a Type B End-of-Phase 2 (EOP2) Chemistry, Manufacturing, and Controls (CMC) meeting, letter dated March 2, 2010, to discuss CMC topics related to Genz-112638 for intended for the treatment of Gaucher Disease (IND 67,589). FDA's initial responses to Genzyme's questions in the CMC briefing package received April 20, 2010, are listed below.

2. DISCUSSION

1. **Based on the data provided, does the Agency agree that Genzyme's designation of the Genz-112638 (b) (4) as the starting material is acceptable?**

   FDA Response:
   Based on the information in your briefing package, the designation of (b) (4) as a starting material is acceptable.

   Discussion:
   The sponsor accepted the responses, and no further discussion was needed.

2. **Does the Agency agree that the proposed list of specifications for (b) (4) is sufficient for adequate control of the starting material?**

   FDA Response:
   Your proposed specification appears reasonable at the present time, but it is premature for us to decide on its adequacy since you plan to conduct further experiments which you believe may result in modifications to the specification.

   Discussion:
   The sponsor accepted the responses, and no further discussion was needed.

3. **Based on the data provided, does the Agency agree that the final proposed specifications for Genz-112638 are sufficient for an NDA application?**

   FDA Response:
   Your proposed specification for the Genz-112638 drug substance appears reasonable, but will need to be further evaluated when you submit your complete NDA application; at that time, based on the information in your submission, we may find that additional tests are required.

   Discussion:
   The sponsor accepted the responses, and no further discussion was needed.

4. **Genzyme plans to utilize (b) (4) (b) (4) (b) (4) Based on the following points, does the Agency agree that the data provided are supportive for approval of the proposed commercial drug product?**

   - (b) (4)
   -

   FDA Response:

   (b) (4)

   Discussion:

   (b) (4)

5. **As the use of the (b) (4) in the proposed commercial capsules complies with 21CFR (b) (4) (b) (4) does the Agency agree that it is acceptable for use?**

   FDA Response:
   Yes, we agree.

   Discussion:
   The sponsor accepted the responses, and no further discussion was needed.

6. **As supportive data demonstrates that neither the drug product manufacturing process, the formulation, nor long term storage of the drug product alters the (b) (4) of the Genz-112638 compound, does the Agency agree that there is sufficient justification for not including (b) (4) in the list of proposed tests for the drug product?**

FDA Response:
The agency notes that the data provided in Table 6 does demonstrate that the provided stability data does indicate that the drug product is (b) (4) for all CTM lots. However, to support your proposal of (b) (4) in the list of proposed tests for the drug product, provide any available data in the submission to indicate that the drug product remains (b) (4) when manufactured within the proposed design space.

Discussion:
The sponsor accepted the responses, and no further discussion was needed.

7. **Does the Agency agree that the proposed list of tests to be included in the Genz-112638 (b) (4) 100 mg, (b) (4) strength capsules release specifications are appropriate for the NDA application?**

FDA Response:
Your proposed specification for the drug product appears reasonable, but will need to be further evaluated when you submit your complete NDA application; at that time, based on the information in your submission, we may find that additional tests are required. Regarding the proposed dissolution specification, if your product is classified as a BCS Class 1 drug product, the specification needs to reflect a fast dissolving product and should be revised to Q= (b) (4)% at (b) (4) minutes.

Discussion:
The sponsor accepted the responses, and no further discussion was needed.

8. **Does the Agency agree that the solubility and permeability data available for Genz-112638 is supportive of BCS Class 1 drug designation, and it is thereby acceptable to present data package supporting a Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms in the NDA?**

FDA Response:
No, we do not agree at this time. The provided information appears to indicate that Genz-112638 is a BCS Class 1 drug substance; however, this information is limited. Please provide the solubility and permeability final study reports with the complete data (i.e., design of the experiment, testing, assay, results, etc.)

Also, please provide the dissolution data demonstrating that your drug product is fast dissolving at pH 1.2, 4.6, and 6.8 (USP Apparatus 2, paddle rotation speed of (b) (4) rpm).

As well as the data demonstrating the stability of your drug in the gastrointestinal tract and that the excipients of your formulation will not affect absorption.

If we determine that the to-be-provided information supports a BCS Class 1 classification for your drug substance and drug product, we would be able to waive the requirement to provide in vivo BA/BE data and/or provide food-effect data for your product.

Discussion:
The sponsor will submit the completed solubility and permeability reports. The sponsor confirmed that studies were done to evaluate the product's gastrointestinal tract stability and will provide an amendment to the IND.

9. If a BCS Class 1 designation is granted for Genz-112638, Genzyme does not plan to conduct additional food-effect studies. Does the Agency agree?

FDA Response:
If a BCS Class 1 designation is granted to your drug product, yes we agree that you do not need to conduct a food-effect study for (b) (4)

Discussion:
The sponsor accepted the responses, and no further discussion was needed.

10. To enhance our process understanding and product knowledge, Genzyme plans to perform studies for the drug substance and drug product to determine the critical quality attributes and establish control strategy. Genzyme plans to present these data in the NDA. Does the Agency agree these experiments are comprehensive enough to support a QbD filing?

FDA Response:
The Agency agrees that your proposed approach does have elements of QbD. However, at this time there is not sufficient information to provide recommendations about the proposed QbD based approach. It would facilitate the review if in addition to risk assessment analysis; you provide supportive experimental data along with a description of the control strategy. It is also recommended to include a discussion about criticality of interaction of parameters.

Specific topics for discussion regarding Genzyme's Proposed QbD Strategy (outlined in Attachments 1 and 2):

a) Do you agree with our strategy to define the Design Space for CPP and CQA?

FDA Response:
The agency agrees with your approach to identify parameters that have an impact on product quality via risk assessment. We recommend that you consider defining a design space in terms of parameters that have a have potential to adversely impact product quality. In addition, provide supporting data to demonstrate that parameters that are not

part of the design space do not have potential to adversely impact product quality at commercial scale.

Discussion:
The sponsor accepted the response so no further clarification was needed. In addition, the agency pointed out that upon obtaining additional data to support the QbD paradigm, the sponsor could request to set up a Type C meeting with ONDQA/FDA to discuss their proposed QbD approach.

As a post meeting note, the agency suggests that the sponsor consider the impact of scale when defining the design space..

b) When we have defined the Design Space for CPP and CQA in-process parameters, will excursions within the design space be permitted to be handled by internal investigations?

FDA Response:
Any excursions within the design space need to be evaluated within your internal Quality System in accordance with cGMP. Knowledge obtained during design space development can be used to aid in the investigation.

Discussion:
The sponsor accepted the response, and no further discussion was needed.

c) Will the results from laboratory scale spiking studies allow us to modify the in-process specification range to control critical impurities at intermediate steps in the drug substance manufacturing process?

FDA Response:
Prior to providing a response to this comment, the agency would like further clarification of the statement "modify the in-process specification range".

Discussion:
The sponsor clarified that they propose to set in-process release specifications based on results from spiking studies. As a post meeting note, the agency commented that specifications for critical impurities may be set on the basis of spiking studies; so long the spiking studies are relevant throughout the proposed design space. Furthermore, specifications once approved, may not be modified without regulatory notification.

d) As demonstrated in the (b) (4) example (Attachment 2), do you agree with our strategy of selecting the critical process, the design of experiments to define the design space and the strategies to control product quality?

FDA Response:
The agency agrees with your approach of implementing risk assessment methodologies (e.g. FMEA) to identify process variables and material attributes that have a significant potential to adversely impact drug product, and then evaluating them further via planned

DoE to define a design space is reasonable. Additionally, to aid in the review process consider providing the following information for critical steps: (a) Raw data about DoE's executed to define design space, including data from actual runs, statistical analysis of DoE data and comparison of predicted versus actual values (b) details about how the design space would be scaled up from laboratory to commercial scale, (c) describe how the design space would be tested and verified at commercial scale, (d) data about interaction of parameters. Furthermore, to support your control strategy based on monitoring of (b) (4) *consider providing the following: (a) details about interfacing the* (b) (4) *to the process* (b) (4) *to ensure that the measurement is representative of the batch (b) data about development, validation and maintenance of models associated with* (b) (4) *Note that acceptability of all data would be determined during the NDA review process.*

Discussion:

The sponsor accepted the response so no further clarification was needed. The agency pointed out that when defining a design space, the sponsor should consider the impact of excipient lot variability on the design space. As a post meeting note, the agency suggested that the sponsor consider providing data for the following: (a) to demonstrate how the (b) (4) *is correlated to* (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)

3.0 ISSUES REQUIRING FURTHER DISCUSSION

Possible having a type C meeting for the sponsor and ONDQA/FDA to discuss proposed QbD approach.

4.0 ACTION ITEMS

Sponsor:

1. Provide complete data supporting the BCS-Class 1 classification for the drug substance/drug product (i.e., solubility, permeability, and fast dissolution) and the drug product stability in the gastrointestinal tract.

2. Include a biowaiver request for (b) (4) and provide the complete information supporting this request in the NDA.

3. Add specifications for relevant in-process intermediates for drug substance synthesis.

5.0 CONCURRENCE

{See appended electronic signature page}

Cathy Tran-Zwanetz
Regulatory Health Project Manager for Quality
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

{See appended electronic signature page}

Terrance Ocheltree, Ph.D., R.Ph.
Division Director
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-67589	GI-1	GENZYME CORP	GENZ-112638 CAPSULES

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/s/

CATHERINE A TRAN-ZWANETZ
08/12/2010

TERRANCE W OCHELTREE
08/12/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 67,589

Genzyme Corporation
Attention: Lauren Sykes, Senior Regulatory Affairs Associate
500 Kendall Street
Cambridge, MA 02142

Dear Ms. Sykes:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Genz-112638.

We also refer to the meeting between representatives of your firm and the FDA on February 5, 2009. The purpose of the meeting was to discuss the results from a Phase 2 clinical study GZGD00304, the results from a Phase 1 clinical study GZGD01707, and feedback on Phase 3 study designs.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1007.

Sincerely,

{See appended electronic signature page}

Cristi L. Stark, M.S.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 5, 2009
TIME: 3:00-4:00pm EDT
LOCATION: CDER WO 1313
APPLICATION: 67589
DRUG NAME: Genz-112638
TYPE OF MEETING: Type B

MEETING CHAIR: Anil Rajpal, MD

MEETING RECORDER: Cristi Stark

FDA ATTENDEES: (Title and Office/Division)

Anil Rajpal, MD, Medical Team Leader, ODEIII/DGP
Cristi Stark, MS, Regulatory Health Project Manager, ODEIII/DGP
Donna Griebel, MD, Director, ODEIII/DGP
Jane Bai, PhD, Clinical Pharmacologist, OCP/DCP3
Christine Garnett, PhD, OT/IRT Reviewer, OCP/PS
Tamal Chakraborti, PhD, Pharm/Tox Reviewer, ODEIII/DGP
Sushanta Chakder, PhD, Supervisory Pharmacologist, ODEIII/DGP
Ilan Irony, MD, Medical Team Leader, ODEIII/DGP
Carla Epps, MD, Medical Officer, ODEIII/DGP
Mike Welch, PhD, Statistical Team Leader, OB/DBIII
Behrang Vali, MS, Statistician, OB/DBIII
Shahla Farr, MS, Statistician, OB/DBIII

EXTERNAL CONSTITUENT ATTENDEES:

Alex Kuta, PhD, VP, Regulatory Affairs
Edward Kaye, MD, Group VP, Clinical Research
Gerald Cox, MD, PhD, VP, Clinical Research
Judith Peterschmitt, MD, Associate Medical Director, Clinical Research
Donna Mackey, Senior Director, Clinical Research
Sharon Smith, MD, Associate Medical Director, Pharmacovigilance
Mark Bree, Scientific Director, Pharmacology and Preclinical Development
Peter Bonate, PhD, Senior Director, Clinical Pharmacology and Pharmacokinetics
Fanny O'Brien, PhD, Senior Director, Biostatistics
Rumana Haque-Ahmed, Senior Director, Regulatory Affairs
Lauren Sykes, Senior Associate, Regulatory Affairs
Jeffrey Litwin, MD, FACC, Executive Vice President and Chief Medical Officer

MEETING OBJECTIVES:

To obtain feedback on Genzyme's product registration plan by discussing the Phase 1 and Phase 2 clinical data, and planned Phase 3 clinical studies.

DISCUSSION POINTS:

FDA PRELIMINARY CLINICAL COMMENT:

We recommend that you submit a Special Protocol Assessment (SPA) for your proposed study in patients not currently receiving treatment (Study GZGD02507) for the Division's review and concurrence before starting the study. Submission of a SPA for this study will allow for discussion and agreement on elements of the study, such as dose selection, appropriate endpoints, trial duration, statistical assessments, and other specific aspects of the study design. Please include for our review in the SPA submission all of the clinical data obtained in your Phase 1/2 program, as well as any other relevant data, such as published medical literature. For additional information on SPA submission, please refer to the SPA Guidance document, which can be found at www.fda.gov/Cber/gdlns/protocol.pdf.

SPONSOR POSED QUESTIONS:

1. Does FDA agree that the cardiac data collected from the current single dose thorough QT/QTc (TQT) study in combination with all other information available from Phase 1 and Phase 2 studies, provide sufficient safety data to permit initiation of the proposed Phase 3 Studies of Genz-112638?

   FDA Response:

   Yes, with ECG monitoring in subsequent studies (see our response to Question 2).

   Discussion at Meeting:
   None.

2. Genzyme considers the Thorough QT/QTc (TQT) study a negative study as defined by ICH E14 and seeks FDA concurrence on the study conclusions. In addition, does the Agency have any specific comments and/or guidance with regard to the QTc gender differences noted?

   FDA Response:

   Even though the study can be claimed to be a negative study as defined by ICH E14, Genz-112638 is clearly prolonging the QTc and PR intervals in a concentration-dependent manner. Additional ECG monitoring after multiple dose administration at T_{max} should be performed in Phase 3 clinical studies to capture any clinical meaningful changes in ECG parameters in the patient population. Your proposed ECG monitoring plan in Studies GZGD02507 and GZGD02607 is acceptable to collect these data.

Based on our analysis, female subjects were found to be more sensitive to the QTc prolonging effects of Genz-112638; however, the clinical significance of this finding is unknown. To determine if this finding is reproducible, we recommend that you evaluate potential sex-related effects of Genz-112638 using the ECGs collected in the phase 3 studies.

Discussion at Meeting:
None.

3. a. Does FDA agree that the two proposed Phase 3 study designs, durations, composite primary endpoints, proposed analyses of the primary endpoints, safety monitoring, and inclusion/exclusion criteria would support a successful NDA filing?

FDA Response:

The final determination of the adequacy of the application will be made at the time of NDA filing. However, we have the following comments below regarding each of the two proposed Phase 3 studies.

Study in Patients Not Currently Receiving Treatment (GZGD02507):

- **Endpoints and Analyses of Endpoints: We do not agree with the proposed composite primary endpoint which is based on change in spleen volume (b) (4) (b) (4) We recommend that you use change in spleen volume as the primary endpoint, change in hemoglobin concentration, change in platelet count, and change in liver volume each as secondary endpoints, and that you use a step-down procedure where spleen volume is tested first followed by each of the three major secondary endpoints.**

  We disagree with the primary endpoint analysis being based on the (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) We recommend that you use a worst case analysis (assigning failure status to patients who drop out of the study prior to Week 39) which you previously presented as a sensitivity analysis in the information package provided. The complete case analysis using the ITT completer population can subsequently act as a valid sensitivity analysis (b) (4)

- **Study Design and Duration: In principle, the proposed randomized placebo-controlled study design and the proposed duration of the double-blind period (39**

weeks) are reasonable; however, we cannot provide agreement on specific study design features until we have performed a detailed review of your protocol in a SPA (see also FDA Preliminary Clinical Comment). Study design features that will be assessed include details about the methods used to calculate organ volumes and to analyze MRI's or spiral CT's (e.g., information about training of readers, a requirement for more than one reader to assess organ volumes, provisions for a third reader if the difference in organ volume determinations between readers exceeds a specified percentage, and criteria for the organ volume assessment to be considered valid).

Regardless of the potential influence of your stratification variables (spleen volume and platelet count), we feel the use of two levels of stratification in a study with such a small sample size may introduce a deterministic element into the randomization thereby increasing the predictability of treatment assignments for patients. This may ultimately create biases which can invalidate your results. Not stratifying prior to randomization and subsequently correcting for these variables in the analysis (which you are already doing) may be sufficient. If however you still feel that stratification is necessary, then we advise you to include in your analysis plan a re-randomization test as an additional sensitivity analysis.

- **<u>Inclusion/Exclusion Criteria and Safety Monitoring</u>: In principle, the proposed inclusion and exclusion criteria and the proposed safety monitoring plan are reasonable; however, we cannot provide agreement on the eligibility criteria and on the safety monitoring provisions until we have performed a detailed review of your protocol in a SPA (see also FDA Preliminary Clinical Comment).**

<u>Study in Prior ERT-treated Patients (GZGD02607)</u>:

- **<u>Endpoints and Analyses of Endpoints</u>: We do not agree with the proposed primary endpoint. The definition of stable hematological parameters allows Hb to decrease up to (b) (4) g/dL in females and up to (b) (4) g/dL in males and allows platelet count to decrease up to (b) (4) from baseline; the definition of stable organ volumes allows spleen volume and liver volume to each increase up to (b) (4) from baseline. (b) (4) (b) (4) Unless you can provide data from a population similar to the population that you wish to study (i.e., patients that have been receiving enzyme replacement therapy for at least 3 years) that supports the proposed definition of stable hematological parameters and stable organ volumes, we recommend that you revise the definition of stable hematological parameters with a lower magnitude of decrease in Hb concentration allowed and a lower magnitude of decrease in platelet count allowed than those currently proposed, and that you revise the definition of stable organ volumes with a lower magnitude of increase in spleen volume allowed and a lower magnitude of increase in liver volume allowed than those currently proposed.**

- **Study Design and Duration: We request that you use a concurrently-controlled trial design rather than** (b) (4) **One option may be a randomized withdrawal design in which prior ERT-treated patients are randomized to either continue on ERT or to switch to Genz-112638. Another option may be a randomized add-on design in which prior ERT-treated patients are randomized to either continue on ERT alone or to receive concurrent therapy with Genz-112638 and ERT.**

  In principle, the study duration that you have proposed, 52 weeks, is reasonable; however, we cannot provide agreement on the study duration until we have performed a detailed review of your protocol.

- **Inclusion/Exclusion Criteria and Safety Monitoring: In principle, the proposed inclusion and exclusion criteria and the proposed safety monitoring plan are reasonable; however, we cannot provide agreement on the eligibility criteria and the safety monitoring provisions until we have performed a detailed review of your protocol.**

b. Does FDA agree with the proposed dosing strategy in the Phase 3 studies?

FDA Response:
In principle, the proposed dosing strategy in each of the Phase 3 studies is reasonable; however, we cannot provide agreement on the proposed dosing strategy until we have performed a detailed review of your protocols (see also FDA Preliminary Clinical Comment).

Discussion at Meeting:
Genzyme proposed the spleen assessment in the untreated GD1 trial to have spleen volume assessed by either MRI or spiral CT. Each subject will be tested at baseline and through the study with the same equipment (test re-test variability are as follows: MRI - ~10%, spiral CT - ~3-5%). There will be a central analysis of data by readers who are experts in Gaucher disease to ensure consistency in organ volume assessments. Also the majority of the study should be MRI (~90%). The reason for two methods of analysis is due to the fact that some sites do not have access to an MRI. In addition, in Europe and the US, a spiral CT poses some obstacles to IRB approval due to radiation levels emitted during testing. FDA replied that this point is still under discussion and a firm answer will be given at a later date; the response is provided below as an addendum.

Genzyme proposed their rationale for hemoglobin as an endpoint in the untreated GD1 trial. FDA stated that additional information will need to be provided for buy-in of clinical utility (a lot has changed since 1998).

Genzyme proposed their rationale for platelets as an endpoint in the untreated GD1 trial. They stated that an increase in platelets gets subjects away from the "critical range of 5 – 10,000". Genzyme added that it is hard to place a value on change if the change is outside of

the critical range. Genzyme has seen anemic subjects with a spleen removed (and raised platelets) respond well to ERT. FDA inquired if Genzyme had looked at studying subjects feeling better. If the spleen volume shrinks, a subject should feel better. How could Genzyme incorporate those findings? Genzyme replied that with Gaucher subjects the SF-36 was explored; however, the tool is rather insensitive and it would take several years to see a difference.

In regards to the maintenance primary endpoint, Genzyme needed clarification if the composite or the threshold was objected to by the Agency. FDA responded that the objection is towards the thresholds; further clarification about FDA's view of the proposed composite endpoint is provided below as an addendum. Genzyme pointed FDA to the Cerezyme Q2Q4 study results where subjects failed the primary endpoint even though clinically they were unchanged due to a narrower range. Genzyme also added that for a typical Gaucher subject, the spleen size is approximately 20X normal. In the maintenance study it will be less than 10X normal and there will be a minimal success rate of 65%. FDA stated that the problem is that in the single-arm, unrandomized study there is no inferential statistics, only descriptive. This will create an issue when interpreting results. Genzyme stated that they will go back and internally review the FDA proposed randomized withdrawal trial.

4. Assuming an acceptable risk-benefit profile of Genz-112638 as determined in the Phase 2 and confirmed in Phase 3 studies, Genzyme seeks FDA concurrence that the size of the safety database will be sufficient to support registration of Genz-112638 as treatment for patients with Gaucher disease type 1.

FDA Response:

The proposed safety database appears reasonable, barring any new safety concerns that may be identified, as it appears to meet the ICH E1A Guidance regarding numbers of patients exposed for the various durations.

The final determination of the adequacy of the safety database will be made in the course of reviewing the complete application.

Discussion at Meeting:
None.

5. Genzyme would like to discuss with the FDA, the use of a change in spleen volume as the primary endpoint instead of a composite endpoint for the proposed untreated, placebo-controlled, double blind Phase 3 Study and the study design and duration implications.

FDA Response:

For the proposed Phase 3, double-blind placebo-controlled study in patients that are not currently being treated with other agents (Study GZGD02507), it would be acceptable to use change in spleen volume as the primary endpoint if change in hemoglobin concentration, change in platelet count, and change in liver volume are

each included as secondary endpoints and the following step-down procedure is incorporated into the protocol and the statistical analysis plan:

- **First, test spleen volume at the 0.05 alpha-level.**
- **If spleen volume is shown to be significant, then proceed with testing the three major secondary endpoints. Please note that you will need to submit a proposal for a method of testing the three major secondary endpoints with the appropriate adjustment for the 0.05 alpha level.**

The change in spleen volume (≥ 20%) that you have proposed appears to be a clinically meaningful result. However, the proposed change in hemoglobin concentration (≥ 1 g/dL) and the proposed change in platelet count (≥ 20%) may not be clinically meaningful; please provide justification for why an increase in Hb concentration of ≥ 1 g/dL and an increase in platelet count of ≥ 20% would represent a clinically meaningful benefit to patients. Please also propose a clinically meaningful change in liver volume, and provide justification for why it represents a clinically meaningful benefit to patients.

You should ensure that the sample size will be adequate to demonstrate efficacy for each of the endpoints (i.e., the primary endpoint and the three major secondary endpoints).

We remind you that should Genz-112638 be approved, the indication for Genz-112638 in the product labeling will be limited to only those endpoints for which substantial evidence of efficacy has been demonstrated.

Discussion at Meeting:
None.

6. Please comment on the proposed indication for Genz-112638 and whether the efficacy data available from the Phase 2 study and the proposed Phase 3 studies would support the proposed indication.

FDA Response:

The first part of the indication (as a long-term therapy for adult patients with Gaucher disease (b) (4) (b) (4) **will be primarily based on the analyses of the primary endpoint and the major secondary endpoints of the Phase 3 study in patients who are not currently being treated with other agents (Study GZGD02507) as described in the Response to Question 5; supportive data may be provided from the Phase 2 study (Study GZGD00304) and the Phase 3 study in prior enzyme-replacement therapy treated patients (Study GZGD02607).**

The second part of the indication (as a long-term therapy for adult patients with Gaucher disease type 1 patients (b) (4) (b) (4) **will be**

primarily based on the analyses of the primary endpoint of the Phase 3 study in enzyme-replacement therapy treated patients (Study GZGD02607); supportive data may be provided from the Phase 2 study (Study GZGD00304) and the Phase 3 study in patients who are not currently being treated with other agents (Study GZGD02507).

Actual wording of the indication would be based on the clinical trial results and would be discussed after a determination that the primary endpoint and the major secondary endpoints were met.

Discussion at Meeting:
Genzyme provided a new proposal to support the first part of the indication proposed in the briefing package. Included in this proposal the untreated study (GZGD02507) would have spleen as a primary endpoint and long term data from the Phase 2 study to support a marketing application. At the time of application filing, Genzyme proposed that the safety database size would be based on the single Phase 3 and Phase 2 trials (approximately 40 patients with 9 months of treatment). FDA stated that as this proposal was outside of the original meeting request, an answer could not be provided during the meeting. The response to the proposal is provided below as an addendum.

7. Does FDA have any comment with respect to the Phase 1 Clinical Pharmacology program that is completed and planned? Specifically:

   a. Does FDA concur that the selection of drugs for completed and planned studies are appropriate to characterize the potential for drug-drug interactions?

   FDA Response:

   Since Genz-112638 showed a high efflux in the intestine and its efflux was blocked by Cyclosporin A (a Pgp inhibitor), it is strongly recommended that you study in humans drug-drug interaction (DDI) with a strong Pgp inhibitor such as Cyclosporin A and with digoxin (a Pgp substrate). You must determine the in-vitro inhibitory potency (Ki) of your product on Pgp-mediated efflux. Your compound showed unusual PK characteristics and a much higher exposure after several weeks of administration, so the DDI studies at steady state (after several weeks of daily administration) are strongly recommended. For any drug-drug interaction study, you must also perform ECG monitoring. Please refer to the guidance for industry entitled "*Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling (September 2006)*".

   Additional comments for the future NDA submission: For the food effect study, it is important that the to-be-marketed formulation is studied. Since your food effect study (Study GZGD00404) has been completed, a bridging bioequivalence study may be needed between the food effect formulation and the to-be-marketed formulation if these two formulations are not the same.

If the to-be-marketed and clinical formulations are different, a bridging bioequivalence study may be needed as well.

We suggest you collect DNA samples during your Phase 3 trials to determine any genetic associations between CYP450 enzymes, uptake/efflux transporters, and serious adverse events.

b. Does FDA concur that given the Orphan status of Gaucher disease and availability of an alternate treatment option with enzyme replacement therapy, that a study evaluating the pharmacokinetics of Genz-112638 in patients with impaired hepatic function is not required for the NDA/CTD filing?

FDA Response:

It is acceptable not to study the PK of Genz-112638 in patients with impaired hepatic function but the proposed labeling language will need to reflect this fact when the NDA application is submitted.

c. Does FDA concur that the planned Phase 1 Clinical Pharmacology program is sufficient for the NDA/CTD filing?

FDA Response:

See above response to part A.

Discussion at Meeting:
Regarding the DDI studies, Genzyme stated that they had recently completed a multidose interaction study with ketoconazole which they felt was a suitable substitute for CsA. The sponsor agreed to conduct a DDI study with digoxin. FDA suggested that Genzyme look into studies with more transporters such as OATP, MRP, and BCRP in addition to PGP in animal studies. The sponsor agreed that when the results of animal studies are available, the issues of DDI with transporter inhibitors should be revisited.

Regarding the collection of DNA for genotyping, Genzyme stated that the planned Phase 3 study will assess CYP2D6 genotypes. They also asked for clarification regarding the uptake/efflux transporters. FDA replied that they were referring to OATP, MRP, and BCRP in liver. It is important to utilize collected samples for testing when an adverse event appears and use that information for individualized medicine. FDA commented it is important to understand the gene/drug interaction. In addition, as an addendum to the minutes there will be suggestions for genotyping that covers many genes.

8. Does FDA have any comment with respect to the Non Clinical program that is completed and planned and does FDA concur that the proposed Non Clinical program would support a successful NDA filing?

FDA Response:

Yes, we concur. However, full reports of all the completed and planned nonclinical studies including carcinogenicity studies in mice and rats must be submitted to the NDA for the Agency's review as previously recommended at the Type C meeting on July 17, 2008 (Memorandum of Meeting Minutes dated August 26, 2008).

Discussion at Meeting:
None.

ADDENDUM TO MINUTES:

Response of spleen volume size testing by MRI and spiral CT from Question 3:

The data will need to be analyzed separately for CT and for MRI spleen volumes, since the characteristic profiles, particularly intra-subject variability, are so different. Even if the CT-imaged population is expected to constitute only 10% of the total sample size, their data may be very useful in determining change from baseline, given the more narrow variability obtained. To reduce the appearance of bias, blinding can be more rigorous if done by radiologists not only blinded to treatment, but also to sequence, with all readings conducted at the end of the treatment period.

Clarification of FDA's view of the proposed primary endpoint for the study in Prior ERT treated patients from Question 3:

For the primary endpoint, a composite of spleen volume, Hb level, and platelet count would be acceptable. Inclusion of liver volume as a component of the primary endpoint would also be acceptable; alternatively, liver volume could be a secondary endpoint.

Response to Genzyme's new study proposal from Question 6:

Your new proposal to conduct [redacted] (b) (4) would not be adequate to demonstrate efficacy in prior ERT-treated patients, the population that is likely to constitute the majority of Gaucher disease type 1 patients that will use the drug if it is approved. In addition, with your new proposal, the safety database would fall short of the ICH E1A Guidance regarding overall numbers of patients exposed for the various durations, and would not include a sufficient number of prior ERT-treated patients. We recommend that you also conduct at least one Phase 3 study in prior ERT-treated patients; you should study both add-on therapy (i.e., concurrent therapy with Genz-112638 and ERT) and switch therapy (i.e., withdrawal from ERT and switch to therapy with Genz-112638 alone) and the comparator arm should be continuation of ERT alone. This may provide important labeling information for prior ERT-treated patients such as the time course and magnitude of the clinical response with add-on therapy and with switch therapy as measured by parameters such as spleen volume, liver volume, hemoglobin level, and platelet count; also, this may help to identify safety concerns particular to the prior ERT-treated population.

Response of suggestions for genotyping that covers many genes:

Genzyme requested that FDA provide the names of commercial kits for genotyping the transporter candidate genes of transporters mentioned during the meetings. The information gathered by the FDA with respect to the genotyping kits that are commercially available is as follows: (1) real-time PCR FRET assays of LightCycler (Roche Diagnostics, Almere, the Netherlands); (2) single base primer extension assay of ABI Prism SNaPShot Multiplex kit (ABI, Foster City, CA, USA); (3) PCR-RFLP assay of TaqI (Roche Diagnostics GmbH, Basel, Switzerland)

Linked Applications	Sponsor Name	Drug Name / Subject
IND 67589	GENZYME CORP	GENZ-112638 CAPSULES

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/s/

CRISTI L STARK
03/13/2009

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205494

LATE-CYCLE MEETING MINUTES

Genzyme Corporation
Attention: Sherwin Sattarzadeh
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Sattarzadeh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cerdelga (eliglustat).

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on June 19, 2014.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Lara Dimick, M.D.
Medical Officer Team Leader
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: June 19, 2014 from 1:00 PM to 2:30 PM EDT
Meeting Location: White Oak Building 22, Conference Room 1311

Application Number: NDA 205494
Product Name: Cerdelga (eliglustat)
Applicant Name: Genzyme

Meeting Chair: Lara Dimick, MD
Meeting Recorder: Jessica M. Benjamin, MPH

FDA ATTENDEES

Julie Beitz, MD, Director, Office of Drug Evaluation III
Donna Griebel, MD, Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Andrew Mulberg, MD, Deputy Director, DGIEP
Joyce Korvick, MD, Deputy Director for Safety, DGIEP
Lara Dimick, MD, Clinical Team Leader, DGIEP
Karyn Berry, MD, Medical Officer, DGIEP
Sushanta Chakder, PhD, Lead Interdisciplinary Scientist, DGIEP
Tamal Chakraborti, PhD, Pharmacologist, DGIEP
Sue Chih Lee, PhD, Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Sandhya Apparaju, PhD, Clinical Pharmacology Reviewer, OCP
Elizabeth Shang, PhD, Clinical Pharmacology Reviewer, OCP
Anshu Marathe, PhD, Pharmacometrics Reviewer, OCP
Nitin Mehrotra, PhD, Pharmacometrics Team Leader, OCP
Sarah Dorff, PhD, Pharmacogenomics Reviewer, OCP
Ping Zhao, PhD, Pharmacologist, OCP
John Stinson, MD, Medical Officer, Division of Bone, Reproductive, and Urologic Products
Jessica Benjamin, MPH, Senior Regulatory Project Manager, DGIEP
Richard Ishihara, Chief Project Manager Staff, DGIEP
Brian Strongin, PharmD, Chief Project Manager Staff, DGIEP
Carolyn McCloskey, MD, Medical Officer, Division of Epidemiology II, Office of Surveillance and Epidemiology (OSE)
Ling-Yu (Eileen) Wu, Lead Pharmacist, OSE
George Neyarapally, Health Scientist, Division of Risk Management, OSE

EASTERN RESEARCH GROUP ATTENDEES

(b) (6)

APPLICANT ATTENDEES

Mish Gerhart, MS, VP Regulatory Affairs
Rumana Haque-Ahmed, Senior Director Regulatory Affairs

Sherwin Sattarzadeh, Associate Director Regulatory Affairs
Gerald Cox, MD, PhD, VP Clinical Research
Judith Peterschmitt, MD, Medical Director Clinical Research
Lisa Von Moltke, MD, VP Clinical Pharmacology
Jennifer Angell, ScM, Director Biostatistics
Leorah Ross, MD, Director GPSRM Risk Management
Kate Alexander, Principal Associate Regulatory Affairs
Cordula Schwarz, Principal Associate Regulatory Affairs
Kimberlee Raymer, Principal Associate Regulatory Affairs CMC

1.0 BACKGROUND

NDA 205494 was submitted on September 20, 2013 for Cerdelga (eliglustat).

Proposed indication(s): long-term treatment of adult patients with Gaucher disease type 1

PDUFA goal date: August 20, 2014

FDA issued a Background Package in preparation for this meeting on June 6, 2014.

2.0 DISCUSSION

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

Discussion:
No further discussion.

2. Discussion of Substantive Review Issues

Dosing in CYP2D6 poor metabolizers (PMs)

Discussion:
Please see attached presentation slides. Genzyme will submit a revised label based on today's discussion next week.

3. Additional Applicant Data

Discussion:
Genzyme will submit a summary and justification and any associated data sets for DDI dose recommendations to justify combining IM and EM populations. The agency would be interested in discussing dosing for indeterminate however we feel that we can not review this data during the current review cycle. The sponsor will submit a efficacy supplement for dosing in indeterminate metabolizers in the future. The agency is open changing the wording in the Limitations of Use section.

Please see attached presentation slides.

4. **Information Requests**

Carton and container comments were issued in an information request letter dated June 4, 2014.

Discussion:
Response received June 16, 2014.

5. Postmarketing Requirements/Postmarketing Commitments

- Conduct a study to evaluate the effects of various degrees of hepatic impairment on eliglustat PK.
- Conduct a study to evaluate the effect of renal impairment on eliglustat PK. A reduced design may be used.
- Develop a 25-mg and/or 50-mg strength formulation for dosing in PMs and to accommodate dosage adjustment in drug-drug interaction scenarios. A 25-mg strength is clinically relevant to allow flexibility in dosage adjustment and eliminate restrictions in some DDI scenarios. Such flexibility may enhance safe use of the product.
- (b) (4)

Discussion:
Genzyme proposes to adjust wording for PMCs requiring lower doses (b) (4) ***. Genzyme noted the difficulty with recruiting hepatic impaired patients. The agency clarified that the patients can be non-Gaucher patients with hepatic insufficiency.***

Please see attached presentation slides

6. **Major labeling issues**

- Pregnancy category should be changed to "Category C" instead of the proposed (b) (4) based on adverse reproductive findings in rats.
- Dosing recommendations in DDI scenarios.

Discussion:
The agency will review Genzyme's request to (b) (4)

Please see attached presentation slides.

7. **Review Plan**

We plan to complete the reviews in accordance with the PDUFA goal dates.

Discussion:

No further discussion.

8. Wrap-up and Action Items

Discussion:
No further discussion.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

LARA DIMICK-SANTOS
08/12/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205494

LATE CYCLE MEETING
BACKGROUND PACKAGE

Genzyme Corporation
Attention: Sherwin Sattarzadeh
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Sattarzadeh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for eliglustat tartrate.

We also refer to the Late-Cycle Meeting (LCM) scheduled for June 19, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, M.D., FAAP, CPI
Deputy Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: June 19, 2014 from 1:00 PM to 2:30 PM EDT
Meeting Location: White Oak Building 22, Conference Room 1311

Application Number: NDA 205494
Product Name: Cerdelga (eliglustat tartrate)
Indication: Long-term treatment of adult patients with Gaucher disease type 1
Sponsor/Applicant Name: Genzyme

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

Clinical Pharmacology

- Dosing in CYP2D6 Poor metabolizers (PMs)

  (b) (4). Considering the totality of evidence pertaining to efficacy & safety of eliglustat, exposure-response analysis

for efficacy & safety, observed PK data and simulations, we recommend a 100 mg QD regimen for CYP2D6 poor metabolizers. A brief rationale for this dosing recommendation is provided below.

Based on the data provided, we predicted that mean C_{max} in poor metabolizers at 100 mg QD dose was approximately 75 ng/mL, which will likely not result in QT related safety concerns based on the concentration-QT relationship established in the TQT study. Furthermore, this C_{max} is within the range of C_{max} observed for eliglustat in the clinical development program. You proposed a 100 mg BID dose for intermediate metabolizers (IMs). With a 100 mg QD dose in PMs, the predicted AUC_{0-24h} is approximately 1000 ng/ml*h, which is comparable to the predicted AUC_{0-24h} for IMs at the 100 mg BID dose and is also within the exposures that were observed in the clinical development program.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

At this time, we do not believe that a REMS will be necessary to ensure the benefits of eliglustat outweigh the risks.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. Pregnancy category should be changed to "Category C" instead of the proposed (b) (4) (b) (4) based on adverse reproductive findings in rats. In rats, eliglustat, at a dose of 120 mg/kg/day (about 6 times the recommended human dose based on body surface area), 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).
2. Summary information on ADME characteristics should be stratified by CYP2D6 phenotype as appropriate.
3. Dosing recommendations for DDIs should be made based on CYP2D6 phenotype. This is because, at the proposed doses, the systemic exposure differs across CYP2D6 phenotypes (EM/IM/PM) and the magnitude of eliglustat exposure change can also differ among these phenotypes. For the cases where eliglustat is a victim drug, the systemic exposure at 100 mg QD in PMs is considered the maximum allowable exposure based on the clinical experience and safety profile of the drug.

We plan to send draft labeling next week that includes these issues and other labeling revisions. At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

LCM AGENDA

1. **Introductory Comments – 5 minutes (RPM/CDTL)**

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. **Discussion of Substantive Review Issues – 20 minutes**

   Each issue will be introduced by FDA and followed by a discussion.

   - Dosing in CYP2D6 poor metabolizers (PMs)

3. **Additional Applicant Data – 20 minutes (Applicant)**

4. **Information Requests – 5 minutes**

   - Carton and container comments were issued in an information request letter dated June 4, 2014.

5. **Postmarketing Requirements/Postmarketing Commitments – 20 minutes**

   - Conduct a study to evaluate the effects of various degrees of hepatic impairment on eliglustat PK.
   - Conduct a study to evaluate the effect of renal impairment on eliglustat PK. A reduced design may be used.
   - Develop a 25-mg and/or 50-mg strength formulation for dosing in PMs and to accommodate dosage adjustment in drug-drug interaction scenarios. A 25-mg strength is clinically relevant to allow flexibility in dosage adjustment and eliminate restrictions in some DDI scenarios. Such flexibility may enhance safe use of the product.

- (b) (4)

6. Major labeling issues – 15 minutes

- Pregnancy category should be changed to "Category C" instead of the proposed (b) (4) based on adverse reproductive findings in rats.
- Dosing recommendations in DDI scenarios.

7. **Review Plan**

We plan to complete the reviews in accordance with the PDUFA goal dates.

8. Wrap-up and Action Items – 5 minutes

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/s/

DONNA J GRIEBEL
06/06/2014