

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-318

CHEMISTRY REVIEW(S)

MEMORANDUM

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

DATE: July 3, 2009

FROM: Donghao (Robert) Lu, Ph.D.
Division of Pre-Marketing Assessment - I
Office of New Drug Quality Assessment

TO: File NDA 22-318

SUBJECT: Renvela® (sevelamer carbonate) for Oral Suspension NDA 22-318
Complete Response (Sequence 0014)

RECOMMENDATION: The drug product Renvela (sevelamer carbonate) for oral suspension, 0.8 and 2.4 g, is recommended as APPROVAL from a CMC perspective.

I. REVIEW NOTE:

This is a second complete response for NDA 22-318. The CMC review for NDA 22-318 was completed on 1/27/2009. All CMC issues have been resolved. The NDA letter sent to the sponsor stated that the application in its present form could not be approved. One of the reasons was that "Although it is more than likely that the powder form for suspension of sevelamer carbonate is a reliable phosphate binder, the single dose strength available (2.4 grams) would not allow sufficient flexibility in dosing. Instructions for dose alterations would, therefore, not be possible. There does not seem to be a way to administer accurately a dose change of less than the 2.4 g contained in a packet, whereas for the tablet formulations dose gradations of 800 mg are available." The sponsor submitted a complete response on February 18, 2009, proposing

~~_____~~
~~_____~~ The approach raised some clinical concerns. Therefore, the sponsor provided in this complete response the information for Renvela for oral suspension available in a 0.8 g packet. This review evaluates the CMC information according to the new and replaced data, as indicated in the cover letter dated on June 12, 2009.

b(4)

II. CHEMISTRY REVIEW

P.1. Description and Composition

Sevelamer carbonate powder for oral suspension is formulated as described in the previous reviews and packaged to contain 0.8 g as anhydrous sevelamer carbonate (in addition to the 2.4 g package). Sevelamer carbonate powder for oral suspension is packaged into opaque, foil lined, heat sealed _____ packets _____

b(4)

The composition of the drug product, 0.8 g or 2.4 g, can be seen below.

Table 3.2.P.1-1: Sevelamer Carbonate Powder for Oral Suspension Composition

Component	Reference to Quality Standard	Function	Composition per Unit (%)	Composition per Unit Dose 0.8 g (mg)	Composition per Unit Dose 2.4 g (mg)
Anhydrous Sevelamer Carbonate	In-house standard				
Natural & Artificial Citrus Cream ^b	Vendor Standard (RB26)				
Propylene glycol alginate	cNF				
Sodium Chloride	cUSP/cPh.Eur.				
Sucralose	cNF/EU Directive 2004/46/CE				
Ferric Oxide (yellow) ^c	cNF				
Totals					
Approximate Fill Volume					

b(4)

b(4)

Further delineation of flavor components and percentages are provided in Table 3.2.P.1-2.
^c Ferric Oxide (yellow) is _____ with specifications set forth in _____ and in _____

Amount

Genzyme Ireland Ltd. performed a study to determine _____

b(4)

Evaluation: Adequate.

P.5.1 Specification

The product specifications for sevelamer carbonate powder for oral suspension has not been changed upon the addition of the 0.8 g packet for sevelamer carbonate powder for oral suspension. The specification table is shown below for reference.

Table 3.2.P.5.1-1: Specifications for Sevelamer Carbonate Powder for Oral Suspension

Test	Regulatory Procedure	Release Specification	Shelf-Life Specification
Appearance	QC-239	Pale yellow powder free from foreign particles	Pale yellow powder free from foreign particles
Appearance of Reconstituted Drug Product	QC-266		
Identification (FTIR)	QC-221	Conforms to sevelamer carbonate reference standard spectrum	Not applicable
	QC-235	NMT	NMT
Total	QC-242	nmol/g ^a	mmol/g ^a
Label Claim	QC-242	of anhydrous sevelamer carbonate	of anhydrous sevelamer carbonate
Residual	QC-234		
Residual	QC-240	NMT	NMT
Uniformity of Dosage Units, Weight Variation	QC-241 (cUSP <905>)	Meets requirements of cUSP <905> (min & max potency percentages and %RSD recorded)	Not applicable
Microbial Limits	QM-126 cUSP <61>/cPh.Eur. 5.1.4	Total viable aerobic count: Molds & yeasts:	Total viable aerobic count: Molds & yeasts:

b(4)

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b(4)

b(4)

b(4)

b(4)

P.5.4 Batch Analyses

The batch analysis data for the 0.8 g packet for sevelamer carbonate powder for oral suspension, i.e. packaged lots 109920 (bulk lot 109917), 109921 (bulk lot 109918) and 109922 (bulk lot 109919) are shown below. *Evaluation:* The data indicated that the batch analysis results were acceptable.

Table 3.2.P.5.4-5: Batch Analysis Data for Sevelamer Carbonate Powder for Oral Suspension 0.8 g Sachet Registration Lots 109920, 109921 and 109922

Test Method ^a	Specification	Lot 109920	Lot 109921	Lot 109922
Appearance	Pale yellow powder, free from foreign particulates	Conforms	Conforms	Conforms
Appearance of Reconstituted Drug Product		Conforms	Conforms	Conforms
Label Claim	1 mmol/g 0.80 mg anhydrous sevelamer carbonate	1 mmol/g	1 mmol/g	1 mmol/g
Residue				
Microbial Limits	Total aerobic: 10 ⁶ fu/g Molds & yeast 10 ³ fu/g Pathogens: 10 ¹ fu/g	10 ⁶ fu/g 10 ³ fu/g 10 ¹ fu/g	10 ⁶ fu/g 10 ³ fu/g 10 ¹ fu/g	10 ⁶ fu/g 10 ³ fu/g 10 ¹ fu/g

b(4)

b(4)

b(4)

b(4)

^a The tests for identity and uniformity of dosage units were not performed as these are not stability indicating tests and these lots were intended to provide additional stability information. The process used to manufacture these batches is in fact representative of the intended commercial process and maintain the same in-process controls and parameters as well as the same equipment utilized in previous registration manufacturing campaigns.

P.7 Container Closure System

Sevelamer carbonate powder for oral suspension, 0.8 g, is packaged in the same configuration as that for the 2.4 g packet. They are packaged in opaque, foil lined, heat sealed, _____ sachets (individual sachet dimension size of _____). See original CMC review for details.

b(4)

P.8 Stability

Three additional registration lots, i.e. packaged lots 109920 (bulk lot 109917), 109921 (bulk lot 109918) and 109922 (bulk lot 109919), were manufactured using drug substance material representative of the _____ manufacturing process (solvent, batch process) and placed on stability in support of the 0.8 g packet fill size. These three lots met the specified shelf life specifications through twelve months at real time, long term storage conditions and were complete through twelve months at accelerated storage conditions.

It is noted that per CMC review for the original NDA 22-318, the drug product expiry period was acceptable as to be 24 months for sevelamer carbonate powder for oral suspension (2.4 g packet) when stored at 25°C. The stability data now also supported the 24 months of expiry period for 0.8 g packet of sevelamer carbonate powder for oral suspension, based on the FDA guidance ($Y = \text{up to } 2X \text{ but not exceeding } X + 12 \text{ months}$)

b(4)

Evaluation: Adequate.

The stability data for the 0.8 g packet were provided, along with the originally submitted stability data for other package sizes. The data for other package sizes were reviewed early and summarized in a table format (see original review in DFS/DARRTS). The representative stability data for the 0.8 g packet can be seen on the next page. *Evaluation:* The stability data for the 0.8 g packet showed that the results tested in the 12 month period met the product specification. The studies and the results were acceptable.

Labeling sections

Review Note: The product name RENVELA was approved in NDA 22-127. The DESCRIPTION section remained the same as that in the previous review on NDA 22-318, except for the additions on Renvela® Powder 0.8 g packet, see below. The HOW SUPPLIED/STORAGE & HANDLING section remained the same as that in the previous review on NDA 22-318, except for the additions on Renvela® Powder 0.8 g packet, see below. The draft colored labels for the 0.8 g packet were also submitted as shown below. These additional changes on labeling are adequate.

(1) DESCRIPTION:

Renvela® Powder: Each packet of Renvela Powder contains 0.8 g or 2.4 g of sevelamer carbonate on an anhydrous basis. The inactive ingredients are natural and artificial citrus cream flavor, propylene glycol alginate, sodium chloride, sucralose, and ferric oxide (yellow).

(2) HOW SUPPLIED/STORAGE & HANDLING:

Powder: Renvela® for Oral Suspension is supplied as opaque, foil lined, heat sealed, packets containing 0.8 g or 2.4 g of sevelamer carbonate on an anhydrous basis, natural and artificial citrus cream flavor, propylene glycol alginate, sodium chloride, sucralose, and ferric oxide (yellow).

1 Box (NDC 58468-0131-2) of 90 ct 2.4 g packets (NDC 58468-0131-1)

1 Box (NDC 58468-0132-2) of 90 ct 0.8 g packets (NDC 58468-0132-1)

(3) DRAFT LABEL:

The draft colored labels for sevelamer carbonate powder for oral suspension, 0.8 g packet (in addition to the previously submitted labels for the 2.4 g packet) were submitted in the present complete response. The labels are similar in design and size to those for the 2.4 g packet but the background color for the 0.8 g strength is blue while that for the 2.4 g strength was green.

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22318	ORIG 1		RENVELA
NDA 22318	ORIG 1		RENVELA

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/s/

DONGHAO R LU
08/03/2009

RAMESH K SOOD
08/04/2009

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§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

MEMORANDUM

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

DATE: January 27, 2009

FROM: Donghao (Robert) Lu, Ph.D.
Division of Pre-Marketing Assessment - I
Office of New Drug Quality Assessment

TO: File NDA 22-318

SUBJECT: EA and OC recommendations

RECOMMENDATION: This NDA for Renvela (sevelamer carbonate) for oral suspension, 2.4 g, may be APPROVED from a CMC perspective.

REVIEW NOTE:

The NDA 22-318 CMC review #1 was completed on 12/17/2008. All CMC issues have been resolved, except two pending issues on environment assessment (EA) recommendation from Office of Pharmaceutical Sciences and the overall recommendation from the Office of Compliance (OC) on manufacturing facilities. We have now received both EA and OC recommendations indicating no review/inspection concerns. A copy of the EER report documenting an overall ACCEPTABLE recommendation is attached. The EA review by R. Bloom, dated 1-26-09, has been signed off in DFS.

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile : .CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 27-JAN-09
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI : 3003809840
GENZYME IRELAND LTD.
OLD KILMEANDEN RD
WATERFORD, , EI

DMF No:

AADA:

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : LIQ OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 27-JAN-09
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : _____ FEI : _____
_____ b(4)

DMF No: _____ AADA: _____

Responsibilities: _____ b(4)

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 06-NOV-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN _____ FEI : _____
_____ b(4)

DMF No: _____ AADA: _____

Responsibilities: _____ b(4)

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 27-OCT-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

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/s/

Kasturi Srinivasachar
1/27/2009 04:05:31 PM
CHEMIST
on behalf of Donghao (Robert) Lu

Ramesh Sood
1/27/2009 04:08:02 PM
CHEMIST

CMC BRANCH CHIEF MEMORANDUM

To: NDA 22-318
From: Ramesh Sood, Ph.D., Branch Chief, ONDQA
Date: 21-Jan-2009
Drug: Renvela (sevelamer carbonate) for oral suspension
Route of administration: Oral
Strength: 2.4 g.
Subject: Recommendation for NDA 22-318

Introduction: Sevelamer carbonate was approved as oral tablets, 800 mg, on October 19, 2007 (NDA 22-127). The current NDA proposes the same active moiety as a powder for oral suspension to control serum phosphorus in patients with chronic kidney disease on dialysis. Sevelamer carbonate is an anion exchange resin with the same polymeric structure as another previously approved product sevelamer hydrochloride (Renagel, NDA 20-926 and NDA 21-179) in which the chloride counter ion is replaced by carbonate ion. The product will be available as 2.4 g powder packaged in a sachet.

Drug Substance: The sevelamer carbonate is a carbonate salt of a highly cross-linked polymer of allyl amine which is cross-linked using _____ It is a white to off-white, free flowing, non-crystalline powder that is insoluble in all tested solvents. It has a general molecular formula of $(C_3H_7N \cdot nH_2CO_3)_{810z} (C_9H_{18}N_2O \cdot nH_2CO_3)_{95z}$. Sevelamer carbonate is synthesized for Genzyme Corporation by a contract manufacturing facility _____
_____. Alternatively, sevelamer carbonate can be manufactured at the Genzyme Limited Haverhill Operations, (Haverhill, Suffolk, UK). Sevelamer carbonate is manufactured by _____

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_____ There are two manufacturing processes developed for the production of sevelamer carbonate drug substance: _____
_____ The first one _____ was approved in NDA 22-127 and the second _____ has been reviewed in this NDA. The quality of the drug substance is ensured through in-process controls and final specification that include appearance, identification (FTIR) _____

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Drug product: Renvela (sevelamer carbonate) for oral suspension is a powder packaged in sachets. Each package contains 2.4 g of deliverable powder. The formulation contains approximately _____ of anhydrous drug substance with remaining _____ made up from excipients for _____ including ferric oxide (yellow), natural/artificial citrus cream, propylene glycol alginate, sodium chloride and sucralose. All excipients are compendial and

b(4)

meet current USP/NF specifications, except the natural/artificial citrus cream [redacted] b(4)
[redacted] The
manufacturing process for sevelamer carbonate for oral suspension is straight forward and
comprised of [redacted] steps: [redacted]

[redacted] Sevelamer carbonate for b(4)
oral suspension is packaged in opaque, foil lined, heat sealed [redacted] sachets (individual
sachet dimension size of [redacted]. The sachets are packaged as [redacted]

[redacted] (90 sachets per carton). The quality of the final product is assured through in-process b(4)
controls and final product specification which includes tests and limits for appearance, of the
powder and the reconstituted solution, identification (IR), [redacted] total [redacted]
label claim, residual [redacted] residual [redacted], uniformity of dosage units (by b(4)
weight variation) and microbial limits.

The stability of the product has been shown through appropriate stability studies. A 24-month
expiration date is assigned for the drug product stored at 25 °C (77 °F) with excursions permitted
to 15-30 °C (59-86 °F) (USP Controlled Room Temperature) based on the evaluation of
provided stability data.

The Office of Compliance has not provided an overall acceptable recommendation for the
manufacturing sites.

Recommendation: All CMC related issues had been resolved for this application. Even though
all the CMC related issues had been resolved, a formal consult for the review of the
environmental assessment was not complete at the time of writing of this memorandum. It is to
be noted that the EA reviewer has notified the CMC reviewer the environmental assessment is
acceptable and that a FONSI for the EA review will be entered in DFS soon. Moreover, at the
time of writing this memorandum, the office of compliance had not provided a final
recommendation for the manufacturing sites in EES. Because of these two pending issues, a
final recommendation from CMC perspective is not made. The CMC reviewer will file a final
memorandum in DFS once the above two recommendations are received.

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/s/

Ramesh Sood
1/21/2009 07:52:55 AM
CHEMIST



NDA 22-318

**Renvela[®] (Sevelamer Carbonate)
For Oral Suspension, 2.4 g**

Genzyme Corporation

Division of Cardio-Renal Drug Products

Donghao (Robert) Lu, Ph.D.

**Division of Pre-Marketing Assessment - I
Office of New Drug Quality Assessment**



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Chemistry Review Data Sheet

1. NDA 22-318
2. REVIEW NUMBER: 1
3. REVIEW DATE: 2 October 2008
4. REVIEWER: Donghao (Robert) Lu, Ph.D.
5. PREVIOUS DOCUMENTS:

PREVIOUS DOCUMENTS	DOCUMENT DATE
--------------------	---------------

6. SUBMISSION(S) BEING REVIEWED:

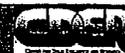
SUBMISSION REVIEWED	DOCUMENT DATE
NDA 22-318	31-MAR-08
NDA 22-318 (Amendment 005, CMC response)	09-DEC-08

7. NAME & ADDRESS OF APPLICANT:

NAME:	Genzyme Corporation
ADDRESS:	500 Kendall Street, Cambridge, MA 02142
REPRESENTATIVE:	Jamie MacPherson, Manager, Regulatory Affairs
TELEPHONE:	617-768-9153



CHEMISTRY REVIEW



Chemistry Assessment Section

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	Renvela
NON-PROPRIETARY NAME (USAN)	Sevelamer Carbonate
CODE NAME/ NUMBER (ONDC ONLY)	GT335-012
CHEMISTRY TYPE / SUBMISSION PRIORITY	3S

9. LEGAL BASIS FOR SUBMISSION: 505(b)1

10. PHARMACOL. CATEGORY: Phosphate binder

11. DOSAGE FORM: Powder for oral suspension

12. STRENGTH/POTENCY: 2.4 g

13. ROUTE OF ADMINISTRATION: Oral

14. R_x/OTC DISPENSED: R_x OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name (USAN):	Sevelamer carbonate
Name (IUPAC):	Allylamine polymer with 1-chloro-2,3-epoxypropane, carbonate salt
Name (CAS):	Poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane), carbonate salt
	2-Propen-1-amine, polymer with (chloromethyl) oxirane, carbonate salt
	Oxirane, (chloromethyl)-, polymer with 2-propen-1-amine, carbonate salt

(CAS) Registry Num: 845273-93-0



CHEMISTRY REVIEW



Chemistry Assessment Section

Mol. Formula: $(C_3H_7N \cdot nH_2CO_3)_{810z} (C_9H_{18}N_2O \cdot nH_2CO_3)_{95z}$
(where z equals a large number)

Mol. Wt.: Highly cross-linked polymer (Wt. vary)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E ¹	STATUS ²	DATE REVIEW COMPLET
_____	_____	_____	_____	_____	Adequate	17-OCT-08
_____	_____	_____	_____	_____	Adequate	14-OCT-08

b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A: There is enough data in the application, therefore the DMF did not need to be reviewed.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	46,601	Renagel (Sevelamer HCl)
IND	66,710	Sevelamer carbonate tablets
IND	71,878	Sevelamer carbonate powder



CHEMISTRY REVIEW

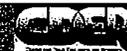


Chemistry Assessment Section

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-926	Sevelamer HCl & Renagel capsule
NDA	21-179	Renagel tablet (Sevelamer HCl)
NDA	22-127	Renvela tablet (Sevelamer carbonate)

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Methods Validation	No validation request	14-OCT-08	Donghao Lu, Ph.D.
ODS DMETS	The "Renvela" name was approved in NDA 22-127	---	---
EA	Pending		
Micro Consultation	N/A		



The Chemistry Review for NDA 22-318

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product Renvela (sevelamer carbonate) for oral suspension, 2.4 g, can not be approved from a CMC perspective because of the following outstanding issues. These issues include environment assessment (EA) recommendation and the overall recommendation from the Office of Compliance on manufacturing facilities. All other CMC issues have been resolved. The final memorandum recommending approval will be submitted once the EA and compliance recommendations are received.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

Sevelamer carbonate has been used for the control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis. The drug product Renvela[®] (sevelamer carbonate) oral tablet, 800 mg, was approved on October 19, 2007 (NDA 22-127). Sevelamer carbonate was developed as a pharmaceutical alternative of sevelamer hydrochloride (Renagel[®], see NDA 20-926, approved on October 30, 1998, and NDA 21-179, approved on July 12, 2000). Sevelamer carbonate is an anion exchange resin with the same polymeric structure as sevelamer hydrochloride in which carbonate replaces chloride as the counter-ion. This NDA was submitted to seek approval for the development of powder for oral suspension dosage form containing 2.4 g sevelamer carbonate in each sachet.

A. Description of the Drug Substance and Drug Product

1. Drug Substance

The drug substance is Sevelamer Carbonate. The chemical name is allylamine polymer with 1-chloro-2,3-epoxypropane, carbonate salt. It has a molecular formula of $(C_3H_7N \cdot nH_2CO_3)_{810z} (C_9H_{18}N_2O \cdot nH_2CO_3)_{95z}$. It is a highly cross-linked polymer with varying molecular weight. The cross-linking agent is _____

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CHEMISTRY REVIEW



Chemistry Assessment Section

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Sevelamer carbonate is synthesized for Genzyme Corporation by a contract manufacturing facility, _____. Alternatively, sevelamer carbonate can be manufactured at the Genzyme Limited Haverhill Operations, (Haverhill, Suffolk, UK). Sevelamer carbonate is manufactured by _____

b(4)

_____ here are two manufacturing processes developed for the production of sevelamer carbonate drug substance: an _____ process and an _____ process. The first one _____ was approved in DNA 22-127 and the second _____ has been reviewed in this NDA.

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2. Drug Product

The finished drug product is sevelamer carbonate powder for oral suspension packaged in sachets (i.e. packets), each containing 2.4 g of sevelamer carbonate. Each sachet contains approximately _____ of the anhydrous drug substance. The remaining _____ is made up of excipients for _____, including ferric oxide (yellow), natural/artificial citrus cream, propylene glycol alginate, sodium chloride and sucralose. All excipients are compendial and meet current USP/NF specifications, except the natural/artificial citrus cream, _____

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b(4)

_____ The manufacturing process for sevelamer carbonate powder for oral suspension is comprised of _____

b(4)

_____ sevelamer carbonate powder for oral suspension is packaged in opaque, foil lined, heat sealed, _____ sachets (individual sachet dimension size of _____). The sachets are packaged as _____

b(4)

_____ (90 sachets per carton). Product stability studies were conducted using the proposed commercial packaging configurations at long term storage conditions of $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{RH}$, and accelerated storage conditions of $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{RH}$. Based on the study results, the drug product expiry period was proposed to be 24 months for sevelamer carbonate powder for oral suspension when stored at 25°C . The drug product is manufactured by Genzyme Ireland Limited, located in Waterford, Ireland.

Chemistry Assessment Section

B. Description of How the Drug Product is Intended to be Used

Renvela[®] (Sevelamer Carbonate) For Oral Suspension is indicated for the control of serum phosphorus in patients with chronic kidney disease on dialysis. The entire contents of each individual sachet should be placed _____ and mixed thoroughly with water (at least 2 ounces for each 2.4 g sachet). Patients should be instructed to stir the mixture vigorously (it does not dissolve) and drink the entire preparation within 30 minutes after preparation. Multiple sachets may be mixed together with the appropriate amount of water. _____ is acceptable. When stored at 25°C (77°F), excursions permitted to 15° to 30°C (59 to 86°F), the product has an expiration period (shelf life) of 24 months.

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b(4)

C. Basis for Approvability or Not-Approval Recommendation

There were several CMC issues and they have been resolved. The CMC issues were described in the comments sent to the sponsor at the end of this document. The sponsor's responses were adequate.

III. Administrative

A. Reviewer's Signature

\\s\ Donghao (Robert) Lu, Ph.D.

B. Endorsement Block

\\s\ Ramesh Sood, Ph.D.

C. CC Block

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/s/

Donghao Lu
12/17/2008 10:42:34 AM
CHEMIST

Ramesh Sood
12/17/2008 11:17:07 AM
CHEMIST

Initial Quality Assessment Branch I

OND Division: Division of Cardio-Renal Drug Products
NDA: 22-318
Applicant: Genzyme Corporation
Letter Date: 31-MAR-08
Stamp Date: 31-MAR-08
PDUFA Date: 31-JAN-09
Trademark: Renvela
Established Name: Sevelamer Carbonate
Dosage Form: Powder, 2.4 g
Route of Administration: Oral
Indication: Control of serum phosphorus in CKD patients
Assessed by: Donghao (Robert) Lu, Ph.D.

Summary

Sevelamer carbonate has been used for the control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis. The drug product Renvela[®] (sevelamer carbonate) oral tablet, 800 mg, was approved on October 19, 2007 (NDA 22-127). Sevelamer carbonate was developed as a pharmaceutical alternative of sevelamer hydrochloride (Renagel[®], see NDA 20-926, approved on October 30, 1998, and NDA 21-179, approved on July 12, 2000). Sevelamer carbonate is an anion exchange resin with the same polymeric structure as sevelamer hydrochloride in which carbonate replaces chloride as the counter-ion. This NDA was submitted to seek approval for the development of powder for oral suspension dosage form containing 2.4 g sevelamer carbonate.

Drug Substance

Sevelamer carbonate is a cross-linked poly(allylamine) polymer. The cross-linking agent

b(4)

Sevelamer carbonate is a _____
r that is insoluble in all tested solvents.

b(4)

Sevelamer carbonate is synthesized for Genzyme Corporation by a contract manufacturing facility _____. Alternatively, sevelamer carbonate can be manufactured at the Genzyme Limited Haverhill Operations, (Haverhill, Suffolk, UK). Sevelamer carbonate is manufactured by _____

b(4)

Sevelamer carbonate drug substance will be manufactured with the same process as described in NDA 22-127.

b(4)

Drug Product

The finished drug product is sevelamer carbonate powder for oral suspension packaged in sachet (i.e. packet) containing 2.4 g of sevelamer carbonate. Each sachet contains approximately _____ of the anhydrous drug substance. The remaining _____ is made up of excipients for _____, including ferric oxide (yellow), natural/artificial citrus cream, propylene glycol alginate, sodium chloride and sucralose. All excipients are compendial and meet current USP/NF specifications, except the natural/artificial citrus cream _____

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b(4)

_____ The manufacturing process for sevelamer carbonate powder for oral suspension is comprised of _____

_____ Sevelamer carbonate powder for oral suspension is packaged in opaque, foil lined, heat sealed, _____ sachets (individual sachet dimension size of _____). The sachets are packaged _____

b(4)

_____ (90 sachets per carton). Product stability studies were conducted using the proposed commercial packaging configurations at long term storage conditions of $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{RH}$, and accelerated storage conditions of $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{RH}$. Based on the study results, the drug product expiry period was proposed to be 24 months for sevelamer carbonate powder for oral suspension when stored at 25°C . The drug product is manufactured by Genzyme Ireland Limited, located in Waterford, Ireland.

b(4)

Critical Issues for Review

For drug substance, the processes are the same as those described in NDA 22-127. Therefore, the review focus will be placed on the drug product. However, reviews will be conducted to evaluate any additional information on the drug substance in this submission. For drug product, from the initial assessment, several issues apparently need to be addressed as follows.

(1) The compatibility of the excipients will need to be evaluated. The mixture composition of the citrus cream flavoured powder needs to be reviewed for its qualification as drug excipients.

(2) Sevelamer carbonate powder for oral suspension is packaged in opaque, foil lined, heat sealed _____ sachets _____

b(4)

_____ The package configuration needs to be reviewed.

(3) The product release specification on _____ was proposed at NMT _____ and the product shelf-life specification on _____ was proposed at NMT _____ it is noted that the drug substance release specification on _____ was proposed at NMT _____

b(4)

(the same as that in NDA 22-127). In the previous NDA 22-127 (cross-referenced) regarding 800 mg sevelamer carbonate tablets, the product release specification and the product shelf-life specification on _____ were both established at NMT _____. The reason why (and the corresponding process how) the product release specification on _____ was established at NMT _____ needs to be reviewed.

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(4) Fill weight and seal integrity are monitored routinely throughout the fill process as in-process controls. The operational parameters used in the process need to be evaluated. The need for controlling the blend uniformity should be assessed.

(5) _____

b(4)

(6) The particle size of the drug substance may need to be controlled for the powder product and the related CMC information needs to be evaluated.

(7) The finished drug product commercial scale manufacturing process needs to be evaluated.

(8) Product specifications need to be evaluated.

(9) Analytical procedures, batch analyses and stability studies (validation and verification) need to be reviewed.

(10) The applicant has proposed an expiry period of 24 months based upon the stability study data. The adequacy of the expiry period needs to be evaluated.

(11) The photostability data need to be reviewed to determine whether the packaging provides adequate protection and if the labeling properly captures the photostability information.

(12) Genzyme Corporation Inc. is providing an environmental assessment (EA) in support of sevelamer carbonate. It is apparently not needed to make a consultation request to OPS, because the environmental assessment was evaluated in NDA 22-127. However, any additional environmental impacts from the powder product need to be evaluated.

Comments and Recommendation:

Sufficient CMC information appears provided in this NDA. The manufacturing site information was provided by the NDA applicant and entered into EES (May 15, 2008).

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/s/

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9/19/2008 08:09:32 AM
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