



Charles R. Nolan, M.D.

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FEB 07 2019

Re: Docket No. FDA-2006-P-0392

Dear Dr. Nolan:

This letter responds to your citizen petition received by the Food and Drug Administration (FDA or the Agency) on May 4, 2006 (Petition).¹ The Petition requests FDA to either withdraw approval of new drug application (NDA) 021179 for Renagel (sevelamer hydrochloride) 400 and 800 milligram (mg) tablets or require a boxed warning² in Renagel labeling. According to the Petition, the basis for these requests is the “disturbing number of reports of intestinal obstructions and perforations associated with the use of Renagel in dialysis patients” (Petition at 1). Alternatively, the Petition requests that FDA require that the labeling of Renagel be revised to warn physicians about an association between Renagel and intestinal obstruction and perforation. Finally, the Petition requests that FDA require dissemination of a “Dear Doctor” letter regarding the labeling change.

We have carefully reviewed the information in the Petition as well as the comment submitted to the Petition docket.³ For the reasons set forth below, your Petition is granted in part and denied in part.

I. BACKGROUND

A. Statutory and Regulatory Framework

FDA’s regulation of drug safety is governed by the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 301, et seq.) and the Agency’s implementing regulations (codified in Title 21 of the Code of Federal Regulations). The FD&C Act makes it unlawful to market a new drug product without first obtaining approval of an NDA or abbreviated new drug application

¹ The Petition was originally assigned docket number 2006P-0186. This number changed when FDA transitioned to its new docketing system, Regulations.gov, in January 2008.

² While the Petition requests a “‘black box’ warning,” the regulation that describes specific requirements on content and format of labeling for most human prescription drug and biological products, including Renagel, 21 CFR 201.57, refers to such a warning simply as a “boxed warning.” See 21 CFR 201.57(c)(1). We will, therefore, use the term “boxed warning” throughout this response.

³ On May 26, 2006 Genzyme Corporation (Genzyme), Renagel’s NDA holder, submitted a letter in response to the Petition. Genzyme’s letter is included as a comment to the Petition’s docket -FDA-2006-P-0392 (formerly 2006P-0186). This document is available on Regulations.gov at www.regulations.gov.

(ANDA).⁴ Before approving an application, FDA must determine that the drug is both safe and effective for use under the conditions prescribed, recommended, or suggested in the product's labeling.⁵

1. Withdrawal of Approval

FDA continues to monitor adverse events associated with a drug after its approval and may take regulatory action as authorized and appropriate. One possible action is withdrawal of a drug product's approval. Section 505(e)(1)-(2) of the FD&C Act provides that FDA shall withdraw approval of a drug product if it finds, after notice and opportunity for a hearing, "that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved," or that:

new evidence of clinical experience, not contained in such application or not available to [FDA] until after the application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to [FDA] when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved[.]

2. Safety Labeling Changes

Section 505(o)(4) of the FD&C Act authorizes FDA to require certain holders of approved applications for prescription drug products to make safety labeling changes – including addition of a boxed warning – if the Agency becomes aware of new safety information that FDA believes should be included in the labeling of the drug.⁶

3. Regulations and Guidances: Boxed Warnings

FDA may require that "[c]ertain contraindications or serious warnings, particularly those that may lead to death or serious injury . . . be presented in a box" in a drug product's labeling:⁷

Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. The box must contain, in uppercase letters, a heading inside the box that includes the word "WARNING" and conveys the general focus of the information in the box. The box must briefly explain the risk and refer to more detailed information in the "Contraindications" or "Warnings and Precautions" section, accompanied by the identifying number for the section or subsection containing the detailed information.

⁴ See section 505(a) of the FD&C Act (21 U.S.C. 355(a)); see also section 301(d) of the FD&C Act (21 U.S.C. 331(d)) (prohibiting the marketing of any article in violation of section 505).

⁵ See section 505(c)(1) and (d) of the FD&C Act.

⁶ See sections 505(o)(2)(C) and 505-1(b)(3) of the FD&C Act.

⁷ 21 CFR 201.57(c)(1).

FDA explained in the guidance entitled *Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011) (Warnings Guidance)⁸ that a boxed warning is ordinarily used to highlight one of the following situations:⁹

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug; or
- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug . . . ; or
- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted

The Warnings Guidance also explains other circumstances in which a boxed warning may be appropriate, including the need to highlight warning information that is especially important to the prescriber.

B. Renagel

FDA approved NDA 021179 for Renagel tablets, 400 and 800 mg, on July 12, 2000. Renagel is a phosphate binder that is indicated for the control of serum phosphorous in patients with chronic kidney disease who are on dialysis.

Renagel is an insoluble non-aluminum, non-calcium-containing polymeric phosphate binder that acts locally and is not systemically absorbed. The hydrogel of cross-linked poly (allylamine hydrochloride) binds phosphate anions through ionic exchange with chloride and has been shown to reduce serum phosphate in patients with chronic kidney disease on dialysis. Historically, aluminum- and calcium-containing antacids were the only phosphate binders available. Patients with end stage renal disease (ESRD) have limited capacity to excrete phosphate and increased serum phosphate (in conjunction with low ionized calcium levels) contributes to the development of secondary hyperparathyroidism and renal osteodystrophy.¹⁰ Renagel is a clinically important medication in the treatment of hyperphosphatemia that occurs in patients with chronic kidney disease on dialysis.

The labeled recommended starting dose of Renagel is 800 to 1600 mg taken with meals (three times daily) to be titrated based on serum phosphorus levels. There is no specific maximum dose described; however, the labeling states that the average dose in a Phase 3 trial designed to lower serum phosphorus to 5.0 mg/dL or less was approximately three Renagel 800 mg tablets per meal and the maximum average daily dose was 13 grams.

⁸ This guidance is available at <https://www.fda.gov/downloads/drugs/guidances/ucm075096.pdf>.

⁹ See Warnings Guidance at 11.

¹⁰ Persy VP, et al. Lanthanum: A Safe Phosphate Binder. Semin Dial. 2006 May-Jun; 19(3):195-9.

C. FDA Safety Reviews of Renagel and Phosphate Binders

In June 2006, FDA completed a safety review of three phosphate binders, including Renagel. FDA examined adverse event reports in the FDA Adverse Event Reporting System (FAERS) because cases of gastrointestinal (GI) complications with Renagel were identified during routine post-marketing surveillance. FDA evaluated 82 reports of GI complications, including intestinal obstructions and perforations, in patients taking Renagel between the years 2000 and 2006.¹¹ In general, these case reports were difficult to interpret because of their poor quality and lack of completeness. For example, there were inconsistencies in some initial and follow-up reports that made it difficult to determine the clinical course of the adverse event and treatments rendered. Importantly, GI complications are common in patients with ESRD regardless of drug therapy and distinguishing a drug-related adverse reaction from underlying disease is difficult. Reports also were confounded by concomitant disease or past medical histories such as diverticulitis, GI cancer, or prior abdominal surgeries. In other instances, confounding medications, such as steroids, calcium or sodium polystyrene sulfonate and sorbitol, were present. Additionally, there were reports of dialysis-related amyloidosis in long-term hemodialysis patients leading to GI-related complications.¹² The existence of these factors limited FDA's ability to assess the relationship between intestinal obstructions and perforations and Renagel. The Agency was unable to identify a causal relationship between Renagel and intestinal obstructions and perforations when it reviewed this issue in 2006; however, the Agency concluded that continued adverse event monitoring was warranted.

FDA conducted several additional reviews of Renagel over the following years. Although the information provided in the FAERS cases was limited, FDA determined there was sufficient information to suggest an association between the use of Renagel and some GI-related adverse events based on temporal association and biologic plausibility (i.e., Renagel expands to several times its original size when exposed to gastric and intestinal fluids). Additionally, the NDA holder for Renagel submitted a supplemental NDA providing for changes to labeling based on worldwide postmarketing adverse event reports. FDA approved the supplemental NDA on August 14, 2007. This supplemental NDA added the underlined phrase to the sentence: "The safety and efficacy of Renagel in patients with severe gastrointestinal (GI) motility disorders including severe constipation or major GI tract surgery have not been established[]" in the PRECAUTIONS/General subsection of the labeling. The supplemental NDA also added the underlined phrase to the sentence "During post-marketing experience, the following adverse events have been reported in patients receiving Renagel although no direct relationship to

¹¹ The majority of these 82 cases (71) were reported from Japan. Five cases were reported from the United States and six were from foreign countries other than Japan. Thirteen of the Japanese cases had fatal outcomes while one of the cases reported from the United States resulted in a fatal outcome and one of the cases from foreign countries other than Japan resulted in a fatal outcome. The range of sevelamer doses administered daily to Japanese patients was from 0.75 to 9 grams with an average of 2.6 grams (non-death cases) and 0.75 to 3.75 grams with an average of 2.5 grams (death cases). For U.S. cases, doses ranged from 2.4 to 7.2 grams daily, and the average was 5.4 grams daily (recommended starting dose was 2.4 to 4.8 grams per day with average doses of up to 13 grams per day for hemodialysis patients). For those foreign cases outside of Japan, doses ranged from 2.4 to 9.6 grams daily with the average dose being 5.3 grams.

¹² See *Am J Nephrol*. 1996;16(2):149-53; *Gastroenterology*. 1999;116(1):217-20.

Renagel could be established: pruritis, rash, abdominal pain and in very rare cases, intestinal obstructions and ileus[1]" in the ADVERSE REACTIONS section of the labeling.¹³

In March 2011, FDA completed a review of FAERS cases reporting esophageal obstructions and dysphagia-related events in patients taking Renagel. FDA identified 44 cases, some with serious outcomes requiring hospitalization with endoscopy for tablet removal. On June 16, 2011, FDA approved a supplemental NDA that, among other things, made the following change to the WARNINGS AND PRECAUTIONS section of Renagel's labeling to be consistent with labeling for other sevelamer-containing products, and because of continued reporting of those events.¹⁴

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."

In 2017, FDA again reviewed safety information associated with the three phosphate binders, including Renagel, as it had in 2006. FDA identified 11 intestinal obstruction and/or perforation adverse event cases associated with one of the three phosphate binders in FAERS and the published medical literature between March 2006 and October 2017. Eight of the cases provided limited information (e.g., unknown concomitant medications, unknown comorbidities) and time-to-onset of the GI adverse event ranged from 2 days to 8 years, showing no consistent pattern across the reported cases.¹⁵ In general, these cases also suffered from poor documentation or lacked important medical information, making analysis difficult.

¹³ See Renagel (sevelamer hydrochloride) tablets labeling, revised October 19, 2007 available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021179s020lbl.pdf (Renagel 2007 labeling).

¹⁴ See Renagel (sevelamer hydrochloride) tablets labeling, revised June 11, 2011 available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021179s029lbl.pdf (Renagel 2011 labeling).

¹⁵ The range of sevelamer doses reported at the time of the adverse event (0.8 to 11.2 grams per day) was within the recommended range.

At this time, the Agency also conducted an epidemiological literature review of 42 articles published between March 15, 2006 and October 3, 2017. Of the five observational studies selected for review, FDA did not identify any cases of GI obstructions or perforations among users of phosphate binders.

II. DISCUSSION

The Petition requests that FDA withdraw Renagel from the market or alternatively add a boxed warning to labeling because of the risk of intestinal obstructions and perforations associated with the use of Renagel. As a third alternative, the Petition requests that, at minimum, FDA require that the labeling of Renagel be revised to warn about an association between the drug and occurrences of intestinal obstruction and perforation. The Petition also asks that FDA require Renagel's sponsor to send a "Dear Doctor" letter to inform physicians of such a labeling change. The Petition makes the following arguments in support of its requests: (1) data from FAERS suggest a high number of intestinal obstructions and perforations associated with the use of Renagel in dialysis patients for treatment of hyperphosphatemia in patients with ESRD (Petition at 2); (2) Renagel's labeling is inadequate in that it mentions some adverse events, including pruritus, rash, and abdominal pain, but does not mention risks of intestinal obstructions and perforations (Petition at 1);¹⁶ and (3) a safe maximum dose of Renagel has not been defined and intestinal obstructions and perforations may be the result of toxicity to the GI tract caused by high-dose Renagel treatments (Petition at 2-3).

A. Request for Withdrawal

The Petition contains a summary of a review and analysis of FAERS adverse events reports for Renagel for the period July 1999 through September 2005, specifically focusing on the period between the first quarter of 2004 through the third quarter of 2005 (Petition at 2, 5). The Petition states that a review of relevant data during that period suggests that Renagel was associated with significantly more adverse event reports of intestinal obstructions and perforations than other phosphate binders. Additionally, the Petition claims that the overall number of adverse events in FAERS during that same period was also significantly greater for Renagel (Petition at 2, 5). The Petition therefore requests that FDA conduct a thorough investigation of Renagel's safety profile, and if such an investigation validates "these safety concerns for Renagel" that FDA withdraw Renagel from the market (Petition at 2).

As discussed above, FDA has conducted several safety reviews of FAERS adverse event reports involving Renagel since the Petition was submitted and approved supplements updating the labeling in 2007 and 2011 to describe the events of concern. Those adverse events are currently listed in the WARNINGS AND PRECAUTIONS section of the labeling. FDA's most recent review of cases and literature did not find any increase in the severity or frequency of events that would justify withdrawing the drug from the market, and we therefore do not believe that withdrawal is warranted at this time. Based on the available data, FDA finds that the benefits of Renagel for use in controlling serum phosphate in patients with chronic kidney disease on dialysis continues to outweigh its risks. Accordingly, FDA declines to withdraw approval of the

¹⁶ Renagel's labeling was updated after this Petition was submitted to address the risks of intestinal obstructions and perforations. See Section I.C. of this response.

Renagel NDA.

B. Request for a Boxed Warning or other Warning and a “Dear Healthcare Provider” Letter

The Petition alternatively requests that the Agency require a boxed warning about the risks of intestinal obstructions and perforations with use of Renagel. According to the Petition, a boxed warning would hopefully result in increased vigilance by doctors such that GI complications in Renagel-treated patients would be thoroughly evaluated and treated. The Petition notes that at the time it was submitted, the labeling did not address the issue of intestinal obstructions and perforations. The Petition in the alternative states that FDA should “at an absolute minimum” have the labeling of Renagel revised to warn physicians of the association between Renagel and these adverse events. It also requests FDA to require the NDA holder for Renagel to send physicians a “Dear Doctor” letter to inform them of labeling changes that provided additional information concerning intestinal obstructions and perforations.

Based on our review of FAERS adverse event data and published literature, the Agency does not believe that a boxed warning regarding the risk of intestinal obstructions and perforations with use of Renagel is warranted. Because the risks of intestinal obstructions and perforations are now adequately described in the WARNINGS AND PRECAUTIONS section of Renagel labeling, FDA is not persuaded that additional highlighting is necessary to inform prescribers of these risks at this time. Accordingly, the Agency declines to require addition of a boxed warning to Renagel’s labeling about the risks of intestinal obstructions and perforations.

We note that, as discussed above, in the years following the submission of the Petition in 2006, FDA has recognized an association between intestinal obstructions and perforations and Renagel. As a result, the Agency approved supplemental NDAs making labeling changes to Renagel’s labeling relating to these risks. As requested by the Petition, the supplemental NDAs updated the WARNINGS AND PRECAUTIONS section of labeling to include the risks of intestinal obstructions and perforations.¹⁷ In addition, Renagel’s labeling has stated since the drug was approved that Renagel is contraindicated in patients with bowel obstruction.¹⁸

Based on its review of the data, the Agency is satisfied that the information contained in Renagel’s current labeling adequately addresses these risks. The association between Renagel and intestinal obstructions and perforations has been well documented for the medical community. Therefore, FDA does not agree that a Dear Healthcare provider letter should be sent at this time.

¹⁷ See Renagel 2007 labeling and Renagel 2011 labeling.

¹⁸ See Renagel (sevelamer hydrochloride) tablets labeling, revised March 9, 2016 available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021179s032lbl.pdf.

III. CONCLUSION

As explained above, we have carefully reviewed the information in the Petition, as well as the comment submitted to the Petition docket. We have also examined safety data available in FAERS and published literature. Based on our review of the available scientific and medical information, the Agency concludes that neither the withdrawal of the Renagel NDA nor the addition of a boxed warning to Renagel labeling is warranted. We also do not believe that a Dear Healthcare Provider letter is needed at this time. However, we note that the Agency has approved supplemental NDAs that updated the WARNINGS AND PRECAUTIONS section of Renagel's labeling to include the association between Renagel use and intestinal obstructions and perforations. Accordingly, your Petition is granted in part and denied in part.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research