

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-318**

**OTHER ACTION LETTER(s)**



NDA 22-318

**COMPLETE RESPONSE**

Genzyme Corporation  
Attention: Jamie McPherson, PharmD, RAC  
500 Kendall Street  
Cambridge, MA 02142

Dear Dr. McPherson:

Please refer to your new drug application (NDA) dated March 31, 2008, received March 31, 2008, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Renvela (sevelamer carbonate) for Oral Suspension, 2.4 grams.

We acknowledge receipt of your submissions dated May 30, June 30, July 3, 30, December 9, 2008, and January 6, 15, February 18, March 18, April 8 and 10, 2009.

The February 18, 2009 submission constituted a complete response to our January 28, 2009 action letter.

We have completed the review of your application for all submissions up to and including March 18, 2009. In our April 8, 2009 teleconference with you, we recommended the inclusion of a graduated device with the drug product to provide assurance that appropriate doses of 800 mg may be obtained from a single 2.4 gram packet and updated draft carton and container labeling to be reviewed by the Division of Medication Error and Prevention and Analysis (DMEPA).

We also acknowledge receipt of your April 10, 2009 submission which included a \_\_\_\_\_ and the draft carton and container labeling. Due to the timing of the submission, we are unable to perform a complete review of the information provided.

**b(4)**

**LABELING**

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(I)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/cder/guidance/2125fnl.htm>).

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please call:

Anna Park, R.Ph.  
Regulatory 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

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

/s/

-----  
Ellis Unger  
4/17/2009 12:56:10 PM  
Signed for Norman Stockbridge, M.D., Ph.D.



NDA 22-318

**COMPLETE RESPONSE**

Genzyme Corporation  
ATTENTION: Jamie McPherson, PharmD  
500 Kendall Street  
Cambridge, MA 02142

Dear Dr. McPherson:

Please refer to your new drug application (NDA) dated March 31, 2008, received March 31, 2008, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Renvela (sevelamer carbonate) for oral suspension, 2.4 grams.

We acknowledge receipt of your submissions dated May 30, June 30, July 3, 30, December 9, 2008 and January 6, 2009.

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described below our reason for this action and, where possible, our recommendations to address these issues.

**CLINICAL**

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. There is insufficient information from a comparison study of the powder to the hydrochloride tablet to define the two formulations as equivalent, so we are even more inclined to expect titrations would be necessary than if the new formulation were bioequivalent.

The following comments and recommendations are not approval issues, but we request that you address them as well.

**CLINICAL PHARMACOLOGY**

A. Comments on the in vitro bioequivalence studies:

1. For future submissions, please provide an explanation for the difference in phosphate binding affinity constant between sevelamer carbonate tablet and sevelamer carbonate powder.
2. The disintegration time data for the sevelamer carbonate tablet formulation should have been provided.
3. There is a discrepancy in the SAS transformed data set and data sets provided in biopharmaceutics legacy study report (TR 2119-06-SC: Drug Discovery & Development Technical MEMO). Please avoid such discrepancies in future submissions.

**B. Comments on sevelamer carbonate with warfarin drug-drug interaction study:**

1. The study design and analysis have the following deficiencies:
  - a) Plasma sampling up to 72 hours is insufficient to characterize the pharmacokinetics of warfarin based on its long half-life of ~2.5 days. In future studies, we recommend extending plasma sampling as long as 168 hours.
  - b) A thorough analysis of the effect of simultaneous administration of sevelamer carbonate and warfarin on the International Normalization Ratio (INR) was not provided. This analysis should be performed in future studies.
2. Please provide a full validation report for warfarin bioanalytical method.

**LABELING**

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/cder/guidance/2125fn1.htm>).

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Anna Park-Hong, Regulatory 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

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

/s/

-----  
Norman Stockbridge  
1/28/2009 09:50:23 AM