DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022127/S-011
NDA 022318/S-005

SUPPLEMENT APPROVAL

Genzyme Corporation
C/O Sanofi US Services Inc
Attention: John Cook
Director, US Regulatory Affairs Marketed Products
55 Corporate Drive
Mailstop 55C-205A
Bridgewater NJ 08807

Dear Mr. Brown:

Please refer to your Supplemental New Drug Applications (sNDAs) dated May 23, 2014, and received May 23, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Renvela (sevelamer carbonate) 800 mg tablets and Renvela (sevelamer carbonate) 0.8g and 2.4g powder for oral suspension.

These "Changes Being Effected" supplemental new drug applications provide for modifications to the **Drug Interactions** and **Clinical Pharmacology** sections of labeling.

In addition to minor editorial changes, the following additions and ~~deletions~~ were made;

In **Highlights of Prescribing Information**;

Under **DRUG INTERACTIONS:**

- ~~Sevelamer decreases the bioavailability of ciprofloxacin by approximately 50%. (7.1)~~
- ~~Sevelamer did not alter the pharmacokinetics of single doses of digoxin, warfarin, enalapril, metoprolol, or iron. (7)~~
- When ~~administering an oral medication where a reduction in the bioavailability of that medication would have a~~ clinically significant ~~effect on its safety or efficacy, administer the~~ drug ~~at least one hour before or three hours after Renvela,~~interactions are expected, consider separation of the timing of administration and/or monitor clinical responses or blood levels of the concomitant medication. (7)
- Sevelamer did not alter the pharmacokinetics of digoxin, enalapril, iron, metoprolol and warfarin. (7)
- ~~drug.~~Sevelamer has demonstrated interaction with ciprofloxacin and mycophenolate mofetil, and therefore these drugs should be dosed separately from Renvela. (7~~.7~~)

In **Full Prescribing Information;**

Under **Drug Interactions:**

~~Sevelamer carbonate has been studied in human drug-drug interaction studies with warfarin and digoxin. Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been studied in human drug-drug interaction studies with ciprofloxacin, digoxin, warfarin, enalapril, metoprolol and iron.~~

~~**7.1 Ciprofloxacin**~~

~~In a study of 15 healthy subjects, a co-administered single dose of 2.8 grams of sevelamer hydrochloride decreased the bioavailability of ciprofloxacin by approximately 50%.~~

~~**7.2 Digoxin**~~

~~In 19 healthy subjects receiving 2.4 grams of sevelamer hydrochloride three times a day with meals for 2 days, sevelamer did not alter the pharmacokinetics of a single dose of digoxin.~~

~~In 18 healthy subjects receiving 9.6 grams of sevelamer carbonate once daily with a meal, sevelamer did not alter the pharmacokinetics of a single dose of digoxin.~~

~~**7.3 Warfarin**~~

~~In 14 healthy subjects receiving 2.4 g of sevelamer hydrochloride three times a day with meals for two days sevelamer did not alter the pharmacokinetics of a single dose of warfarin.~~

~~In 14 healthy subjects receiving 9.6 grams of sevelamer carbonate once daily with a meal, sevelamer did not alter the pharmacokinetics of a single dose of warfarin.~~

~~**7.4 Enalapril**~~

~~In 28 healthy subjects a single 2.4 gram dose of sevelamer hydrochloride did not alter the pharmacokinetics of a single dose of enalapril.~~

~~**7.5 Metoprolol**~~

~~In 31 healthy subjects a single 2.4 gram dose of sevelamer hydrochloride did not alter the pharmacokinetics of a single dose of metoprolol.~~

~~**7.6 Iron**~~

~~In 23 healthy subjects, a single 2.8 gram dose of sevelamer hydrochloride did not alter the absorption of a single oral dose of iron as 200 mg exsiccated ferrous sulfate tablet.~~

~~**7.7 Other Concomitant Drug Therapy**~~

There are no empirical data on avoiding drug interactions between Renvela and most concomitant ~~drugs. During postmarketing experience, very rare cases of increased thyroid stimulating hormone (TSH) levels have been reported in patients co-administered sevelamer hydrochloride and levothyroxine. Monitor TSH levels and signs of hypothyroidism in patients receiving both medications. When administering an~~oral drugs. For oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy~~, there is no information that suggests a dosing regimen that would be universally appropriate for all drugs. One may, however, administer the drug one hour before or three hours after Renvela, and monitor blood levels of the drug. Patients taking anti-arrhythmic medications for the control of arrhythmias and anti-seizure medications for the control of seizure disorders were excluded from the clinical trials.~~ (e.g., cyclosporine, tacrolimus, levothyroxine), consider separation of the timing of the administration of the two drugs *[see Clinical Pharmacology (12.3)]*. The duration of separation depends upon the absorption characteristics of the medication concomitantly administered, such as the time to reach peak systemic levels and whether the drug is an immediate release or an extended release product. Where possible consider monitoring clinical responses and/or blood levels of concomitant drugs that have a narrow therapeutic range.

Table 4. Sevelamer Drug Interactions

Oral drugs for which sevelamer did not alter the pharmacokinetics when administered concomitantly	
Digoxin Enalapril Iron Metoprolol Warfarin	
Oral drugs that have demonstrated interaction with sevelamer and are to be dosed separately from Renvela	
	Dosing Recommendations
Ciprofloxacin	Take at least 2 hours before or 6 hours after sevelamer
Mycophenolate mofetil	Take at least 2 hours before sevelamer

Under **Clinical Pharmacology, Pharmcokinetics** section:

12.3 Pharmacokinetics

A mass balance study using ^{14}C-sevelamer hydrochloride, in 16 healthy male and female volunteers showed that sevelamer hydrochloride is not systemically absorbed. No absorption studies have been performed in patients with renal disease.

Drug Interactions

In vivo

Sevelamer carbonate has been studied in human drug-drug interaction studies (9.6 grams once daily with a meal) with warfarin and digoxin. Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been studied in human drug-drug interaction studies (2.4-2.8 grams single dose or three times daily with meals or two times daily without meals) with ciprofloxacin, digoxin, enalapril, iron, metoprolol, mycophenolate mofetil and warfarin.

Co-administered single dose of 2.8 grams of sevelamer hydrochloride in fasted state decreased the bioavailability of ciprofloxacin by approximately 50% in healthy subjects.

Concomitant administration of sevelamer and mycophenolate mofetil in adult and pediatric patients decreased the mean MPA C_{max} and $AUC_{0\text{-}12h}$ by 36% and 26% respectively.

Sevelamer carbonate or sevelamer hydrochloride did not alter the pharmacokinetics of a single dose of enalapril, digoxin, iron, metoprolol and warfarin when co-administered.

During postmarketing experience, cases of increased thyroid stimulating hormone (TSH) levels have been reported in patients co-administered sevelamer hydrochloride and levothyroxine. Reduction in concentrations of cyclosporine and tacrolimus leading to dose increases has also been reported in transplant patients when co-administered with sevelamer hydrochloride without any clinical consequences (for example, graft rejection). The possibility of an interaction cannot be excluded with these drugs.

APPROVAL & LABELING

We have completed our review of this supplemental application. It is 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 that includes labeling changes 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).

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 Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
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
11/26/2014