

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-318**

**OTHER REVIEW(S)**



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: July 30, 2009

To: Norman Stockbridge, M.D., Director  
Division of Cardiovascular and Renal Products

Through: Kristina Arnwine, Pharm.D., Acting Team Leader  
Denise Toyer, Pharm.D., Deputy Director  
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Division of Medication Error Prevention and Analysis  
(DMEPA)

From: Lori Cantin, R.Ph., Safety Evaluator  
Division of Medication Error Prevention and Analysis  
(DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Renvela (Sevelamer Carbonate) for Oral Suspension,  
0.8 g and 2.4 g packets

Application Type/Number: NDA 22-318

Applicant/sponsor: Genzyme Corporation

OSE RCM #: 2009-1222

## 1 INTRODUCTION

This review was written in response to a request from the Division of Cardiovascular and Renal Products to evaluate revisions to the container labels and carton labeling submitted by the Applicant on June 12, 2009, for Renvela (Sevelamer Carbonate) for Oral Suspension.

## 2 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels, carton, and insert labeling submitted as part of the June 12, 2009, submission (see Appendix A and B).

## 3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels, carton and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 2.1 *Comments to the Division* for discussion during the review team's labeling meetings. Section 2.2 *Comments to the Applicant* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 2.2 be communicated to the Applicant prior to approval.

We note that our recommendations from the previous review dated December 31, 2008, have not yet been communicated to the Applicant. Therefore, the recommendations provided in this review of the labels and labeling submitted June 12, 2009, have been consolidated with the recommendations from our previous review of the labels and labeling, dated December 31, 2008.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Sean Bradley, Project Manager, at 301-796-1332.

### 3.1 COMMENTS AND QUESTIONS FOR THE DIVISION

1. The Applicant has revised the dosage form and the term \_\_\_\_\_ on all labels and labeling to state 'for Oral Suspension' and 'packet' respectively, which is consistent with the recommendation made in our December 31, 2008 review
2. We recommend that instructions regarding preparation of the powder for oral use be included in Section 17 (PATIENT COUNSELING INFORMATION) in the FULL PRESCRIBING INFORMATION. Per 21 CFR 201.57(c)(18), this section of the label must contain necessary information for the patient to use the drug safely and effectively.
3. In section 2.2 of the DOSAGE AND ADMINISTRATION section in the FULL PRESCRIBING INFORMATION, the mixing instructions state that the patient should "stir the mixture vigorously (it does not dissolve) and drink

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the entire preparation within 30 minutes.” However, DMEPA is unsure if the patient needs to re-suspend the mixture if they wait 30 minutes to administer the dose or if the mixture remains adequately suspended for 30 minutes. We note this issue has been discussed at labeling meetings and that the Division will have the applicant revise the container label, carton and insert labeling as appropriate.

### 3.2 COMMENTS TO THE APPLICANT

#### A. All Container Labels and Carton Labeling

1. Your container labels and carton labeling use the same blue and green colors for the trade dress and to differentiate the 0.8 gram and 2.4 gram strengths. Using the same colors (i.e., blue and green) on the labels and labeling of both strengths diminishes the usefulness of color for product strength differentiation and may lead to confusion and selection of the wrong strength. Revise your labels and labeling so that the colors utilized for strength differentiation do not overlap with colors used in the trade-dress.
2. Relocate the product strength to immediately follow the dosage form statement ‘for oral suspension.’ Thus, the strength should be relocated above \_\_\_\_\_ statement. The usual presentation and the preferred format of information on labels and labeling is proprietary name, followed immediately by the established name, dosage form, and strength. When such items appear in different locations and vary from the preferred format, it takes practitioners longer to locate the information or, information that appears in place of this typical format can be confused.

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#### C. Carton Labeling

Revise the net quantity statement to read “Contains 90 packets” rather than “\_\_\_\_\_” and “\_\_\_\_\_”

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

✓ § 552(b)(4) Draft Labeling

\_\_\_\_\_ § 552(b)(5) Deliberative Process

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**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: December 31, 2008

To: Norman Stockbridge, M.D., Director  
Division of Cardiovascular and Renal Products

Through: Kristina Arnwine, Pharm.D., Acting Team Leader  
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From: Lori Cantin, R.Ph., Safety Evaluator  
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Subject: Label and Labeling Review

Drug Name(s): Renvela (Sevelamer Carbonate) for Oral Suspension, 2.4 g

ApplicationType/Number: NDA 22-318

Applicant: Genzyme Corporation

OSE RCM #: 2008-1077

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## **EXECUTIVE SUMMARY**

The results of the Label and Labeling Risk Assessment found that the presentation of information on the proposed container label and carton labeling for Renvela (sevelamer carbonate) Powder for Oral Suspension is vulnerable to confusion that could lead to medication errors. A detailed discussion can be found in Section 4.1.

The Division of Medication Error Prevention and Analysis (DMEPA) believes the risks we have identified can be addressed and mitigated prior to approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

This review was written in response to a request from the Division of Cardiovascular and Renal Products to evaluate the container labels, carton labeling and the revised package insert for Renvela, for the potential to contribute to medication errors.

### **1.2 REGULATORY HISTORY**

Renvela (sevelamer carbonate) Tablets (NDA 22-127) was approved on October 19, 2007. On March 31, 2008, the sponsor (Genzyme Corporation) submitted a new drug application (NDA 22-318), which provides for a new dosage form (Powder for Oral Suspension) for Renvela. The revised package insert submitted under NDA 22-318 combines the approved tablet dosage form and the proposed powder for oral suspension dosage form into one package insert.

### **1.3 PRODUCT INFORMATION**

Renvela (sevelamer carbonate) is a phosphate binder indicated for the control of serum phosphorus in patients with chronic kidney disease on dialysis. The usual dose is one 2.4 gram packet mixed with at least two ounces of water three times daily with meals. Renvela 2.4 g packets may be prescribed in place of the three Renvela 800 mg tablets for patients who are taking 2.4 g three times a day with meals or 2.4 g of Renagel (sevelamer hydrochloride) tablets three times a day with meals. Renvela, powder for oral suspension, will be supplied as opaque, foil-lined, heat-sealed, packets containing 2.4 g of sevelamer carbonate each. The 2.4 g packets will be available in a 90-count box for dispensing and a 90-count box for sample use.

## **2 METHODS AND MATERIALS**

This section describes the methods and materials used by medication error prevention staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.<sup>1</sup>

### **2.1 LABEL AND LABELING RISK ASSESSMENT**

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form,

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<sup>1</sup> National Coordinating Council for Medication Error Reporting and Prevention.  
<http://www.nccmerp.org/about/MedErrors.html>. Last accessed 10/11/2007.

container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.<sup>2</sup>

Because medication error prevention staff analyze reported misuse of drugs, our staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on March 31, 2008, the following labels and labeling for our review:

- Container Labels: 2.4 g sachet label and 2.4 g sample sachet label (see Appendix A for images)
- Carton Labeling: 90 packet trade carton and 90 packet sample carton (see Appendix B for images)
- Package Insert (no image)

## **2.2 ADVERSE EVENT REPORTING SYSTEM (AERS)**

On July 23, 2008, the Division of Medication Error Prevention conducted a search of the FDA Adverse Event Reporting System (AERS) database to determine if any medication errors involving Renvela have been reported. The following criteria were used: MedDRA High Level Group Term (HLGT) 'Medication Errors' and the Preferred term (PT) 'Pharmaceutical Product Complaint' with the active ingredient (sevelamer carbonate), trade name (Renvela), and verbatim term 'Renv%'.

The cases were manually reviewed to determine if medication errors occurred. Those cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

## **3 RESULTS**

### **3.1 LABEL AND LABELING RISK ASSESSMENT**

Review of the container labels, carton labeling, and package insert labeling identified certain areas of vulnerability that could lead to medication error, specifically regarding the prominence, presentation, and clarity of information on the container label and carton labeling.

#### ***3.1.1 All Labels and Labeling***

The dosage form is designated as 'Powder for Oral Suspension'.

#### ***3.1.2 All Container Labels and Carton Labeling***

The relationship of the established name 'sevelamer carbonate' to the proprietary name 'Renvela' is not made clear (i.e., the established name is not bracketed or preceded by the phrase "brand of") as required per 21 CFR 201.10(g)(1).

Intervening matter \_\_\_\_\_ is presented between the established name and the strength. **b(4)**

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<sup>2</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

### 3.1.3 All Container Labels and Carton Labeling

The relationship of the established name 'sevelamer carbonate' to the proprietary name 'Renvela' is not made clear (i.e., the established name is not bracketed or preceded by the phrase "brand of") as required per 21 CFR 201.10(g)(1).

Intervening matter \_\_\_\_\_ is presented between the established name and the strength.

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### 3.1.4 Trade and Sample Container Labels

The dosage form is not presented immediately after the proprietary and established names on the container labels.

### 3.1.5 Trade and Sample Container Labels

The dosage form is not presented immediately after the proprietary and established names on the container labels.

The strength is not presented immediately after the proprietary name, established name, and dosage form on the container labels.

The directions for use on the container (trade packet and sample packet) labels instruct the patient to prepare the product using 2 ounces (4 tablespoons) of water.

### 3.1.6 Trade and Sample Carton Labeling

The net quantity is not stated on the principal display panel of the carton labeling

The net quantity appears next to the product strength on the side panel of the carton labeling.

The dosage form is not indicated on the side panel of the carton labeling.

### 3.1.7 Package Insert Labeling

The package insert refers to the packaging configuration for the powder as \_\_\_\_\_ which is inconsistent with the container labels and carton labeling which refer to the packaging configuration as a "packet".

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## 3.2 ADVERSE EVENT REPORTING SYSTEM (AERS)

The Adverse Event Reporting System (AERS) search did not retrieve any medication error cases that involved the drug product, Renvela.

## 4 DISCUSSION

Our analysis of the Label and Labeling Risk found that the presentation of certain information on the container labels and carton labeling lack prominence, is not consistent with USP standards, is poorly presented, and needs clarity. With respect to the package insert labeling, problems with inconsistencies, incomplete information, and the use of dose designations were identified.

### 4.1 ALL CONTAINER LABELS AND CARTON LABELING

The applicant refers to the dosage form for sevelamer carbonate as 'Powder for Oral Suspension'. For powders intended for oral suspension, the USP definition of the pharmaceutical dosage form is 'for Oral Suspension'. Additionally, we noted that the intervening matter \_\_\_\_\_ is presented between the established name and the strength, and that the presentation of the dosage strength and the dosage form 'for oral suspension' are not consistent with the preferred format on all labels and labeling. The usual presentation of information on labels and labeling is: proprietary name, followed immediately by the

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established name, dosage form, and strength. When labels and labeling vary from the preferred format, it takes practitioners longer to locate important information, and can lead to confusion.

#### 4.1.1 Trade and Sample Container Labels

The directions for use on the container (trade packet and sample packet) labels instruct the patient to prepare the product using 2 ounces (4 tablespoons) of water. The volume unit 'ounce' may not be as recognizable to some patients and/or caregivers, as other more commonly known volume units, such as '1/4 cup'. Additionally, some patients may rely on the use of household teaspoons or tablespoons which are inaccurate measuring devices for medications and can lead to dosing errors. Per consultation with the ONDQA reviewer, smaller amounts of water than the recommended 2 ounces could make the suspension thicker and cause more residual material to remain in the \_\_\_\_\_ . Therefore, it is important that the patient mix each Renvela 2.4 g packet with *at least* 2 ounces of water in order to adequately suspend each 2.4 g dose. With regard to Renvela powder preparation specifically, it is possible that the patient/caregiver may mix the powder in an insufficient volume of water to properly suspend the prescribed dose, resulting in the patient not receiving the intended dose. Since some patients may not be savvy enough to resuspend and administer significant amounts of residual material left in the \_\_\_\_\_ a more recognizable volume unit, such as 'cup', is preferred. Alternatively, a dosing device with appropriate markings that correspond to the correct amount of water to be measured could be provided with the product in order to ensure accurate mixing of the prescribed dose.

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#### 4.1.2 Trade and Sample Carton Labeling

The placement of the strength is inconsistent on the carton labeling. On the flap the strength is not presented, whereas on the side panel the strength is presented next to the net quantity and after the \_\_\_\_\_ statement. This differs from the usual presentation of information on labels and labeling where the strength immediately follows the established name (see 4.1 above).

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### 4.2 PACKAGE INSERT LABELING

The package insert refers to the primary container closure system for the powder as a '\_\_\_\_\_ ' which is inconsistent with the container labels and carton labeling which refer to the primary container closure system as a 'packet'. The term used should be consistent in all labels and labeling for the drug product in order to minimize the potential for confusion. The term 'packet' is more accurate and is preferred by DMEPA to designate the primary container closure system for the drug product in the package insert, as well as in the carton labels and container labeling. The CDER Data Standards Manual defines a packet as an envelope into which only one dose of a drug product, usually in the form of granules or powder, has been directly placed. The term \_\_\_\_\_ is not defined by the CDER Data Standards Manual.

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Section 17 (PATIENT COUNSELING INFORMATION) in the FULL PRESCRIBING INFORMATION does not contain preparation instructions for the powder for oral suspension. Per 21 CFR 201.5(c)(18), this section of the label must contain necessary information for the patients to use the drug safely and effectively.

## 5 CONCLUSIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information on the proposed container labels and carton labeling introduces vulnerability to confusion that could lead to medication errors. The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

## 6 RECOMMENDATIONS

### 6.1 COMMENTS TO THE DIVISION

Based upon our assessment of the labels and labeling, and the review of post-marketing medication error reports, the Division of Medication Error Prevention and Analysis has identified areas of needed improvement. These recommendations are provided in Section 6.2 and we request that this information be forwarded to the Applicant.

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the applicant with regard to this review. If you have further questions or need clarifications, please contact Sean Bradley, Project Manager, at 301-796-1332.

### 6.2 COMMENTS TO THE APPLICANT

Based upon our assessment of the labeling, the Division of Medication Error Prevention and Analysis identified the following areas of needed improvement.

#### A. All Container Labels and Carton Labeling

1. The usual presentation and the preferred format of information on labels and labeling is: proprietary name, followed immediately by the established name, dosage form, and strength. When such items appear in different locations and vary from the preferred format, it takes practitioners longer to locate the information, or information that is in its place can be confused. Thus, in order to provide consistency with other currently marketed drug products and to minimize the potential for confusion, relocate the intervening matter \_\_\_\_\_ from between the established name and the strength to a more suitable location. Additionally, relocate the dosage form, followed by the product strength, to the position directly under the established name on the trade and sample container labels. Add the dosage form statement 'for oral suspension' to the side panel of the carton labeling in the position immediately following the established name. b(4)
2. Per 21 CFR 201.10(g)(1), the "established name shall be made clear by the use of a phrase such as "brand of" preceding the established name, by brackets surrounding the established name, or by other suitable means." Clarify the relationship of the established name 'sevelamer carbonate' to the proprietary name 'Renvela'.
3. Revise the dosage form on all labels and labeling to state 'for Oral Suspension'. The dosage form is currently designated as 'Powder for Oral Suspension' which is inconsistent with the USP definition of this type of pharmaceutical dosage form which is 'for Oral Suspension'.

#### B. Trade and Sample Container Labels

Revise the preparation instructions for the oral suspension to instruct the user to empty the packet into a cup containing "at least ¼ cup (4 Tablespoons) of water", as opposed to "at least 2 ounces (4 tablespoons) of water." We believe the term 'cup' is more recognizable to patients, and most are likely to have a cup available for measuring, as opposed to a measuring device with gradations in ounces. As an alternative, you may choose to provide a measuring device as part of the packaging and revise the labels and labeling accordingly.

#### C. Carton Labeling

1. On the side panel of the carton labeling, relocate the product strength (2.4 g) to the space directly under the established name and identify the net quantity as '90 packets' in its current location on the label. Alternatively, you may more clearly distinguish and separate the net quantity from the product strength by stating the information in another format, such as:

Contains 90 packets  
(2.4 g per packet)

2. Add the net quantity of contents, i.e., '90 packets', to the principal display panel of the carton labeling. This information should be displayed with "prominence and conspicuousness" per 21 CFR 201.51(f).

**D. Package Insert Labeling**

1. Use the term 'packet' consistently in all labels and labeling for the primary container closure system. The package insert refers to the primary container closure system for the powder as a \_\_\_\_\_ which is inconsistent with the carton labels and container labeling which refer to the primary container closure system as a 'packet'. 'Packet' is defined by the CDER Data Standards Manual as "an envelope into which only one dose of a drug product, usually in the form of granules or powder, has been directly placed", and it is the more accurate and correct designation for the primary container closure system. b(4)
2. Include instructions regarding preparation of the powder for oral use in Section 17 (PATIENT COUNSELING INFORMATION) in the FULL PRESCRIBING INFORMATION. Per 21 CFR 201.5(c)(18), this section of the label must contain necessary information for the patient to use the drug safely and effectively.

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

✓ § 552(b)(4) Draft Labeling

\_\_\_\_\_ § 552(b)(5) Deliberative Process

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