ATTACHMENT

MEMO OF FILING MEETING

DATE: February 7, 2007

NDA #: 22-127

DRUG NAMES: Renvela (sevelamer carbonate)

APPLICANT: Genzyme Corporation (Genzyme)

BACKGROUND: Genzyme seeks approval of Renvela (sevelamer carbonate) tablets for the control of serum phosphorus in patients with Chronic Kidney Disease (CKD) on dialysis. Sevelamer carbonate is the pharmaceutical alternative to their currently approved product, Renagel (sevelamer hydrochloride) under NDAs 20-926 and 21-179. They propose that the data in this NDA will provide evidence that the carbonate formulation has similar phosphate binding activities, efficacy, and safety characteristics as the hydrochloride. The Agency has had several meetings with the sponsor to aid them in the development of this product.

ATTENDEES:

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical Officer
Gail Moreschi, M.D., M.P.H.	Medical Officer
Kasturi Srinivasachar, Ph.D.	Pharmaceutical Assessment Lead, Pre-marketing, Chemistry
Charles Resnick, Ph.D.	Team Leader, Pharmacology/Toxicology
Edward Fromm	Chief, Project Management Staff
Dianne Paraoan	Regulatory Health Project Manager

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Ququan (Cherry) Liu, M.D.	Statistician
Donghao (Robert) Lu, Ph.D.	Chemist
Xavier Joseph, D.V.M.	Pharmacologist/Toxicologist
Robert Kumi, Ph.D.	Clinical Pharmacologist

Discipline/Organization	**Reviewer**	**Completion Date**
Medical:	Gail Moreschi	August 24, 2007
Secondary Medical:		
Statistical:	Ququan Liu	August 24, 2007
Pharmacology:	Xavier Joseph	August 24, 2007
Statistical Pharmacology:		
Chemistry:	Donghao Lu	August 24, 2007
Environmental Assessment (if needed):		
Biopharmaceutical:	Robert Kumi	August 24, 2007
Microbiology, sterility:		
Microbiology, clinical (for antimicrobial products only):		
DSI:		
OPS:		
Regulatory Project Management:	Dianne Paraoan	
Other Consults:	DDMAC DMETS	

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☐ NO ☒
  If no, explain: per clinical team, none is needed because this product is a change of salt
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO ☒
  YES

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☐ NO ☒
  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5.☒ Convey document filing issues/no filing issues to applicant by Day 74.

Dianne Paraoan
Regulatory Project Manager

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-127

Genzyme Corporation
Attention: Mr. Dennis Bucceri
Vice President, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Bucceri:

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

Name of Drug Product: Renvela (sevelamer carbonate) 800 mg Tablets

Review Priority Classification: Standard (S)

Date of Application: December 20, 2006

Date of Receipt: December 20, 2006

Our Reference Number: NDA 22-127

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 February 18, 2007 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 20, 2007.

Please cite the NDA number listed above 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 Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact:

Ms. Dianne Paraoan
Regulatory Health Project Manager
(301) 796-1129

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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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/

Edward Fromm
1/11/2007 04:17:20 PM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 WO22, RM 4447

FROM: Dianne Paraoan, RPM
Division of Cardiovascular and Renal Products
301-796-1129

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 10, 2007	66,710	22-127	NDA	December 20, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
(Renvela) sevelamer carbonate	standard		April 10, 2007

NAME OF FIRM: Genzyme Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: A tradename review was originally completed by you in Aug 06 under the IND.

PDUFA DATE: October 20, 2007
ATTACHMENTS: Draft Package Insert, Container and Carton Labels—This is an electronic submission. Please refer to the EDR.
CC: Archival IND/NDA 22-127
HFD-110/Division File
HFD-Dianne Paraoan/RPM
HFD-110/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Dianne Paraoan 301-796-1129	☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

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

/s/

Dianne Paraoan
1/10/2007 11:18:45 AM

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genzyme

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142

ORIGINAL

December 20, 2006

Dianne Paraoan
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: **New Drug Application 022127**
Renvela™ Tablets (sevelamer carbonate)

Dear Ms. Paraoan:

In accordance with 505(b)(1) of the Food, Drug and Cosmetic Act and Title 21 of the Code of Federal Regulations, Part 314.50, Genzyme Corporation is pleased to submit an original New Drug Application (NDA) for sevelamer carbonate tablets. The proposed trade name for this product is Renvela™.

Sevelamer carbonate, a polymeric phosphate binding agent, is a pharmaceutical alternative to our currently approved product, Renagel® (sevelamer hydrochloride), NDA 20-926 and NDA 21-179. The proposed indication for Renvela™ is for the control of serum phosphorus in patients with Chronic Kidney Disease (CKD) on dialysis. Data in this NDA will provide evidence that sevelamer carbonate (Renvela™) has similar phosphate binding activity, efficacy, and safety characteristics as sevelamer hydrochloride (Renagel®).

As discussed in our pre-NDA meeting on September 29, 2006, Genzyme is providing this NDA in the International Conference on Harmonization (ICH) Common Technical Document (CTD) format. This submission contains five major sections:

- Module 1: Administrative Information and Prescribing Information
- Module 2: Common Technical Document Summaries
- Module 3: Quality
- Module 4: Nonclinical Study Reports
- Module 5: Clinical Study Reports

As agreed in our pre-NDA meeting, this NDA will include reports of *in vitro*, nonclinical, and clinical studies conducted with sevelamer carbonate and CMC information. In addition, this NDA will be supported by re-submission of nonclinical and clinical study reports from the Renagel NDAs.

This submission contains the agreed upon stability data set as determined in our Type C CMC Meeting of October 24, 2006; the remainder of the required 12 months of stability data will be provided in an amendment within 120 days of the review cycle start date.

This submission also contains preliminary information on [redacted]

Genzyme plans [redacted] Drug substance commercial manufacturing will be carried out at the [redacted] using the [redacted] process, the same process which was used to produce clinical trial material at Genzyme Ltd., which is also included in this submission as required.

Genzyme is submitting this NDA in eCTD format according to *Guidance for Industry: M4 Organization of the CTD (August 2001), M4 Granularity Annex (October 2005)* and all applicable Agency electronic submission and eCTD guidances. This submission will be sent via the FDA Electronic Submissions Gateway (ESG) web interface.

As required by the Prescription Drug User Fee Act, a check in the amount of $896,200.00 has been deposited to Mellon Bank under the User Fee ID Number PD3006813.

Should you have any questions or require additional information, please do not hesitate to contact the following individuals:

- Mary Beth Clarke, Director, Regulatory Affairs (617) 768-6907
- Tim Belt, Principle Associate, Regulatory Affairs (617) 768-6993

Sincerely,

Dennis Bucceri
Vice President, Regulatory Affairs

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Genzyme Corporation	12/15/2006
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
781-434-3560	781-895-4981

APPLICANT ADDRESS *(Number, Street, City, State, Country. ZIP Code or Mail Code, and U.S. License number if previously issued)*:

Corporate Address:
500 Kendall Street
Cambridge, MA 02142

Correspondence Address:
153 Second Avenue
Waltham, MA 02451

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Not Applicable

RECEIVED
DEC 20 2006
CDER White Oak DR 1

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 22-127

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
sevelamer carbonate	Renvela

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane) carbonate salt	GT335-012

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	800 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Original Application

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

(See attachment)

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 66,710 sevelamer carbonate tablets
IND 46,601 Renagel (sevelamer hydrochloride)
NDA 20-926 Renagel Capsules
NDA 21-179 Renagel Tablets

This application contains the following items: *(Check all that apply)*	
☒	1. Index
☒	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
☒	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☒	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☒	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☒	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☒	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☒	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☒	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☒	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☒	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☒	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☒	15. Establishment description (21 CFR Part 600, if applicable)
☒	16. Debarment certification (FD&C Act 306 (k)(1))
☒	17. Field copy certification (21 CFR 314.50 (l)(3))
☒	18. User Fee Cover Sheet (Form FDA 3397)
☒	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	Dennis Bucceri, Vice President Regulatory Affairs	12/15/2006

ADDRESS *(Street, City, State, and ZIP Code)*		Telephone Number
Corporate Address: 500 Kendall Street Cambridge, MA 02142	Correspondence Address: 153 Second Avenue Waltham, MA 02451	(781) 434-3560

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
GENZYME CORP Mary Beth Clarke Genzyme Corporation 500 Kendall Street Cambridge MA 02142 US	22-127

2. TELEPHONE NUMBER	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
617-768-6907	[X] YES [ ] NO
	IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:
	[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION
	[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME	6. USER FEE I.D. NUMBER
Renvela (Sevelamer Carbonate Tablets)	PD3006813

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act	[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	VP Regulatory Affairs	11/8/06

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$896,200.00

Form FDA 3397 (12/03)

IBE_PRMT_CLOSE_G) (Print Cover sheet)

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

GENZYME CORP
Mary Beth Clarke
Genzyme Corporation 500 Kendall Street
Cambridge MA 02142
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

22-127

2. TELEPHONE NUMBER
617-768-6907

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME
Renvela (Sevelamer Carbonate Tablets)

6. USER FEE I.D. NUMBER
PD3006813

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	VP Regulatory Affairs	11/8/06

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$896,200.00

Form FDA 3397 (12/03)

IBE_PRMT_CLOSE_G) (Print Cover sheet)

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Meeting Date and Time:	October 24, 2006, 11:00 am – 12:00 noon EDT
Meeting Type:	Type C
Meeting Category:	CMC Teleconference
Meeting Location:	CDER White Oak Campus, Silver Spring, MD
Application Number:	IND 66,710
Product Name:	sevelamer carbonate 800 mg tablets (GT335-012)
Received Briefing Package	September 7, 2006
Sponsor Name:	Genzyme Corporation
Meeting Requestor:	Alicia Jeannotte Associate, Regulatory Affairs
Meeting Chair	Ramesh Sood, Ph.D. Office of New Drug Quality Assessment
Meeting Recorder/Facilitator:	Scott N. Goldie, Ph.D. Office of New Drug Quality Assessment

The following consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for October 24, 2006, 11:00 a.m. - 12:00 noon EDT, CDER White Oak 2650 Conference Room between Genzyme Corporation (Genzyme) and the Food and Drug Administration, Center for Drug Evaluation and Research, Office of New Drug Quality Assessment (FDA). This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Scott N. Goldie, Ph.D., Regulatory Health Project Manager, (301) 796-2055). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. **Please note that if there are any major changes to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.** If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

1.0 BACKGROUND

Genzyme Corporation is developing sevelamer carbonate 800 mg tablets (GT335-012) proposed for the control of serum phosphorus in patients with chronic kidney disease (CKD) on hemodialysis. Genzyme requested a Type C teleconference to ask questions about and receive feedback regarding the Chemistry, Manufacturing and Controls (CMC) information for New Drug Application (NDA) filing. The request dated September 6, 2006, received September 7, 2006, also contained the corresponding briefing package that provided additional information on discussion topics and questions. The following are the written preliminary responses to all questions outlined in the briefing to be discussed between Genzyme and FDA at the teleconference on October 24, 2006.

2.0 DISCUSSION

The questions from the Genzyme meeting package are related verbatim. Section references in the questions refer to the meeting background package.

2.1 Does the Division agree with the filing strategy for the alternate manufacturing facility [redacted] as delineated in **Section 1.11.1.2**?

2.1.1 ***FDA Preliminary Response***: As indicated in the package, the equipment utilized [redacted] will be of the same operating principles although scaled accordingly. Otherwise the specifications, in-process controls, method of analysis of all materials, method of preparation, and detailed route of synthesis are the same between [redacted]. Therefore, the alternate manufacturing facility ([redacted]) appears acceptable. However, the qualification process of [redacted] needs to be approved by FDA office of compliance. A request note has been sent to FDA Office of Compliance, specifically for the issue regarding the availability of [redacted] for sevelamer carbonate for Prior Approval Inspection (PAI), approximately 8 months after the initial application.

2.2 Does the Division agree with our strategy for filing of drug product stability data for registration batches and support of expiry as provided in Section 1.11.2.2?

2.2.1 ***FDA Preliminary Response:*** Please clarify the site of the registration batch manufacturer. Further, please clarify the entry on Page 14, table 1.11-2 which shows [redacted] as the registration batch. It was not clear why [redacted] was not listed in the substance specifications for the stability test (while [redacted] was listed in the product specifications for the stability test). [redacted] impurity listed in the substance and product specifications for the stability test. Please provide the justification for not including other impurities. Disintegration was set NMT [redacted] min., which is relatively [redacted] Please provide justification.

2.3 Does the Division agree with our environmental assessment plans as well as providing additional provisional data more specific to the EMEA requirements but relevant to the application (see Section 1.11.3)?

2.3.1 ***FDA Preliminary Response:*** Based on the information provided in the meeting package, your proposed environmental assessment plans are acceptable.

3.0 CONCURRENCE:

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

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/s/

Ramesh Sood
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Pre-NDA Meeting with Sponsor

Application Number: IND 667, 10

Sponsor: Genzyme Corporation

Drug: Sevelamer carbonate tablets

Type of Meeting: Pre-NDA

Classification: B

Meeting Date: September 29, 2006
Preliminary Responses Sent: September 21, 2006
Briefing Package Received: September 1, 2006

Meeting Chair: Norman Stockbridge, M.D., Ph.D.
Recorder: Dianne Paraoan

List of Attendees:

Division of Cardiovascular and Renal Products

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Ellis Unger, M.D.	Deputy Director
Gail Moreschi, M.D., M.P.H.	Medical Officer
Steven Bai, Ph.D.	Statistician
Robert Kumi, Ph.D.	Clinical Pharmacologist/Biopharmaceutist
Monika Houstoun, Pharm. D.	Safety Evaluator, Office of Drug Safety
Edward Fromm	Chief, Project Management Staff
Dianne Paraoan	Regulatory Health Project Manager

Genzyme Corporation

Dennis Bucceri	VP Regulatory
Tim Belt	Principle Associate Regulatory
Mary Beth Clarke	Director, Regulatory
Rich Moscicki Sr.	VP Biomedical and Regulatory Affairs
Andrew Blair	VP Clinical Research
Maureen Dillon	Sr. Director, Regulatory
Ajay Duggal	Medical Director, EU
Scott Chasen-Taber	Sr. Director Statistics
Jeff Goldberg	Program Manager, sevelamer carbonate

Nancy Mulrow	VP Medical Director, Pharmacovigilence
Nicole Oliynyk	Associate Director, CMC Regulatory
Amie Hillock	Manager, Pharmacovigilence
Eugene Zhorov	Scientific Director

BACKGROUND

Genzyme Corporation (Genzyme) submitted a Pre-NDA meeting request to discuss the development of a sevelamer carbonate tablet formulation for the control of serum phosphorus in patients with Chronic Kidney Disease (CKD) on hemodialysis.

Sevelamer carbonate is a pharmaceutical alternative to their currently approved product, Renagel® (sevelamer hydrochloride). Reference is made to NDA 20-926 and 21-179.

In a December 9, 2004 meeting, the Division informed Genzyme that in order to reference the preclinical and clinical data from the sevelamer hydrochloride NDAs, they must demonstrate the equivalence of sevelamer carbonate tablets to sevelamer hydrochloride tablets.

DISCUSSION

Genzyme provided the Division with brief presentations on 1) their rationale for approving the sevelamer carbonate formulation, 2) results of their *in vitro* equivalency studies, and 3) their clinical study results. The slides are attached at the end.

QUESTIONS

1. Genzyme plans to evaluate the safety information for sevelamer carbonate clinical safety database with separate sevelamer hydrochloride databases described in Section 4.1 and believe it will provide the most meaningful assessment of the safety of sevelamer carbonate tablets to demonstrate that the safety profile of this product is comparable to that of Renagel (sevelamer hydrochloride) tablets.

Does the Agency concur with this plan?

Preliminary Response: Your plan is acceptable.

Discussion during Face to Face Meeting

Dr. Stockbridge informed Genzyme that the strategies presented look reasonable, but we are not ready to agree on the contents of the labeling. The Division needs to consider how to apply the safety results of the hydrochloride formulation. The Division will likely take a conservative approach and include the safety results of the hydrochloride in the carbonate formulation until there are adequate safety data with carbonate.

2. The sevelamer carbonate package insert will include the sevelamer carbonate NDA information. The sevelamer carbonate package insert is based on the demonstration of equivalence with sevelamer hydrochloride and will also include statements or information from sevelamer hydrochloride, as appropriate. This package insert will be submitted in the new content and format, per guidelines.

Does the Agency agree with the proposed labeling content and format?

Preliminary Response: See general comments below.

Discussion during Face to Face Meeting

Please refer to the Discussion above.

3. Genzyme plans to submit the in eCTD format according to *Guidance for Industry: M4 Organization of the CTD (August 2001), M4 Granularity Annex (October 2005)* and all applicable Agency electronic submission and eCTD guidances. We have requested that a representative of the Office of Business Development to attend as is recommended by the Agency. Further, Genzyme would like to offer any assistance to the reviewing division, if needed, to support the eCTD.

Would the Division and Office of Business Process Development be interested in working with Genzyme to facilitate this assistance and support?

Preliminary Response: If you have not yet submitted an eCTD application, or would like feedback on the current application prior to submission, we invite you to submit a test application prior to submission of the planned eCTD.

Discussion during Face to Face Meeting

Genzyme informed the Division that they have experience submitting eCTD applications. The Division welcomed the sponsor to submit their NDA in the eCTD format and encouraged them to contact the Office of Business Process Support to provide a draft version prior to their actual submission.

4. Genzyme will present an overview of the cumulative safety data for sevelamer hydrochloride since marketing approval in 1998, submit an interim PSUR (9 month October 2005 - July 2006) in the sevelamer carbonate NDA on Renagel to support the post marketing safety section of the NDA. Genzyme proposes to submit the annual Renagel PSUR (October 2005 - October 2006) at the time of the 120 day safety update and provide any serious, unexpected adverse drug reaction (ADRs) individually.

Does the Agency agree with this proposal?

Preliminary Response: See general comments below.

Discussion during Face to Face Meeting

Dr. Stockbridge noted that the most important safety data for NDA approval does not come from the post-marketing experience. The Division is more interested in the data from controlled trials to support their application.

OTHER DISCUSSION

Preliminary General Comments:

We feel that further discussion of questions 2 and 4 is needed. In particular, please be prepared to discuss the basis of approval of the sevelamer carbonate product, as well as the added claim for use in patients on peritoneal dialysis. We look forward to meeting with you to discuss these issues.

Discussion during Face to Face Meeting

Dr. Stockbridge informed the sponsor that it would have been the Division's preference that the washout was done upfront and if the study utilized higher doses; however, we would be willing to look at the data they already have available to support their application.

Peritoneal Dialysis Claim
Genzyme informed the Division that they intend to submit an efficacy supplement to support the use of Renagel® in peritoneal dialysis before submitting their NDA for the sevelamer carbonate formulation.

Genzyme intends to submit their NDA by the end of this year.

Recorder: Dianne Paraoan

Concurrence, Chair: *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

Attachment:
Slides presented by sponsor.

Draft: 10/2/06 Final: 10/10/06

RD:
Stockbridge 10/10/06
Fromm 10/06/06
Unger 10/06/06
Moreschi 10/05/06
Bai 10/4/06
Houstoun 10/3/06

FDA Cardio-Renal Division/Genzyme Pre-NDA Meeting

September 29, 2006

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Proposed Agenda:

- Introductions
- FDA Preliminary Response – Basis For Approval (10 min)
- Questions and Discussion (75 min)
- Wrap Up (5 min)

Basis of Approval for Sevelamer Carbonate NDA Introduction

- Sevelamer carbonate tablets: phosphate binder for controlling serum phosphorus in hemodialysis patients
  - Intended as a pharmaceutical alternative to Renagel (sevelamer hydrochloride) tablets
  - Sevelamer carbonate is a polymeric anion exchange pharmaceutical—carbonate replaces chloride as the counterion
  - In acidic environment of the stomach, converts to the same moiety – sevelamer
  - Counterion plays no role in phosphate binding

Basis of Approval for Sevelamer Carbonate NDA Rationale

- Chloride does not provide any known therapeutic benefit for dialysis patients, and may be absorbed but then cleared with dialysis; In addition, sevelamer hydrochloride does not contain alkali supplementation
- Sevelamer hydrochloride has a labeled precaution that serum chloride and serum bicarbonate levels should be monitored
- Replacement of the chloride counterion with carbonate is intended to preclude the need for more frequent monitoring of serum chloride and serum bicarbonate above the standard clinical practice of monthly monitoring

Basis of Approval of Sevelamer Carbonate NDA

- Therefore, NDA will be based on:
  - In vitro data (per FDA guidelines)
    - relative standard deviation (RSD) of k_2 approximately 6% - confirms equivalent phosphate binding
  - Clinical pharmacodynamic equivalence (clinical study GD3-163-201)
    - equivalency established: ratio = 0.99 (90% CI 0.95 – 1.03) and safety and tolerability demonstrated
  - Preclinical
    - confirms comparable safety profile and non-absorption
  - Sevelamer hydrochloride data
    - additional preclinical & clinical support for labeling by cross-reference to NDAs

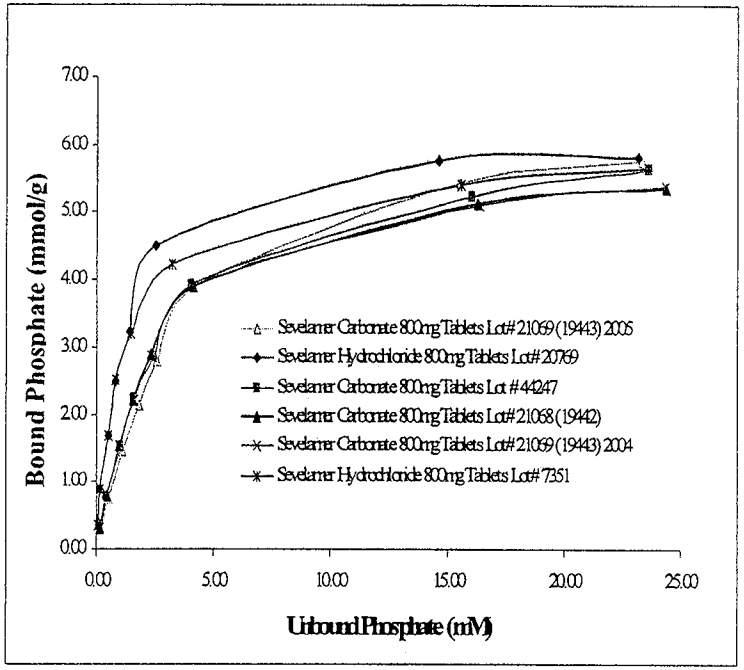
Rationale: *in-vitro* Equivalency Study

- Study was performed according to the Cholestyramine Guidance
  - Sevelamer is a non absorbed cross-linked polymeric ion exchange resin similar to Cholestyramine
  - Sevelamer hydrochloride and carbonate have the same polymer backbone and same functional groups
  - A polymeric ion exchange resin consists of the polymer backbone and attached functional groups that interact with the ions (for sevelamer these are amine functional groups)

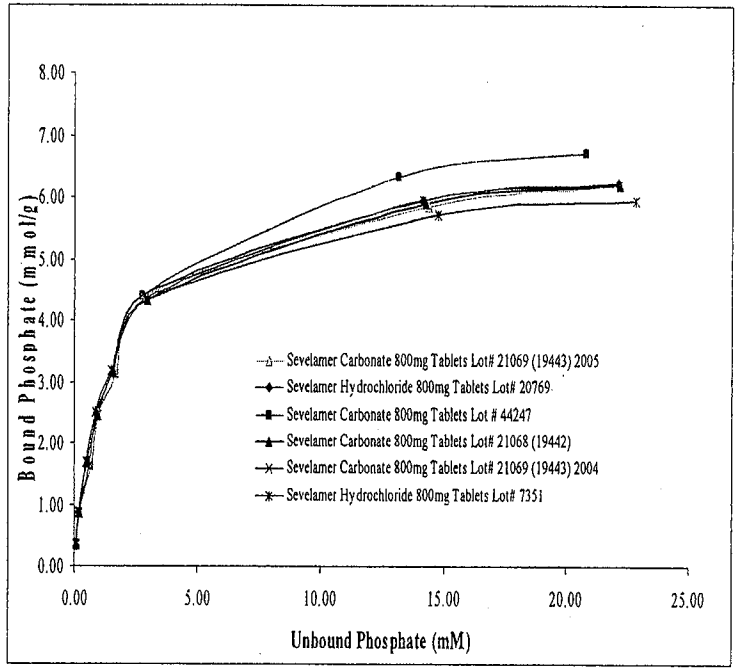
- Use of Cholestyramine guidance was presented to Agency and agreed upon multiple times for this and other non-absorbed polymers
  - Reference correspondence between FDA and Genzyme
    - FDA comments on the equivalence assay were incorporated in the study
  - NDA 20-926 utilized this approach for Renagel capsules to tablets to demonstrate equivalency of formulations

Phosphate Binding Isotherms for Equilibrium Samples

- Without Acid Pre-treatment
- k_2; 5.2% RSD



- After Acid Pre-treatment
- k_2; 5.8% RSD



The binding isotherms show similarity with or without pre-treatment

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Conclusions for *in-vitro* Equivalency Study

- Sevelamer hydrochloride (Renagel, 800 mg tablets) and sevelamer carbonate (800 mg tablets):
  - equivalent in the equilibrium study of phosphate binding with and without acid pre-treatment
  - no significant differences in phosphate binding capacity (k_2) characteristics in both acid pre-treated and non treated tablets
- Sevelamer hydrochloride (Renagel, 800 mg tablets) and sevelamer carbonate (800 mg tablets) bind phosphate in a similarly rapid manner independent of initial phosphate concentration
  - equilibrium level of binding for all the tested tablets was reached at low and high initial phosphate concentration in approximately 15 minutes
- Results from three independent studies performed over the course of 1.5 years demonstrate the *in vitro* equivalence of sevelamer hydrochloride tablets and sevelamer carbonate tablets

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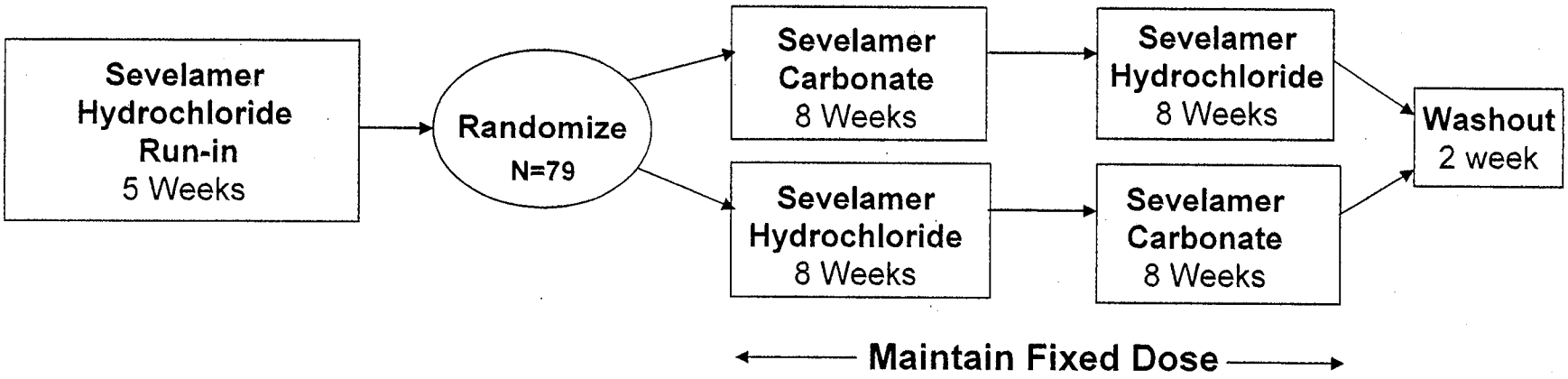
A Double-Blind, Cross-Over Design Study of Sevelamer Hydrochloride (Renagel®) and Sevelamer Carbonate in Chronic Kidney Disease Patients on Hemodialysis (GD3-163-201)



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GD3-163-201: Serum Phosphorus Efficacy Results*

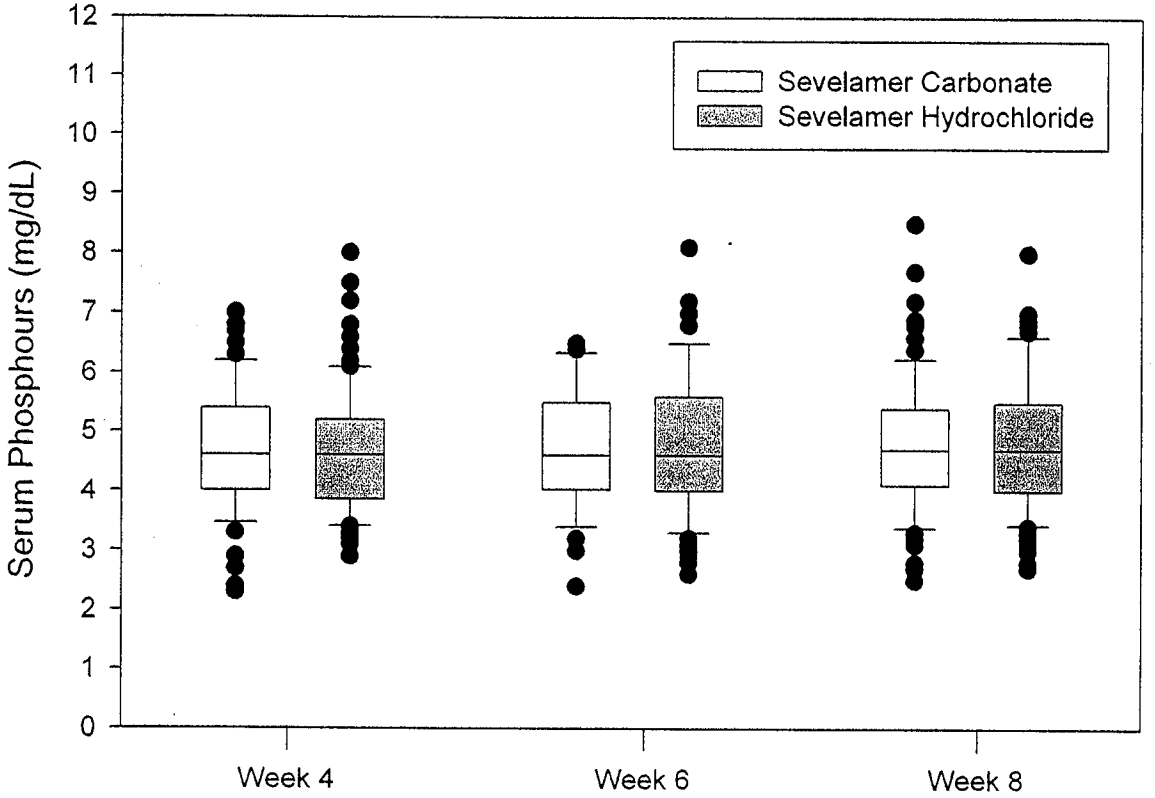
Analysis Set	Sevelamer Carbonate [mean ± SD]	Sevelamer Hydrochloride [mean ± SD]	Geometric LS Mean	90 % CI of Ratio
Per Protocol Set	N=56 4.6 ± 0.9	N=56 4.7 ± 0.9	0.99	0.95-1.03**
Full Analysis Set	N=73 4.8 ± 0.9	N=78 4.8 ± 1.0	0.99	0.96-1.02**

* Uses time-weighted mean at 4, 6, and 8 weeks on treatment

**90 % CI for the ratio is within the interval (0.8, 1.25)

No dose changes during randomized treatment period

GD3-163-201: Serum Phosphorus



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GD3-163-201 Washout Period: Confirmation of Hyperphosphatemia

Full Analysis Set	**Sequence 1 Carbonate to Hydrochloride**	**Sequence 2 Hydrochloride to Carbonate**
N	19	21
End of Washout (mean ± SD)	6.3 ± 1.85	6.6 ± 2.02
Change (mean ± SD)	1.7 ± 1.51	1.3 ± 2.21
P-Value	<0.001	0.022

Basis of Approval of Sevelamer Carbonate NDA Conclusion

- In vitro data (per FDA guidelines)
  - relative standard deviation (RSD) of k_2 approximately 6% - confirms equivalent phosphate binding
- Clinical pharmacodynamic equivalence (clinical study GD3-163-201)
  - equivalency established: ratio = 0.99 (90% CI 0.95 – 1.03) and safety and tolerability demonstrated
- Preclinical
  - confirms comparable safety profile and non-absorption
- Sevelamer hydrochloride data
  - additional preclinical & clinical support for labeling by cross-reference to NDAs

Sevelamer Carbonate Pre-NDA Meeting Questions

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Question 1

- Genzyme plans to evaluate the safety information for sevelamer carbonate clinical safety database with separate sevelamer hydrochloride databases described in **Section 4.1** and believe it will provide the most meaningful assessment of the safety of sevelamer carbonate tablets to demonstrate that the safety profile of this product is comparable to that of Renagel (sevelamer hydrochloride) tablets.

- **Question:** Does the Agency concur with this plan?

Question 2

- The sevelamer carbonate package insert will include the sevelamer carbonate NDA information. The sevelamer carbonate package insert is based on the demonstration of equivalence with sevelamer hydrochloride and will also include statements or information from sevelamer hydrochloride, as appropriate. This package insert will be submitted in the new content and format, per guidelines.

- **Question:** Does the Agency agree with the proposed labeling content and format?

Question 3

- Genzyme plans to submit the in eCTD format according to *Guidance for Industry: M4 Organization of the CTD (August 2001)*, *M4 Granularity Annex (October 2005)* and all applicable Agency electronic submission and eCTD guidances. We have requested that a representative of the Office of Business Development to attend as is recommended by the Agency. Further, Genzyme would like to offer any assistance to the reviewing division, if needed, to support the eCTD.

- **Question:** Would the Division and Office of Business Process Development be interested in working with Genzyme to facilitate this assistance and support?

Question 4

- Genzyme will present an overview of the cumulative safety data for sevelamer hydrochloride since marketing approval in 1998, submit an interim PSUR (9 month October 2005 - July 2006) in the sevelamer carbonate NDA on Renagel to support the post marketing safety section of the NDA. Genzyme proposes to submit the annual Renagel PSUR (October 2005 - October 2006) at the time of the 120 day safety update and provide any serious, unexpected adverse drug reaction (ADRs) individually.

- **Question:** Does the Agency agree with this proposal?

Peritoneal Dialysis Question 1

1. Genzyme believes the data from Protocol REN00304 support the extension of the current Renagel labeling to include the peritoneal dialysis patient population.

- **Question:** Does the Agency agree?

FDA Cardio-Renal Division/Genzyme Pre-NDA Meeting

September 29, 2006

Backup Slides

genzyme

GD3-163-201: Serum Phosphorus by Dose Group

Prescribed Daily Dose (grams)	N	Ratio	Confidence Interval
≤4.8	22	0.97	0.91-1.04
>4.8 to <9.6	14	0.95	0.85-1.05
≥9.6	20	1.04	0.98-1.10

*90 % CI for the ratio is within the interval (0.8, 1.25)

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/s/

Norman Stockbridge
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Pre-NDA Meeting Preliminary Response

Application:	IND 66,710
Sponsor:	Genzyme Corporation
Drug:	Sevelamer Carbonate Tablets
Type of Meeting:	Pre-NDA Meeting
Classification:	B
Date of Internal Meeting:	September 15, 2006
Date of Meeting with Sponsor:	September 29, 2006
Briefing Package Received:	September 1, 2006

List of Internal Meeting Participants:

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Abraham Karkowsky, M.D., Ph.D.	Medical Team Leader
Gail Moreschi, M.D., M.P.H.	Medical Officer
Steve Bai, Ph.D.	Statistician
John Lawrence, Ph.D.	Statistics Team Leader
Xavier Joseph, Ph.D.	Pharmacologist
Gary Gensinger	Electronics Submissions Staff
Russell Fortney	Regulatory Health Project Manager

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 29, 2006, between Genzyme and the Division of Cardiovascular and Renal Products. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything in it that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and are not expected to be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM), but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principal questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to the purpose of the meeting (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

The following questions were addressed:

1. Genzyme plans to evaluate the safety information for sevelamer carbonate clinical safety database with separate sevelamer hydrochloride databases described in Section 4.1 and believe it will provide the most meaningful assessment of the safety of sevelamer carbonate tablets to demonstrate that the safety profile of this product is comparable to that of Renagel (sevelamer hydrochloride) tablets.

   Question: Does the Agency concur with this plan?

   FDA response: Your plan is acceptable.

2. The sevelamer carbonate package insert will include the sevelamer carbonate NDA information. The sevelamer carbonate package insert is based on the demonstration of equivalence with sevelamer hydrochloride and will also include statements or information from sevelamer hydrochloride, as appropriate. This package insert will be submitted in the new content and format, per guidelines.

   Question: Does the Agency agree with the proposed labeling content and format?

   FDA response: See general comments below.

3. Genzyme plans to submit the in eCTD format according to *Guidance for Industry: M4 Organization of the CTD (August 2001), M4 Granularity Annex (October 2005)* and all applicable Agency electronic submission and eCTD guidances. We have requested that a representative of the Office of Business Development to attend as is recommended by the Agency. Further, Genzyme would like to offer any assistance to the reviewing division, if needed, to support the eCTD.

   Question: Would the Division and Office of Business Process Development be interested in working with Genzyme to facilitate this assistance and support?

   FDA response: If you have not yet submitted an eCTD application, or would like feedback on the current application prior to submission, we invite you to submit a test application prior to submission of the planned eCTD.

4. Genzyme will present an overview of the cumulative safety data for sevelamer hydrochloride since marketing approval in 1998, submit an interim PSUR (9 month October 2005 - July 2006) in the sevelamer carbonate NDA on Renagel to support the post marketing safety section of the NDA. Genzyme proposes to submit the annual Renagel PSUR (October 2005 - October 2006) at the time of the 120 day safety update and provide any serious, unexpected adverse drug reaction (ADRs) individually.

   Question: Does the Agency agree with this proposal?

   FDA response: See general comments below.

General Comments: We feel that further discussion of questions 2 and 4 is needed. In particular, please be prepared to discuss the basis of approval of the sevelamer carbonate product, as well as the added claim for use in patients on peritoneal dialysis. We look forward to meeting with you to discuss these issues.

Minutes preparation: *{See appended electronic signature page}*
Russell Fortney

Concurrence, Chair: *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

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/s/

Russell Fortney
9/21/2006 08:54:25 AM

Norman Stockbridge
9/21/2006 10:26:25 AM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 66,710

Genzyme Corporation
Attention: Timothy Belt
500 Kendal Street
Cambridge, MA 02142

Dear Mr. Belt:

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

We also refer to your amendment dated August 31, 2005 (serial # 015), containing a request for a pre-market review of your proposed proprietary names for your product.

We have completed, in consultation with the Division of Medication Errors and Technical Support, our review of your submission and have the following comments.

1. We recommend against the use of "———" as a proprietary name.

2. We have no objections to the use of "Renvela" as a proprietary name. This is a tentative decision and this name will be re-evaluated with its associated labels and labeling upon submission of the NDA, and again approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

If you have any questions, please call Ms. Dianne Paraoan, Regulatory Health Project Manager, at (301) 796-1129.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
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IND 66,710
Sevelamer carbonate tablets
Genzyme Corporation
Preliminary Responses to Sponsor

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for June 30, 2006 from 9:00- 10:30 AM between Genzyme Corporation and the Division of Cardiovascular and Renal Products. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything in it that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and are not expected to be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM), but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principal questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to the purpose of the meeting (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

Does the Agency concur with our plans to not include the case report forms or SAS data sets for the Renagel (sevelamer hydrochloride) clinical studies?

Preliminary response
The Division concurs with your plans.

We would like to remind you that the need for phosphate binders has not been established in pre-dialysis patients.

If you have any questions, please contact:

Dianne Paraoan
Regulatory Health Project Manager
301-796-1129

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
6/16/2006 10:19:21 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-926
NDA 21-179
IND ——

Genzyme Corporation
Attention: Timothy Belt
Principle Associate, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mr. Belt:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Renagel (sevelamer hydrochloride) Capsules and Renagel (sevelamer hydrochloride) Tablets.

Reference is also made to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sevelamer carbonate powder.

We also refer to your January 12, 2006 meeting request and your February 6, 2006 briefing package, containing background information and data to support discussions regarding pediatric studies.

We have reviewed the referenced material and find that it is premature to have a meeting at this time to discuss your interest in pediatric studies. We do, however, have the following comments and recommendations.

1. The Division recognizes that you are interested in obtaining a Written Request for an unapproved salt (carbonate) of sevelamer. We therefore encourage you to discuss obtaining a Written Request at the time of submitting your NDA for the sevelamer carbonate.

2. In the future, your Proposed Pediatric Study Request will need to address several issues:
   a. establishing an appropriate pediatric dose
   b. a single-arm trial will not likely satisfy the requirements
   c. age groups to be included (i.e. 0-16 years)

3. As discussed in previous meetings with you, patients with chronic renal disease who are not yet on dialysis is a new indication. Thus, a complete development program will need to be submitted to support this use. You would probably need to obtain the indication in adults prior to initiating the —— program in children.

If you have any questions, please call:

Ms. Dianne Paraoan
Regulatory Health Project Manager
301-796-1129

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
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Meeting Minutes

Meeting Date: May 19, 2005

Type of Meeting: Guidance

IND Application: 66, 710

Sponsor: Genzyme Corporation

Classification: C

Meeting Request Date: March 10, 2005
Confirmation Date: March 15, 2005
Briefing Package Received: April 22, 2005

Meeting Chair: Norman Stockbridge, M.D., Ph.D.
Meeting Recorder: Dianne Paraoan

Attendees:

Division of Cardio-Renal Drug Products

Robert Temple, M.D.	Director, Office of Drug Evaluation I, HFD-001
Norman Stockbridge, M.D., Ph.D.	Acting Director, Div of Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Acting Deputy Director, HFD-110
Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
Gail Moreschi, M.D., M.P.H.	Medical Officer, HFD-110
Mehul Desai, M.D.	Medical Officer, HFD-110
Charles Le, Ph.D.	Statistician, HFD-710
Kris Raman, Ph.D.	Chemist, HFD-810
Robert Kumi, Ph.D.	Clinical Pharmacologist, HFD-860
Dianne Paraoan	Regulatory Health Project Manager, HFD-110

Genzyme Corporation

Eduardo Slatopolsky, M.D.	Clinical Expert
Steve Burke, M.D.	Senior Vice President Clinical Research
Andrew Blair, M.D.	Senior Medical Director
Dennis Bucceri	Vice President Regulatory Affairs
Mary Beth Clarke	Director Regulatory Affairs
Jeff Goldberg	Senior Program Manager
Scott Chasan-Taber, M.D.	Program Statistician

BACKGROUND

On December 9, 2004, Genzyme Corporation met with the Division of Metabolic and Endocrine Drug Products (DMEDP) for an End of Phase 2 meeting. During the meeting, DMEDP provided comments to their protocol. Then, on January 21, 2005, the sponsor provided DMEDP with an updated protocol. However, the phosphate binder group was transferred to the Division of

Cardio-Renal Drug Products (DCRDP). On March 8, 2005, the Division had a teleconference with the sponsor. We recommended that they schedule a meeting to discuss the study population with Dr. Temple. We informed the sponsor that we do not have any issues with the carbonate formulation, but do have concerns about extending a claim to include the ——— when sevelamer hydrochloride already has an indication for use in dialysis patients.

Genzyme Corporation does not believe that a distinction should be made regarding the treatment of hyperphosphatemia in late stage chronic kidney disease (CKD) patients based on ———

DISCUSSION POINTS

After introductions, Genzyme Corporation began with a presentation to support the clinical relevance of hyperphosphatemia in CKD patients ——— as well as their revised protocol proposal. The sponsor stated that sevelamer HCl is indicated for patients on hemodialysis. They wish to revise their label to include ——— CKD patients based on recommendations of the National Kidney Foundation and because of the increased off label use of their product.

[

]

Discussed at length was how the sponsor could design their study and the endpoints they should

[

]

Discussion about the relationship between dialysis patients with hyperphosphatemia and cardiovascular events took place. Dr. Temple said that we will need to discuss internally whether ——— There are no drugs approved for that indication.

Possibilities of accelerated approval, using a surrogate endpoint to support the clinical benefit,

[

]

Dr. Stockbridge cautioned the sponsor that there is a certain risk to accelerated approval. [ ] recommendation.

Briefly discussed by the sponsor was the possibility of conducting a trial, incorporating our suggestions regarding , and submitting it to be part of the clinical trials section in the label. Dr. Temple told the sponsor that a claim is still a claim, even if it is placed in clinical trials and that the legal standard for approval applies.

Dr. Stockbridge said that to get the new salt sevelamer carbonate approved for use in dialysis patients, the sponsor could conduct a PK/PD trial

CONCLUSIONS/ RECOMMENDATIONS

The information provided in the briefing package does not support Genzyme's proposal to change their current label to include patients. The benefit/risk profile is unclear.

The Division recommended that they provide the Division with a stronger argument, including a proposed protocol, paying attention to the safety and risks of treating We offered the sponsor assistance if needed, especially in simplifying the data collection.

Genzyme Corporation should conduct studies to support the use of sevelamer carbonate in the

In the future they should discuss with us whether or not accelerated approval can be an option for them.

We encouraged the sponsor to contact the Division if they need additional assistance.

Recorder: Dianne C. Paraoan

Concurrence, Chair: *(see appended page for electronic signature)*
Robert Temple, M.D.

Draft: 5/27/05 Final: 6/10/05
RD:
Temple: 6/8/05
Stockbridge: 6/605
Marciniak: 6/6/05
Moreschi: 6/3/05
Desai: 6/3/05
Le: 6/2/05
Kumi: 6/2/05
Raman: 6/1/05

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/s/

Robert Temple
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 66,710

Genzyme Corporation
Attn: Dennis Bucceri
Vice President, Regulatory Affairs
153 Second Avenue
Waltham, MA 02451

Dear Mr. Bucceri:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned:	66,710
Sponsor:	Genzyme Corporation
Name of Drug:	GT335-012 (sevelamer carbonate) Tablets
Date of Submission:	January 4, 2005
Date of Receipt:	January 5, 2005

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before February 4, 2005, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to the following address:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please contact me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Randy Hedin
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 66,710

Genzyme Corporation
Attention: Mary Beth Clarke
Associate Director, Regulatory Affairs
500 Kendal Street
Cambridge, MA 02142

Dear Ms. Clark:

Please refer to the meeting between representatives of your firm and FDA on December 9, 2004. The purpose of the meeting was to discuss a clinical study with sevelamer carbonate for the control of serum phosphorus levels in patients with chronic kidney disease

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6392.

Sincerely,

Randy Hedin
Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Meeting Date: December 9, 2004 Time: 3:00 - 4:30 PM Location: Conference Room "C"

PIND 66,710 GT335-012

Type of Meeting: End-of-phase 2

External participant: Genzyme Corporation

Meeting Chair: Dr. Eric Colman

External participant lead: Ms. Mary Beth Clark

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Division of Metabolic and Endocrine Drug Products:
David Orloff, M.D., Division Director
Eric Colman, M.D., Clinical Team Leader
Karen Davis-Bruno, Ph.D., Pharmacology Team Leader
Randy Hedin, R.Ph., Senior Regulatory Management Officer

Division of Pharmaceutical Evaluation II
Johnny Lau, Ph.D., Reviewer

Division of Biometrics II
Joy Mele, M.S., Reviewer

External participant Attendees and titles:
Andrew Blair, M.D., Senior Medical Director, Clinical Research
Dennis Bucceri, Vice President, Regulatory Affairs
Steven Burke, M.D., Senior Vice President, Medical & Regulatory Affairs
Scott Chasan-Taber, Ph.D., Consultant, Statistician
Mary Beth Clark, Associate Director, Regulatory Affairs
Ajay Duggal, M.B., Ch.B., Medical Director Renal (Europe)
Jeff Goldberg, Program Manager for GT335-012 (sevelamer carbonate)
Francisco Llach, M.D., Clinical Consultant

Meeting Objectives:

Sevelamer hydrochloride is approved for the control of serum phosphorus in patients with Chronic Kidney Disease (CKD) on hemodialysis (i.e., Stage 5 CKD). In hemodialysis patients, sevelamer hydrochloride decreases the incidence of hypercalcemic episodes but increases the incidence of hypocalcemia relative to patients on calcium treatment. The meeting was requested by Genzyme Corporation to discuss a clinical study protocol for

sevelamer carbonate for the control of serum phosphorus levels in patients with CKD ——

Discussion Points and Decisions (agreements) reached:

- The firm submitted the following questions in a background document dated October 27, 2004. The Division's answers and discussion, in *italics*, follow the questions.

    1. Does the Agency agree with our approach to perform a single Phase 3 study, outside the United states, in accordance with 21 CFR 312.120, with sevelamer carbonate in order to support an NDA seeking approval of this indication in CKD patients ——— ?

    The Division does not object to the idea of submitting a NDA seeking approval of an indication for the treatment of hyperphosphatemia in patients ——— on a single, multi-center Phase 3 study. However, the Division does have a number of recommendations regarding the study design:

    - *The study should have a dose-titration phase followed by a dose-maintenance phase.*
    - *The study should be at least six months in duration.*
    - *The study should be double-blind and placebo-controlled.*
    - *The study should have escape criteria for inappropriately high serum phosphate levels.*
    - *The study should include, as a secondary efficacy endpoint, an integrated measure of how often patients' serum phosphorus levels are within the target range per the most recent issue of the K/DOQI guidelines.*
    - *Patient randomization should be done before dietary restrictions (i.e., phosphate) are placed on the subjects.*
    - *To the extent feasible, the study should conform to the major treatment recommendations outlined in the most recent edition of the K/DOQI guidelines.*

    The firm stated that the frequent measurement of serum levels of phosphorus and calcium and the size of the Renagel tablet would make it difficult to conduct a double-blind, placebo-controlled trial. The Division acknowledged these difficulties, but pointed out that Nabi Biopharmaceutics conducted a double-blind study of PhosLo vs. Renagel, which indicates that it is possible to use placebo Renagel tablets.

    Regarding the ethics of conducting a placebo-controlled trial of a phosphate-binder in patients ——— the Division in not aware of any compelling evidence that would prohibit the use of a placebo in this population. Moreover, the use of escape criteria for inappropriately high serum phosphate levels should alleviate any concern about treating ——— patients with a placebo phosphate binder.

The Division asked why the firm is doing the study outside the U.S., and the firm responded that logistically it is easier.

The Division asked if the standard-of-care is the same at the foreign sites as it is in the U.S., and the firm responded that the care is similar. The Division asked why the protocol is not going to be submitted to the IND, and the firm responded that it will send the protocol to the IND for review.

2. Does the Agency agree that our proposed 8-week treatment period will be sufficient to demonstrate the efficacy and safety of sevelamer carbonate in the proposed indication?

   Refer to the answer to question 1.

3. Does the Agency agree that the 100 patients proposed to be enrolled into this study, together with the Renagel (sevelamer hydrochloride) existing data and data obtained with sevelamer carbonate from the additional non-clinical studies and the bioequivalence study will provide sufficient safety data to support our proposed indication?

   With the proviso that the study will be placebo-controlled, 100 patients treated with Renagel for at least 6 months is a reasonable sample size.

4. Does the Agency agree with our proposal to use a single arm study where each patient will serve as his or her own control (where the comparison will be to baseline and washout}?

   The Division does not agree with the proposal to have subjects' baseline value for serum phosphorus serve as the "control" and it was again strongly recommended that the study be placebo-controlled. (See the answer to question1).

5. Does the Agency agree with the definition of [redacted] mmol/L)?

   Yes, the Division agrees with this definition of [redacted].

6. Does the Agency agree with the proposed starting dose and dose titration strategy?

   Yes, the Division agrees with the proposed starting dose and dose-titration strategy. However, it should be noted that a dose response for adverse events, as suggested on the last page of the briefing packet, cannot be assessed in a dose-

titration study since patients not doing well often drop out of the study and therefore are not titrated.

- The Division asked if Genzyme intends to [redacted].

- The Division asked if Genzyme plans to have an in-vitro bioequivalence study and an in-vivo bioequivalence study to compare sevelamer hydrochloride with sevelamer carbonate, and the firm responded that they do.

Unresolved or issues requiring further discussion:

- The firm agreed to consider our recommendations for the study design and submit an amended protocol.

Action Items:

- None

Signature, minutes preparer: Randy Hedin

Concurrence Chair: Eric Colman

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/s/

Randy Hedin
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: April 14, 2003

To: Mark Murray	**From:** Randy Hedin
Company: GelTex Pharmaceuticals, Inc.	Division of Division of Metabolic and Endocrine Drug Products
Fax number: 781-434-3615	**Fax number:** 301-443-9282
Phone number: 781-434-3443	**Phone number:** 301-827-6392

Subject: Questions from the December 11, 2002 submission to IND 66,710.

Total no. of pages including cover: 2

Comments: The answers to your questions from the December 11, 2002 background document follow the questions in *italics*. If you have any questions contact me at the above telephone number.

Document to be mailed: ☐ YES ☑ NO

1. Does the Agency concur with our proposal to establish the bioequivalence of sevelamer carbonate with Renagel (sevelamer hydrochloride) via the *in vitro* phosphate binding assay and the 24 patient clinical trial?

   In vitro phosphate binding assay including an equilibrium binding study and a kinetic binding study is acceptable.

2. Does the Agency agree that the proposed preclinical studies are sufficient to demonstrate that sevelamer carbonate is not absorbed and has a similar toxicological profile to sevelamer hydrochloride?

   Cross-reference to the nonclinical studies in approved NDAs 20-926 and 21-179 is acceptable. Your plan to perform bridging 28-day toxicity studies in a rodent and non-rodent species and single dose toxicokinetics may demonstrate a toxicity profile similar to sevelamer hydrochloride and allow us a link to the additional studies in the approved NDAs. However, this information will not necessarily demonstrate that sevelamer carbonate is not absorbed.

3. Assuming that the responses to 1 & 2 above are affirmative, does the Agency agree that these studies are sufficient to justify cross-reference to NDA 20-926 for Renagel for data necessary to support conduct of the proposed clinical trial?

   See the answer to question 2.

4. Does the Agency believe that the overall plan described would support an NDA seeking the approved indications/claims of Renagel?

   Even though the changes from sevelamer hydrochloride involve only the anion (hydrochloride to carbonate), this is a new molecular entity and the proposed overall development plan would not support an NDA for the approved indications/claims of NDAs 20-926 and 21-179. We would require a clinical trial with more safety exposure, as well as efficacy determination. The overall design (crossover study comparing sevelamer hydrochloride to sevelamer carbonate) proposed is fine. However, we would want to see at least 60 patients studied, with each patient exposed to at least eight weeks to each of the two drugs.

5. Does the Agency believe that the overall plan described would support eliminating the recommendation to monitor chloride levels?

   This is a review issue. Depending on the results of the study the recommendation to follow chloride levels could be dropped.

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/s/

Randy Hedin
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CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 66,710

GelTex Pharmaceuticals, Inc.
Attention: Mark Murray
Director, Regulatory Affairs
153 Second Avenue
Waltham, MA 02451

Dear Mr. Murray:

We received your December 11, 2002 correspondence on December 12, 2002 requesting a meeting to discuss developing sevelamer carbonate, a polymeric phosphate binding agent intended as an oral treatment for control of serum phosphorus levels in patients with ——— renal disease.

We considered your request and concluded the meeting is unnecessary. The questions in your submission will be answered via written correspondence.

If you disagree with our decision, you may discuss the matter with Randy Hedin, Regulatory Project Manager, at (301) 827-6392. If the issue cannot be resolved at the division level, you may formally request reconsideration according to our guidance for industry titled *Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). The guidance can be found at http://www.fda.gov/cder/guidance/2740fnl.htm.

In addition, we have opened a PIND file for this drug product. Forward all future communications concerning this PIND in triplicate, identified by the above PIND number, to the following address:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Fishers Document Room 8B45
5600 Fishers Lane
Rockville, Maryland 20857

Studies in humans may not be conducted under this PIND. Before you may conduct studies in humans, you must submit an Investigational New Drug Application (IND, see 21 CFR Part 312). **Include the above PIND number in Box 6 of the form FDA 1571 submitted with your IND.** Send your IND submission in triplicate to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Ave.
Rockville, MD 20852-1833

If you have any questions call Randy Hedin at the above number.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Kati Johnson
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signing for David Orloff, MD

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