CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-127

CHEMISTRY REVIEW(S)

Initial Quality Assessment
Branch I

OND Division:	Division of Cardio-Renal Drug Products
NDA:	**22-127**
Applicant:	Genzyme Corporation
Letter Date:	20-DEC-06
Stamp Date:	20-DEC-06
PDUFA Date:	20-OCT-07
Trademark:	Renvela™
Established Name:	Sevelamer Carbonate
Dosage Form:	800 mg Tablets
Route of Administration:	Oral
Indication:	Control of serum phosphorus in CKD patients
Assessed by:	**Donghao Robert Lu, Ph.D.**

Summary

Sevelamer hydrochloride, Renagel®, (NDA 20-926 and NDA 21-179, Genzyme Co.) was approved for the control of serum phosphorus in patients with Chronic Kidney Disease (CKD) on haemodialysis. NDA 20-926 (403 mg oral capsule) was approved on October 30, 1998 and NDA 21-179 (400 and 800 mg oral tablets) on July 12, 2000. The purpose of this NDA program was to develop Renvela as a pharmaceutical alternative to Renagel, with a new drug substance which is only different in the counterion. The replacement of chloride counterion with carbonate counterion is intended to preclude the need for more frequent monitoring of serum chloride and serum bicarbonate. The sponsor had a CMC Pre-NDA meeting (24-OCT-06) involving the following discussions: (1) the alternate manufacturing facility (Genzyme); (2) filing strategy of drug product stability data; and (3) environmental assessment plans. Minutes for the meeting can be found in DFS (IND 66710).

Drug Substance

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

[redacted]

controlled by the manufacturing process. Sevelamer carbonate is synthesized for Genzyme Corporation by a contract manufacturing facility, [redacted]. Alternatively, sevelamer carbonate may be manufactured at the Genzyme Limited Haverhill Operations, (Haverhill, Suffolk, UK). Sevelamer carbonate is manufactured by cross-linking a [redacted] hydrochloride) to give [redacted]

Drug Product

The finished drug product is sevelamer carbonate 800 mg tablet, in a tablet formulation containing 800 mg of anhydrous sevelamer carbonate. Each coated tablet contains approximately —% of the anhydrous drug substance. The remaining— % is made up of excipients, . All excipients are compendial and meet current USP/NF, and EP specifications. Pharmaceutical development was performed to determine the effects of excipient concentrations on drug product manufacturability and final dosage form quality. Equilibrium binding studies were conducted under conditions of constant time and varying concentrations of phosphate on samples prior and subsequent to acid pretreatment. The manufacturing process used in the manufacture of clinical trial material is similar to that of the proposed commercial process with the exception that ink will be used for print purposes. Sevelamer carbonate 800 mg tablets are packaged in 30 count ' — configuration bottles, with a child resistant closure.

Critical Issues for Review

For drug substance: from the initial assessment, several issues apparently need to be addressed.

(1) Molecular weight.

(2) Manufacturing process and controls, e.g. controls.

(3) The specifications, e.g.

(4) Analytical procedures, batch analyses and stability – validation and verification.

(5) Manufacturing site qualification (vs. Genzyme).

For the drug product: from the initial assessment, several issues apparently need to be addressed.

(1) The finished drug product commercial scale manufacturing process, which needs to be evaluated.

(2) Manufacturing process and controls, e.g. in-process controls including [redacted].

(3) Product specifications, e.g. uniformity of dosage, [redacted], and disintegration.

(4) Analytical procedures, batch analyses and stability – validation and verification.

Comments and Recommendation:
The NDA appears to be fileable from a CMC perspective. The manufacturing site information is provided by the NDA applicant and entered into EES. The environmental assessment information is provided by the NDA sponsor and a consultation request is made to OPS. As I participated in the pre-NDA meeting and addressed the pre-NDA questions, I am interested in reviewing this NDA.

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/s/

Donghao Lu
2/15/2007 02:46:19 PM
CHEMIST

Ramesh Sood
2/15/2007 03:05:01 PM
CHEMIST

NDA 22-127

(Review #2)

Renvela™ (Sevelamer Carbonate)
Oral Tablet
800 mg

Genzyme Corporation

Division of Cardio-Renal Drug Products

Donghao (Robert) Lu, Ph.D.

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

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-127
2. REVIEW NUMBER: 2
3. REVIEW DATE: 12 October 2007
4. REVIEWER: Donghao (Robert) Lu, Ph.D.
5. PREVIOUS DOCUMENTS:

PREVIOUS DOCUMENTS	DOCUMENT DATE
NDA 22-127	20-DEC-06
NDA 22-127 (Amendment 003, CMC, Stability)	17-APR-07
NDA 22-127 (Amendment 004, CMC, Labeling)	13-JUN-07
NDA 22-127 (Amendment 005, CMC, Labeling)	09-AUG-07

6. SUBMISSION(S) BEING REVIEWED:

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 22-127 (Amendment 006, CMC, Response)	13-SEPT-07
NDA 22-127 (Amendment 007, CMC, Response)	28-SEPT-07
NDA 22-127 (Amendment 008, CMC, Response)	12-OCT-07

7. NAME & ADDRESS OF APPLICANT:

NAME:	Genzyme Corporation
ADDRESS:	153 Second Avenue, Waltham, MA 02451
REPRESENTATIVE:	Dennis Bucceri, VP Regulatory Affairs
TELEPHONE:	781-434-3560

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	**2S**

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

10. PHARMACOL. CATEGORY: Phosphate binder

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 800 mg

13. ROUTE OF ADMINISTRATION: Oral

14. R_x/OTC DISPENSED: _x_ R_x ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___x___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 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
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	

Note: DMFs of [redacted] are associated with bottles. DMFs of [redacted] and [redacted] are associated with child resistant closures.

[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	66,710	Sevelamer carbonate tablets
IND	46,601	Renagel (Sevelamer HCl)
NDA	20-926	Renagel capsule (Sevelamer HCl)
NDA	21-179	Renagel tablet (Sevelamer HCl)

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	03-AUG-07	S. L. Adams
Methods Validation	No validation request	15-JUN-07	Donghao Lu, Ph.D.
ODS DMETS	Acceptable	25-JAN-07	Linda M. Wisniewski, RN
EA	Acceptable	15-JUN-07	Donghao Lu, Ph.D.
Micro Consultation	N/A		

Chemistry Assessment Section

The Chemistry Review for NDA 22-127

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product Renvela (Sevelamer carbonate) oral tablet, 800 mg, is recommended as APPROVAL from a CMC perspective.

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

II. Summary of Chemistry Assessments

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 starting materials for the manufacture of sevelamer carbonate is poly(allylamine hydrochloride). The primary potential impurities in sevelamer carbonate drug substance include

Sevelamer carbonate drug substance is commercially manufactured for Genzyme Ltd. by ———— However, Genzyme Ltd. is responsible for the storage and testing of all drug substance stability samples and is designated as an alternate release testing facility. For commercial production of sevelamer carbonate drug substance, there were — processes developed for synthesis and purification, the

[ ]

2. Drug Product

The drug product is Renvela™ (Sevelamer carbonate) 800 mg tablet. It is intended for oral administration. Sevelamer carbonate functions as a non-absorbed phosphate binder for the control of serum phosphorous in patients with chronic kidney disease on dialysis. The product contains 800 mg of anhydrous sevelamer carbonate. It is a white oval, film-coated, compressed tablet imprinted with "R800" on one side. The tablet product is packed for commercial use in a ——— bottle containing ——— sevelamer carbonate tablets. It may also be packed, as physician samples, in a ——— bottle containing 30 sevelamer carbonate tablets. The inactive ingredients are hypromellose, diacetylated monoglycerides, microcrystalline cellulose, sodium chloride and zinc stearate. The tablet imprint contains iron oxide black ink. All container closures have a child resistant cap and ——— seal. Several critical parameters are monitored during the manufacturing process, including ———

[ ]

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

Renvela™ (sevelamer carbonate) is indicated for the control of serum phosphorus in patients with Chronic Kidney Disease (CKD) on dialysis. The recommended starting dose of Renvela is 2.4 to 4.8 grams per day which can be administered as one to two Renvela 800 mg tablets three times per day (TID) with meals based on serum phosphorus level. The tablets ———, When stored at 25°C (77°F), excursions permitted to 15° to 30°C (59 to 86°F), the products have an expiration period (shelf life) of 24 months.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, Genzyme has submitted sufficient and appropriate information to support the approval of the drug product. In our CMC review #1, there were several CMC issues which needed to be resolved before the final approval. The CMC issues were listed in the comments sent to the sponsor on July 31, 2007. Genzyme has adequately addressed these CMC comments (as presented in NDA 22-127, Amendments 006, 007 and 008, respectively). Their responses and the CMC evaluations for these responses are described below.

III. Administrative

A. Reviewer's Signature

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

B. Endorsement Block

\s\ Ramesh Sood, Ph.D.

C. CC Block

70 Page(s) Withheld

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/s/

Donghao Lu
8/27/2007 11:38:59 AM
CHEMIST

Ramesh Sood
8/28/2007 08:06:38 AM
CHEMIST