

May 3, 2006

Division of Dockets Management  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, Maryland 20852

**CITIZEN PETITION**

The undersigned submits this petition to request that the approval of the prescription drug Renagel<sup>®</sup> be withdrawn. I am a physician board certified in Internal Medicine and Nephrology and in an academic practice setting as Professor of Medicine and Surgery at the University of Texas Health Sciences Center at San Antonio. I am also Medical Director of the Kidney and Pancreas Transplant Programs at University Hospital in San Antonio. I have been a practicing Nephrologist for over 20 years and have been a principal investigator on a number of clinical studies of phosphate binders and have authored several scientific publications on phosphate binder therapy in patients with end-stage renal disease.<sup>1</sup>

**A. ACTION REQUESTED**

This Petition requests that the Commissioner withdraw approval of the new drug application (NDA 21-179) for Renagel<sup>®</sup> Tablets (sevelamer hydrochloride) 400 and 800 mg, a treatment for hyperphosphatemia in patients with end-stage renal disease (ESRD). Renagel<sup>®</sup> is marketed by Genzyme Corporation. Alternatively, this Petition requests that the Commissioner require a "black box" warning on Renagel Tablets.

As described in detail below, a systematic review of the Food and Drug Administration's (FDA's) Adverse Event Reporting System (AERS) database shows that there have been a disturbing number of reports of intestinal obstructions and perforations associated with the use of Renagel<sup>®</sup> in dialysis patients. A number of these serious adverse events have resulted in death. Despite the alarming number of serious and potentially life-threatening adverse gastrointestinal events documented in the AERS database, the FDA-approved labeling for Renagel<sup>®</sup> fails to even mention intestinal obstruction or perforation as potential adverse events, let alone warn against them. As a matter of fact, the Renagel<sup>®</sup> package insert from 2005 contains the following statement: "During post-marketing experience, the following adverse events have been reported in patients receiving Renagel<sup>®</sup> although no direct relationship to Renagel<sup>®</sup> could be established: pruritus, rash and abdominal pain". There is absolutely no mention of intestinal perforation and obstruction although these events have been frequently reported since 2003 (see below).

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<sup>1</sup> Although I have served as a consultant to Nabi Biopharmaceuticals, the manufacture of PhosLo<sup>®</sup>, I am not being compensated by Nabi or anyone else for submitting this Petition.

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## **B. STATEMENT OF GROUNDS**

The attached analysis, which was conducted using FDA's AERS database, shows that treatment with Renagel<sup>®</sup> is associated with previously undisclosed serious safety risks that are not present with other FDA-approved products that are indicated for the treatment of hyperphosphatemia in patients with chronic kidney disease. Since Renagel approval in 1999, AERS data indicate that 80 cases of gastrointestinal obstruction and 79 cases of gastrointestinal perforation (some fatal) have been reported [Table 1]. Comparative data on the three phosphate binders licensed for treatment of hyperphosphatemia in end-stage renal disease patients (Renagel<sup>®</sup>, Fosrenol<sup>®</sup> and PhosLo<sup>®</sup>), were analyzed from the first quarter of 2004 through the third quarter of 2005 [Table 2]. During this period, Renagel<sup>®</sup> was associated with significantly more adverse events of intestinal obstruction and perforation than the other two drugs combined. Renagel<sup>®</sup> was associated with 133 such events (65 intestinal obstructions, 68 intestinal perforations), Fosrenol<sup>®</sup> with 3 intestinal obstructions and PhosLo<sup>®</sup> with no such GI adverse events. A number of the intestinal obstructions and perforations in Renagel-treated patients had a fatal outcome. The overall number of adverse events compiled in the FDA AERS database over that period of time was also significantly greater for Renagel (1633 for Renagel<sup>®</sup>, 354 for Fosrenol<sup>®</sup> and 21 for PhosLo<sup>®</sup>) [Table 2]. In this context, it is important to emphasize that the overall exposure in terms of prescriptions written for Renagel<sup>®</sup> or PhosLo<sup>®</sup> was very similar during this same timeframe. These 136 gastrointestinal adverse events were identified in the AERS database by using the key words "obstruction," "perforation" and "ileus." The 136 events were reported from 112 unique individuals (109 patients on Renagel<sup>®</sup> and 3 patients on Fosrenol<sup>®</sup>). While the AERS database is a critical source of information, it is well-recognized that this voluntary reporting system captures only a small fraction of actual adverse drug experiences. Nevertheless, the limited information in the AERS database regarding the alarmingly high rate of gastrointestinal complications in Renagel-treated patients and the severity of these adverse events calls for an immediate and thorough investigation by FDA. If further investigation validates these safety concerns for Renagel<sup>®</sup>, in my opinion, the FDA should immediately initiate proceedings to withdraw approval of Renagel.

It is clear that all drugs have potential side effects and therefore the overall risk-benefit ratio of any drug must be assessed. In this regard, there are two alternative phosphate binders (PhosLo<sup>®</sup> and Fosrenol<sup>®</sup>) which are FDA-approved and marketed in the United States. These drugs are at least as effective as Renagel for the approved indication (treatment of hyperphosphatemia), and they have not been reported to cause gastrointestinal perforations. In this light, there is no valid justification for allowing Renagel to remain on the market. It should be noted that the package insert for Renagel<sup>®</sup> lists the average daily dose of Renagel<sup>®</sup> employed in clinical trials as 6.5 grams per day. However, a safe maximum dose of Renagel<sup>®</sup> has never been defined and is not stated in the labeling. In the initial clinical studies which led to FDA approval of Renagel<sup>®</sup> the average serum phosphorus achieved with this dose of Renagel was typically in the range of 6.5 mg/dL [Table 3]. However, in 2003 the National Kidney Foundation published

Kidney Dialysis Outcome Quality Initiative (NKF-K DOQI) bone guidelines which mandated more rigorous control of serum phosphorus to less than 5.5 mg/dL. To achieve this lower goal for serum phosphorus clinicians now routinely prescribe doses of Renagel<sup>®</sup> substantially larger than the “average daily dose” employed in the early clinical studies. In the last two years, I have frequently consulted on dialysis patients treated with five to six 800 mg tablets of Renagel three times a day with meals (12 – 14 grams per day). To my knowledge, toxicology studies have not been conducted with the high-dose Renagel treatment which has become common practice in many dialysis clinics. It is entirely possible that the increasingly frequent serious gastrointestinal adverse effects in Renagel-treated patients since 2003 (see Table 1) may be a consequence of direct toxicity to the GI tract caused by high-dose Renagel. Postulated mechanisms of Renagel-induced bowel injury include mechanical obstruction due to swelling of the anion exchange resin when it contacts intestinal fluids (the sevelamer resin swells 6-8 fold its original volume following hydration). Diabetic dialysis patients with autonomic neuropathy and impaired GI motility may be at higher risk of bowel obstruction. If obstruction is not promptly alleviated, bowel perforation can occur. Chemical injury to the bowel wall leading to ischemia and perforation has been reported with other exchange resins such as sodium polystyrene [Kayexalate<sup>®</sup>]) and a similar mechanism of injury may be operative in Renagel-induced bowel perforation. In my opinion, given that intestinal perforation in a dialysis patient represents a life-threatening complication, drug approval for Renagel<sup>®</sup> should be immediately withdrawn until Genzyme has performed the requisite safety studies to define a safe “maximum dose” of Renagel<sup>®</sup> for use in dialysis patients.

If for some reason the Commissioner decides not to withdraw the approval of Renagel<sup>®</sup>, the FDA should require a “**black box warning**” about the risk of intestinal obstruction and perforation. This type of warning would hopefully result in increased vigilance by Nephrologists such that gastrointestinal complaints in Renagel-treated patients would be thoroughly evaluated and life-threatening complications possibly averted. It is my understanding that FDA regulations provide that the labeling of a prescription drug is required to include information about serious adverse reactions and potential safety hazards and that a black box warning can be required by FDA for special problems that can result in death or serious injury, as is clearly the case with Renagel<sup>®</sup>.

As a consequence of the number of injuries and deaths reported in the AERS database, FDA should, at an absolute minimum, require that the labeling of Renagel be revised promptly to warn physicians about an association with Renagel<sup>®</sup> use and occurrences of intestinal obstruction and perforation. In addition, FDA should also require that Genzyme send physicians a “Dear Dr.” letter to inform them of this important labeling change.

In conclusion, the evidence suggesting an alarmingly high incidence of gastrointestinal obstruction and perforation in Renagel-treated patients warrants the immediate removal of Renagel<sup>®</sup> from the market. If the Commissioner disagrees, FDA should require a black box warning about the risk of death and serious injury from Renagel-induced intestinal obstruction and perforation.

**C. ENVIRONMENTAL IMPACT**

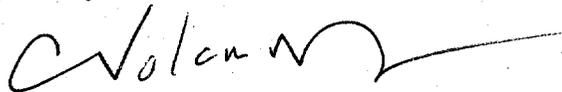
The requested relief does not require an environmental assessment or environmental impact statement under 21 C.F.R. § 25.31.

**D. ECONOMIC IMPACT**

If requested by the Commissioner, this information will be provided.

The undersigned certifies that, to the best of his knowledge and belief, this petition includes all information known to the petitioner that is unfavorable to the petition.

Sincerely,



Charles R. Nolan, M.D

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Attachments

**Table 1.** Number of unique subjects with gastrointestinal obstruction and perforation reported to the FDA adverse event database with Renagel<sup>®</sup> versus PhosLo<sup>®</sup> from July 1999 to September 2005.

Year	Renagel <sup>®</sup>		PhosLo <sup>®</sup>	
	GI Obstruction	GI Perforation	GI Obstruction	GI Perforation
3 <sup>rd</sup> Quarter 2005	2	5	0	0
1 <sup>st</sup> Half 2005	13	15	0	0
2 <sup>nd</sup> Half 2004	7	17	0	0
1 <sup>st</sup> Half 2004	24	26	0	0
2 <sup>nd</sup> Half 2003	25	13	0	0
1 <sup>st</sup> Half 2003	1	2	0	0
2002	1	1	0	0
2001	3	0	0	0
2000	4	0	0	0
2 <sup>nd</sup> Half 1999	0	0	0	0
<b>Total</b>	<b>80</b>	<b>79</b>	<b>0</b>	<b>0</b>

(Only the most severe event was counted for each patient; for example, if both obstruction and perforation were reported, the event was coded on the basis of the most severe adverse event. GI = gastrointestinal)

**Table 2.** Comparison of the reported number of adverse events in the FDA post-marketing adverse event database from January 2004 through September 2005 for Renagel<sup>®</sup>, Fosrenol<sup>®</sup>, and PhosLo<sup>®</sup>.

Phosphate Binder	# Adverse Events	# GI Obstruction	# GI Perforation
Renagel <sup>®</sup>	1633	65	68
Fosrenol <sup>®</sup>	354	3	0
PhosLo <sup>®</sup>	21	0	0

(GI = gastrointestinal)

**Table 3.** Achieved serum phosphorus in patients with ESRD on maintenance dialysis treated with Sevelamer hydrochloride (Renagel®)

Authors	Journal	Design	n	Length	Baseline Serum P	Treatment Serum P	Renagel Dose (gm/day)
Slatopolsky	KI 55: 299, 1999	Dose Titration	172	8 wk	9.1 ± 2.4	6.6 ± 1.9	5.4
Goldberg	NDT 13: 2303, 1998	Dose Titration	48	8 wk	8.1	6.5	4.1
Chertow	Clin Nephrol 51: 18, 1999	Dose Titration	71	12 wk	8.9 ± 2.6	6.7 ± 2.2	4.7 ± 2.5
Bleyer	AJKD 33: 694, 1999	Randomized	42	8 wk	8.4 ± 2.3	6.4 ± 1.7	4.9
Chertow	Clin Nephrol 51: 18, 1999	Dose Titration	71	12 wk	8.9 ± 2.6	6.7 ± 2.2	4.7 ± 2.5
Chertow	NDT 14: 2907, 1999	Dose Titration	192	46 wk	8.7 ± 2.0	6.4 ± 2.4	6.3
Chertow <sup>1</sup>	KI 62: 245, 2002 (TTG)	Randomized	100	52 wk	7.6 ± 1.8	5.1 ± 1.2	6.5 ± 2.9
Qunibi	KI 65: 1914, 2004	Randomized Double Blind	48	8 wk	7.7 ± 2.0	6.6 ± 1.7	6.9 ± 3.6
Brewster	Nephrology 11: 142, 2006	Cross Section	30	52 wk	NR	6.5 ± 1.2	7.8 ± 3.4
Block	KI 68: 1815, 2005	Randomized	53	18 mo	5.2 ± 1.6	5.2 ± 0.9	8.0

(In the Treat-to-Goal study<sup>1</sup>, adequate control of serum phosphorus was achieved using the same daily dose of Renagel that had failed to achieve adequate phosphorus control in other studies by the same investigators. This discrepancy is likely the result of patient selection bias whereby patients with baseline serum phosphorus exceeding 8 mg/dL were excluded from participation in the Treat-to-Goal study. P = phosphorous in units of mg/dL; n = number of subjects; KI = Kidney International; NDT = Nephrology Dialysis and Transplant; Clin Nephrol = Clinical Nephrology; AJKD = American Journal of Kidney Disease; TTG = Treat-to-Goal study)