DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021179/S-029
NDA 022127/S-008
NDA 022318/S-003

SUPPLEMENT APPROVAL

Genzyme Corporation
Attention: Mary Beth Clarke, MSc
Senior Director, Regulatory Affairs
500 Kendall Street
Cambridge,MA 02142

Dear Ms. Clarke:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received May 31, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Renagel (sevelamer hydrochloride) 400 mg and 800 mg Tablets (NDA 021179), and Renvela (sevelamer carbonate) Powder for Oral Suspension (NDA 022318) and 800 mg Tablets (NDA 022127).

These "Prior Approval " supplemental new drug applications provide for labeling revised as follows:

The following changes were made for NDA 021179:

1. In **HIGHLIGHTS/CONTRAINDICATIONS**, the first bullet was changed from:

   - In patients with hypophosphatemia or bowel obstruction. (4)

   To:

   - In patients with bowel obstruction. (4)

2. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS,** the first bullet was changed from:

   The safety and efficacy of Renagel in patients with dysphagia, swallowing disorders, severe GI motility disorders including severe constipation, or major GI tract surgery have not been established. Caution should be exercised when Renagel is used in patients with these GI disorders. (5.1)

   To:

Serious cases of dysphagia, bowel obstruction, and perforation have been associated with sevelamer use, some requiring hospitalization and surgery. (5.1)

3. In **HIGHLIGHTS/DRUG INTERACTIONS,** the third bullet was deleted:

    - During postmarketing experience, very rare cases of increased TSH levels have been reported in patients co-administered sevelamer hydrochloride and levothyroxine. Closer monitoring of TSH levels is therefore recommended in patients receiving both medications. (7.7)

4. In **FULL PRESCRIBING INFORMATION: CONTENTS**, the heading for 5.1 was changed from:

    5.1 Use Caution in Patients with Gastrointestinal Disorders

    To:

    5.1 Gastrointestinal Adverse Events

5. Under **CONTRAINDICATIONS**, the word "hypophosphatemia" was deleted from the first sentence. The sentence now reads:

    Renagel is contraindicated in patients with bowel obstruction

6. Under **WARNINGS AND PRECAUTIONS**, the section was changed from:

    5.1 Use Caution in Patients with Gastrointestinal Disorders
    The safety of Renagel has not been established in patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders including severe constipation, or major GI tract surgery. Use caution in patients with these GI disorders.

    To:

    5.1 Gastrointestinal Adverse Events
    Cases of dysphagia and esophageal tablet retention have been reported in association with use of the tablet formulation of sevelamer, some requiring hospitalization and intervention. Consider using sevelamer suspension in patients with a history of swallowing disorders.

    Cases of bowel obstruction and perforation have been reported with sevelamer use. Patients with dysphagia, swallowing disorders, severe gastrointestinal (GI)

motility disorders including severe constipation, or major GI tract surgery were not included in the Renagel clinical studies.

7. Under **CLINICAL STUDIES**, Table 4 was changed from:

	Renagel (N=81)	Active-Control (N=83)
Baseline at End of Washout	8.4	8.0
Change from Baseline at Endpoint (95% Confidence Interval)	-2.0 (-2.5, -1.5)	-2.1 (-2.6, -1.7)

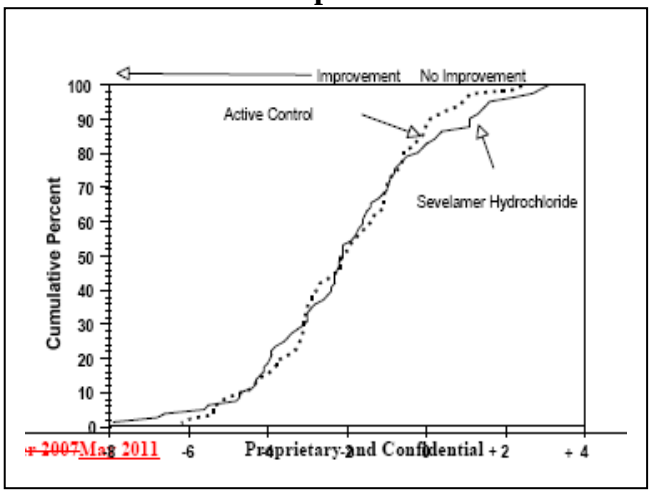
To:

	Renagel (N=81)	Active-Control (N=83)
Baseline at End of Washout	8.4	8.0
Endpoint	6.4	5.9
Change from Baseline at Endpoint (95% Confidence Interval)	-2.0* (-2.5, -1.5)	-2.1* (-2.6, -1.7)

*p<0.0001, within treatment group comparison

8. Under **CLINICAL STUDIES**, figure 2 was changed from:

Figure 2 shows that the proportion of patients achieving a given level of serum phosphorus lowering is similar in the two treatment groups. Median decrease in phosphorus was 2 mg/dL on each treatment. Figure 2. Cumulative percent of patients (Y-axis) attaining a phosphorus change from baseline at least as great as the value of the X-axis. A shift to the left of a curve indicates a better response.

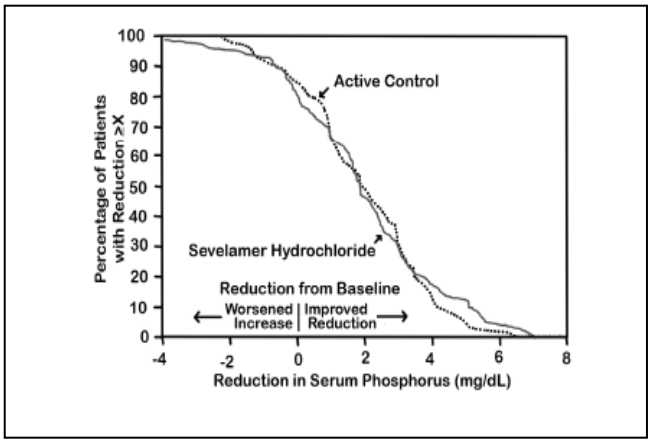


~~8 2007~~ 8 2011

To:

The distribution of responses is shown in Figure 2. The distributions are similar for sevelamer hydrochloride and active control. The median response is a reduction of about 2 mg/dL in both groups. About 50% of subjects have reductions between 1 and 3 mg/dL.

Figure 2. Percentage of patients (Y-axis) attaining a phosphorus reduction from baseline (mg/dL) at least as great as the value of the X-axis.



9. The revision date and version number were updated.

There are no other changes from the last approved package insert from May 20, 2009.

The following changes were made for NDAs 022127 & 022318:

1. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS,** the first bullet was changed from:

   The safety and efficacy of Renagel in patients with dysphagia, swallowing disorders, severe GI motility disorders including severe constipation, or major GI tract surgery have not been established. Caution should be exercised when Renagel is used in patients with these GI disorders. (5.1)

   To:

Serious cases of dysphagia, bowel obstruction, and perforation have been associated with sevelamer use, some requiring hospitalization and surgery. (5.1)

2. In **FULL PRESCRIBING INFORMATION: CONTENTS**, the heading for 5.1 was changed from:

   5.1 Use Caution in Patients with Gastrointestinal Disorders

   To:

   5.1 Gastrointestinal Adverse Events

3. Under **WARNINGS AND PRECAUTIONS**, the section was changed from:

   5.1 Use Caution in Patients with Gastrointestinal Disorders
   The safety of Renagel has not been established in patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders including severe constipation, or major GI tract surgery. Use caution in patients with these GI disorders.

   To:

   5.1 Gastrointestinal Adverse Events
   Cases of dysphagia and esophageal tablet retention have been reported in association with use of the tablet formulation of sevelamer, some requiring hospitalization and intervention. Consider using sevelamer suspension in patients with a history of swallowing disorders.

   Cases of bowel obstruction and perforation have been reported with sevelamer use. Patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders including severe constipation, or major GI tract surgery were not included in the Renagel clinical studies.

10. The revision date was updated.

We have completed our review of these supplemental applications, and they are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Lori Anne Wachter, RN, BSN
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

MARY R SOUTHWORTH
06/16/2011