CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-127

SUMMARY REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: October 2, 2007

FROM: Abraham Karkowsky, M.D., Ph.D., Acting Deputy Director, Division of Cardiovascular and Renal Products HFD-110

TO: Norman Stockbridge, M.D., Ph.D., Director, Division of Cardiovascular and Renal Products HFD-110

SUBJECT: Approvable recommendation for Renvela® (sevelamer carbonate).

This memo supports the approval of the carbonate salt of sevelamer (named Renvela®) for use as a phosphate binder. The salt should be indicated for the treatment of hyperphosphatemia in patients undergoing dialysis, similar to the indication of the chloride salt (Renagel®). This approval recommendation is almost entirely based on the *a priori* mechanistic considerations that in the acid environment of the stomach, the carbonate salt, once disintegrated, will completely be transformed to the chloride salt. It is clear that the in vitro performance of the two salts differ, particularly in an environment that significantly differs from the pH of the stomach.

Given this strong *a priori* supposition of rapid transformation of the carbonate to the chloride salt, only a minimal supportive data is necessary for approval. There is adequate supportive data derived from one clinical study that is sufficient to recommend approval of Renvela®. The data will be described below. I have to say that this development program was so poor, that it should not be referenced as a prototype for the development of other phosphate binders.

One of the pivotal assessments which support this approval is the speed of disintegration of the carbonate tablet. Currently the release specifications for Renvela® require disintegration at times not more than — minutes. The batches tested so far generally disintegrated within ——— at pH 1. The specifications should be tightened to disintegration at NMT than ——— In addition, the sponsor should assess the disintegration times at less acidic pH values (e.g., pH 4). This information can be supplied post approval. Should the sponsor not agree to tighter specifications for disintegration, I have no guarantee that the two salts will perform equivalently and would recommend a not approval letter be sent.

The labeling of the Renvela® (the carbonate salt) should, in general, mirror that of Renagel® (the chloride salt). The initial dose of the carbonate salt should be the same as that of the hydrochloride, although the label should indicate that further titration may be necessary. I saw no data that indicates a benefit of the carbonate relative to the hydrochloride salt.

Although a pediatric waiver was issued for Renvela®, renal failure does occur in children. A development program to address the need of this under supported population, with this or a related formulation should be submitted.

The following reviews were consulted in the construction of this memo:

- Joint medical/statistical review by Gail Moreschi, M.D., M.P. H. and Ququan Liu, M.D., M.S. Completed August 24, 2007.
- Clinical pharmacology and biopharmaceutics review by Robert O. Kumi, Ph.D. dated August 22, 2007
- Pharmacology and Toxicology review by Xavier Joseph, D.V.M. dated August 8, 2007
- Chemistry review by Donghao (Robert) Lu, Ph.D. dated August 27, 2007.
- Division of medication errors and technical support review by Linda M. Wisniewski, RN dated January 25, 2007.
- DDMAC consult by Lisa Hubbard, R.Ph, Regulatory Review Officer dated May 8, 2007

Housekeeping issues:

- DMETS considered the name Renvela® as acceptable from the medication errors perspective, although they suggested that the base-name of the new salt should be the same as that of the currently marketed chloride salt (Renagel®). The concern expressed by DMETS was that the Sevelamer requires electrolyte monitoring because of potential for metabolic acidosis. Since, however, a dialysis population is frequently monitored for their electrolyte status and there is no reason to diminish electrolyte follow-up with Renvela® the concern does not appear to be an impediment to the use of the proposed trade name.
- DDMAC has reviewed the PI for Renvela® and their comments will be incorporated in the PI.
- A pediatric deferral was granted on December 20, 2006. Since, however, renal failure requiring phosphate control does occur in a pediatric population, I see no reason that pediatric studies should not be requested.
- The financial disclosure statement appears acceptable.
- The establishment evaluation report was acceptable.
- The environmental assessment impact was considered as acceptable.

Chemistry:

From a chemistry perspective the original application of Renvela® is acceptable. The deficiencies that were noted by the chemist were related to the need of additional specifications of the product and clarification of the results from already performed studies.

Since the time of the chemist's review, the sponsor submitted additional information that according to Dr. Lu addresses these unresolved issues.

As noted above, the sponsor needs to tighten the disintegration specification. Since once the carbonate has disintegrated it would likely immediately become the chloride salt and the identical effects of the two salts would be expected. The disintegration of the carbonate salt should also be assessed at less acidic conditions (e.g., pH 4).

Pharmacology:

The only studies performed with sevelamer carbonate included *in vitro* phosphate binding studies, a 28-day mass balance and pharmacokinetic study in dogs with radio-labeled carbonate and 4-week oral toxicity studies in dogs and rats.

The phosphate binding studies were more fully described in the biopharmaceutic review and I will address these studies there.

The tracer-labeled studies in dogs that were dosed with labeled sevelamer carbonate on days 1 and 28 showed that 94% of the radioactivity was excreted in the feces within 24 hours. Only 0.04-0.07% of the label was excreted in the urine.

Four week toxicity studies in both rats and dogs showed no differences in toxicity comparing the two salt forms. There were decreases in fat-soluble vitamins (Vitamin E and D) in dogs for both salts. In summary, no additional concerns (or benefits) were observed in short term studies with the chloride or carbonate salts.

None of these results are surprising.

Biopharmaceutics:

The key portion in this submission is an assessment of the binding of phosphate to the two salts of sevelamer. Three types of studies were performed.

- Equilibrium studies that required a 24-hour pretreatment of Renvela® with 1 N HCl
- A binding study for which the incubation time for Renvela® was 4 hours without HCl and
- Kinetic studies of binding of Renvela® at two phosphate concentrations 2.5 and 38.7 mM phosphate.

With respect to the binding studies the data was modeled to a Lagmuir-type equation.

Equation 1

$$\frac{x}{m} = \frac{k_1 k_2 C_{eq}}{1 + k_1 C_{eq}}$$

Rearranging

Equation 2

$$\frac{C_{eq}}{x/m} = \frac{1}{k_1 k_2} + \frac{C_{eq}}{k_2}$$

Where:

Ceq= The amount of free phosphate remaining in the supernatant at the time of assay

x= The amount of phosphate bound to the resin (derived from total incubated –free)

m= The amount of resin

The constant k_1 is an affinity constant of the binding of phosphate (units are $mmol^{-1}$),

k_2 corresponds to the maximum capacity of binding at equilibrium (units are mmol phosphate/g resin

The values for k_1 and k_2 are derived a plot of equation 2.

The affinity for the two salts differed when they were not pre-incubated with HCl but were similar when they were pre-incubated with 1 N HCl. The capacity constants were not that dissimilar comparing the two salts either when or when not pre-incubated with HCl.

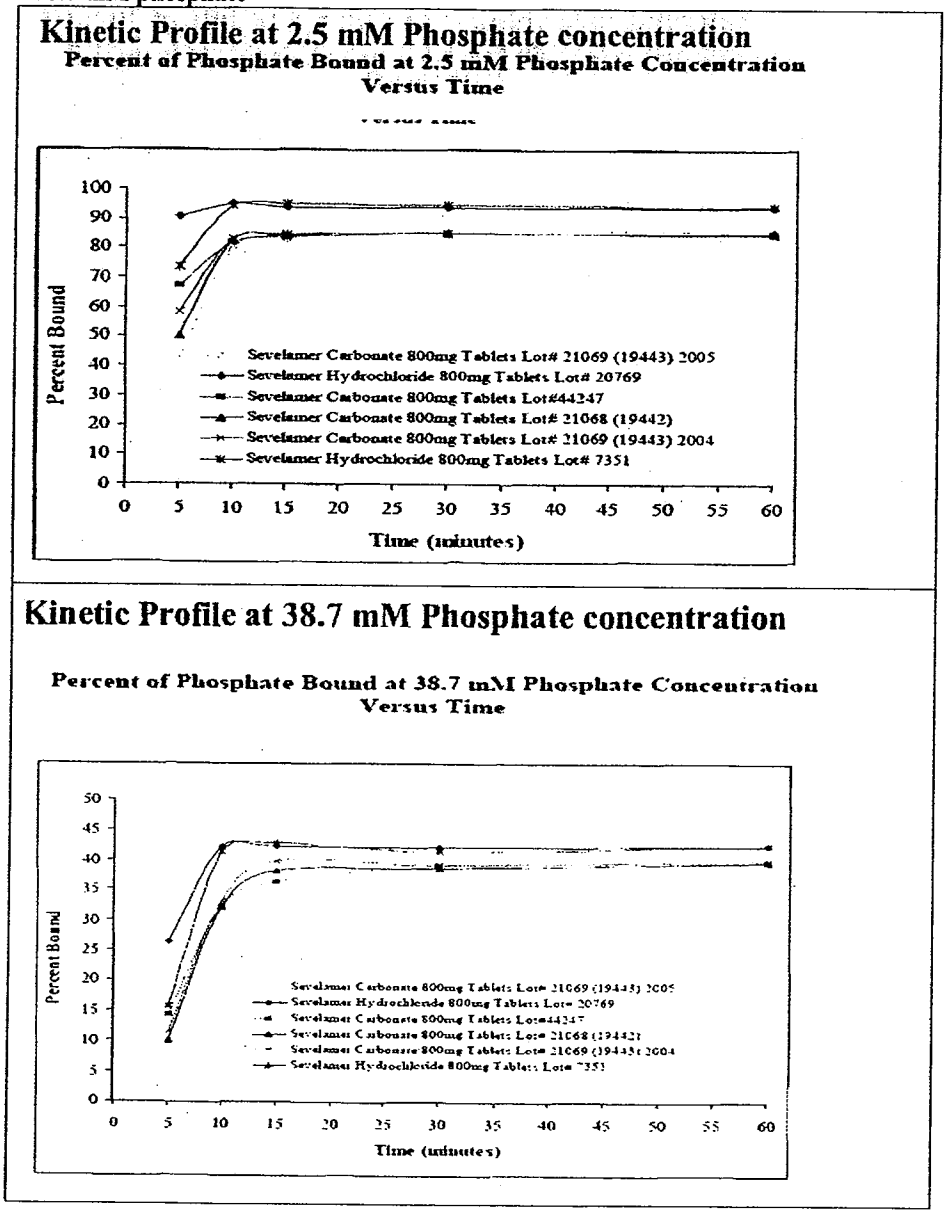
Table 1: In vitro binding constants for the chloride and carbonate salts of sevelamer with and without acid pretreatment

	No pre-incubation			Pre-incubated with HCl	
	Carbonate	Chloride		Carbonate	Chloride
# of batches	4	2		4	2
Affinity (k_1, $mmol^{-1}$)	0.36 + 0.05	0.85 + 0.04		0.61 + 0.09	0.71 + 0.11
Capacity (k_2, mmol phosphate/g resin)	6.24 + 0.35	6.04 + 0.27		6.77 + 0.40	6.47 + 0.33

With respect to the kinetic characteristics of the binding comparing the carbonate to chloride salt, there were substantial differences early on that converged within 10-15 minutes after the start of the incubation. Although, in addition, there are clear but small differences in total amount of phosphate bound (capacity) comparing the carbonate to chloride salt, the difference is less than 10%.

The kinetic profiles at two different phosphate concentrations are shown below.

Figure 1: Time course of two batches of hydrochloride and four batches of carbonate at 2.5 and 38.7 mM phosphate



In summary, the binding affinity and binding capacity of the two different salts of sevelamer differ. The assertion of that the salts are interchangeable, therefore, rests on the assumption that once exposed to HCl in the gut, with rapid disintegration, the two salts act equivalently. In the absence of rapid disintegration there is insufficient information to assert reasonable phosphate binder behavior of the carbonate salt of sevelamer.

Clinical:

Only a single clinical study was submitted. This study as a randomized cross-over study in which 79 subjects requiring dialysis were randomized in a 1:1 ratio to one of two

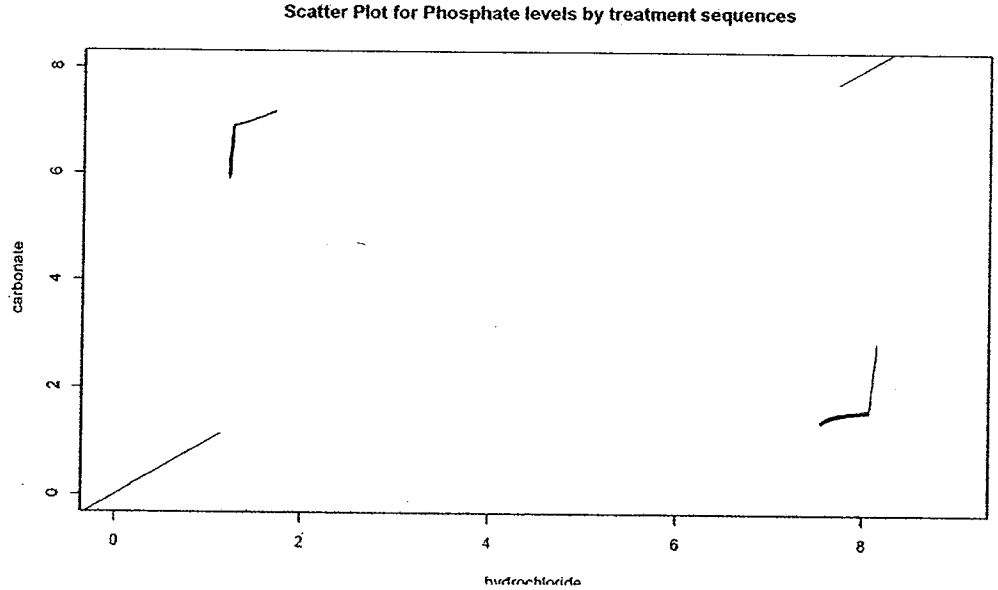
treatment sequences. The two sequences differed as to which salt (carbonate or hydrochloride) was administered first with the second salt following. Each of the treatment sequences lasted eight weeks. Prior to entering the study, each subject was on 5 weeks of stable sevelamer hydrochloride doses. After the study was initiated, at the request of this Division, a subgroup (not pre-specified at the time of randomization) were randomly withdrawn from treatment. The daily dose of either phosphate binder is shown below.

Table 2: Doses used during cross-over study

	Total daily dose		
	≤ 4.8	>4.8 to <9.9	≥ 9.6
N	22	14	20

There did not appear to a difference between the effects of the two salts on mean phosphate levels. The mean $\pm$ SD for the carbonate treated patients was 4.8 ± 0.9 and for the hydrochloride-treated subjects was. 4.8 ± 0.9. However, there was considerable variability in the effect of the two treatments. Given the large variability it is difficult to assert that the two formulations are bioequivalent (plot supplied by Dr. Q Liu).

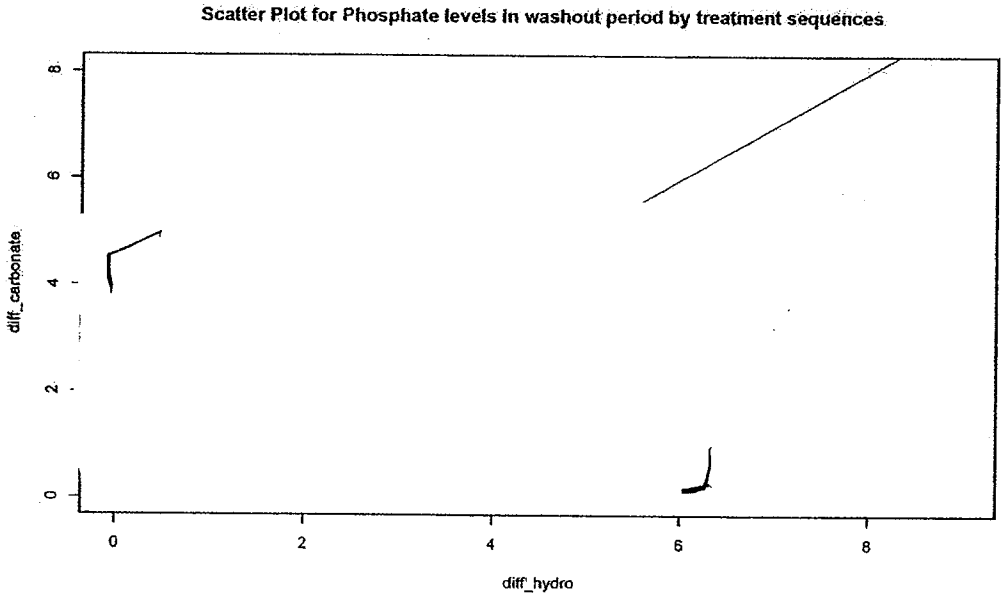
Figure 2: Scatter plat of phosphate levels on the hydrochloride salt (X-axis) and the carbonate salt (Y-axis).



With respect to the magnitude of effect, the plot below consists of a scatter plot comparing the effect in the cohort of patients who had phosphate levels at the end of the two-week withdrawal with their response at the end of the cross-over period. The key effect that I was looking for was whether the population that was enrolled actually had some effect on phosphate binders. The scatter plot indicates that some subjects did not really respond to either phosphate binder with some subjects having a robust response. Consequently, the data

do support that the phosphate binders both alter phosphate levels. It is, however, impossible to assert that the formulations are bioequivalent (plot supplied by Dr. Q Liu)..

Figure 3: Scatter plot comparing the difference of phosphate levels at withdrawal compared to the end of treatment for the hydrochloride salt (X-axis) and carbonate salt (Y-axis).



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/s/

Abraham Karkowsky
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