CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-318

SUMMARY REVIEW

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 22-318 (Renvela powder; sevelamer carbonate for hyperphosphatemia)

Sponsor: Genzyme

Review date: 10 January 2009

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 22-318
HFD-110/Project Manager

This memo conveys the Division's recommendation to issue a Complete Response letter for this formulation of sevelamer carbonate, pending development of a marketable 800-mg dose or of instructions for use adequate to get reliable 800 mg from the existing formulation.

Sevelamer hydrochloride tablets (Renagel) and sevelamer carbonate tablets (Renvela) have previously been approved.

This NDA was submitted 31 March 2008 and the PDUFA goal date is 31 January 2009. The NDA has primary reviews by Drs. Lu (CMC; 17 Decmber 2008), Younis (clinical pharmacology; 10 December 2008) and Moreschi and Liu (medical and statistical; 1 December 2008[1]). There are no pharmacology, toxicology, or carcinogenicity reviews. I concur with issues raised in Dr. Karkowsky's CDTL memo (7 January 2009). There are three studies of some interest:

The sponsor did a drug-drug interaction study with warfarin. This study was considered adequate, and I concur with incorporating its description into labeling.

Study 205 took dialysis patients, titrated them to an individualized TID dose of sevelamer hydrochloride, and then randomized them to 6-week crossover periods with TID dosing with either the hydrochloride salt or the same dose (800 mg units) of carbonate powder. One-third of subjects had phosphate levels differing by >1 mg/dL between the two periods, usually lower on powder. Dr. Karkowsky interprets this study as providing evidence for the need to titrate, probably in 800-mg steps, and I concur.

Study 301 took dialysis patients, hyperphosphatemic after washout, and randomized them to titrated dosing with sevelamer hydrochloride tablets given TID or sevelamer carbonate powder given once daily at the largest meal. This study used only the 2400-mg carbonate packets that the sponsor proposes to market. Subjects were followed for 24 weeks. Withdrawals were higher with the once-daily carbonate regimen (35% vs. 15%), usually for tolerability problems, and phosphate control was less good (mean changes from baseline were -2.0 and -2.9 mg/dL, with an upper 95% confidence limit for the difference of 1.5 mg/dL[2]). The review team concludes that [redacted] is not supported, and I concur. b(4) b(4)

The sponsor proposed to [redacted] 2400-mg packets, whereas the currently marketed forms are 800-mg tablets. The sponsor provides no means for accurately

[1] *Medical review. Identical statistical review was filed 11 December 2008.*

[2] *Exceeding the sponsor's NI margin of 1.0 mg/dL.*

obtaining 800 mg from a 2400-mg packet. The sponsor provides no argument why patients are not equally well served by the larger unit dosing. However, I note that patients generally are not well controlled on phosphate binders; the KDOQI guidelines do not even aspire to bring patients into the normal range. Thus, were the powder so well tolerated that it did better at controlling serum phosphate levels, having only the larger unit dose might make sense, at least for adults. However, that does not appear to be the case.

The powder formulation should be better for children. The sponsor has not conducted studies in a pediatric population. Such a study should be conducted post-marketing. The details for that study should be part of the sponsor's response to our CR letter.

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/s/

Norman Stockbridge
1/12/2009 10:52:36 AM
MEDICAL OFFICER

MEMORANDUM

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

DATE: January 7, 2009

FROM: Abraham Karkowsky, M.D., Ph.D. Group Leader, Division of Cardiovascular and Renal Products, HFD-110.

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

SUBJECT: Complete Response for NDA 22, 318 (Renvela® Sevelamer Carbonate for oral suspension; Genzyme Corporation)

With this memo I am outlining my rationale to not approve the powder formulation (for suspension) of sevelamer. A complete response letter with the deficiencies should be sent to the sponsor. Although it is more than likely that the powder form for suspension of sevelamer carbonate is a reliable phosphate binder, the single dose strength available (2.4 grams) would not allow sufficient flexibility in dosing. Instructions for dose alterations would, therefore, not be possible. There doesn't seem to be a way to accurately administer a dose change of less than the 2.4 g contained in a packet, whereas for the tablet formulations dose gradations of 800 mg are available. There is insufficient information from a comparison study off the powder to the hydrochloride tablet to define the two formulations as equivalent. A substitution recommendation for tablet and powder formulations should not be entertained.

The results of study #GD3-199-301 (in this review #301), suggest that larger asymmetrically distributed doses of sevelamer carbonate powder, increases adverse events and discontinuations while having less effects on serum phosphate than a TID regimen. The once a day regimen should not be approved.

Should the sponsor consider marketing a packet of 800 mg as was used in the clinical trial SVCARB00205 (in this review #205), the powder for suspension formulation could be approved. The sponsor also has several other paths available that would allow for appropriate dose titration instructions for the new formulation. If a dry powder formulation with a scoop for accurate measurement of sevelamer would be made available, or if the sponsor could generate data that shows that an administering an aliquot of a recently stirred slurry of powder results in an accurate dose, accurate dosing instructions could be constructed. Under any of these scenarios, there would then be adequate flexibility in doses and a rationale set of dosing instructions could be constructed and this formulation would be approvable.

Parenthetically, this powder formulation of sevelamer would be used to study phosphate control in a pediatric population. [redacted] b(4)

[redacted] Again, the current formulation of 2.4 grams would require some way to allow for accurate and finer dosing adjustments for the pediatric study.

The sponsor appears to integrate the formulation for oral suspension to the already marketed package insert of sevelamer carbonate tablets. Given the different dosing regimens that would be necessary for this application, the use of a common package insert could create problems. Again, should a smaller packet size be available, pooling of labels would be acceptable.

There are still outstanding issues that constrain approval. These issues should be resolved shortly and consist of the evaluation of the environmental assessment as well as a completed EER.

No DSI consults were requested.

DMETS's reviewed the label of sevelamer their comments are appended to the end of this review. In general, I agree with their concerns.

The following reviews or memos were consulted in writing this memo.

- Chemistry review by Donghao (Robert) Lu, Ph.D., dated December 17, 2008.
- Clinical pharmacology review by Islam R. Younis, Ph.D., dated December 10, 2008.
- Joint medical and statistical review by Gail Moreschi, M.D., M.P.H, (medical) and Ququan Liu, M.D., M.S. (statistics) dated December 1, 2008.
- Review by Lori Cantin, R.Ph., Safety evaluator, Division of Medication Error Prevention and Analysis dated December 31, 2001.

Sevelamer is a cross-linked polymer of poly-allyl amine with the cross-linkages derived from [redacted] The polymer was originally approved as the chloride salt (Renagel®) and subsequently as the carbonate salt (Renvela®). The current application contains the same active ingredient as both Renagel® and Renvela® as well as the same counter-ion as for Renvela®, but the new formulation is a powder that is administered as a suspension in a small amount of water. Both Renagel® and Renvela® are available as 800 mg tablets. The proposed formulation [redacted] 2.4 gram packet to be mixed in two ounces of water and ingested completely. The current formulation also contains [redacted] b(4) b(4)

Biopharmaceutics:

The sponsor submits a study on the pharmacokinetic interaction of sevelamer powder with warfarin. The study was a cross-over study in 18 subjects who received single doses of warfarin (2 x 10 mg tablets) with and without single doses of sevelamer carbonate

powder (4 x 2.4 gram packets). There appears to be no clinically meaningful interaction between sevelamer and warfarin.

In addition, the sponsor submits an assessment of the binding of phosphate to sevelamer as both the chloride and carbonate salts. The carbonate was studied both as a tablet and powder. Three types of studies were performed.

- Equilibrium studies in which sevelamer was pretreated for 24 hours with 1 N HCl
- Equilibrium studies in which sevelamer was pretreated for 4 hours without HCl pretreatment and
- Kinetic studies of binding of Renvela® at two phosphate concentrations 2.5 and 38.7 mM phosphate.

With respect to the equilibrium 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)

There were four formulations that were studied

- Sevelamer hydrochloride tablets (800 mg)
- Sevelamer carbonate tablets (800 mg)
- Sevelamer carbonate packets (800 mg)
- Sevelamer carbonate packets (2.4 g).

There were differences in the affinity constant both with and without pretreatment with 1 N HCl when comparing the sevelamer hydrochloride salt to that of the carbonate either as tablets or as packets. The binding constant for the three formulations were

similar. Despite the fact that these incubation conditions do not reflect the in vivo milieu and the results are therefore, not surrogates for the in vivo effect, clearly reflect differences between the chloride and the carbonate salts.

Table 1: Constants for sevelamer as various salts and formulations with and without acid pretreatment

	Without acid pretreatment				With acid pretreatment			
Sevelamer salt→ Parameter↓	HCl	Carbonate tablets	Carbonate powder 0.8 g	Carbonate powder 2.4 g	HCl	Carbonate tablets	Carbonate powder 0.8 g	Carbonate powder 2.4 g
Affinity constant k_1 ($mmol^{-1}$)	0.85	0.26	0.33	0.33	0.63	0.74	0.49	0.85
Binding constant k_2 (mmol phosphate/g resin)	6.2	6.8	6.4	6.2	6.7	6.5	7.3	6.7

There were also differences in comparing the time-course of binding (kinetic study) at different concentrations of phosphate 2.5 and 38.7 mM (data taken from Dr. Younis's review; for black and white representations of these curves, the curve connecting the lowest squares is the sevelamer carbonate tablets). The carbonate powder actually is closer to the binding kinetics of the chloride formulation than is the carbonate tablet. The binding capacity of the hydrochloride tablets is actually greater than any of the other formulations, particularly evident at the lower phosphate concentration at the longer time points. The curves tend to converge at about 10-15 minutes.

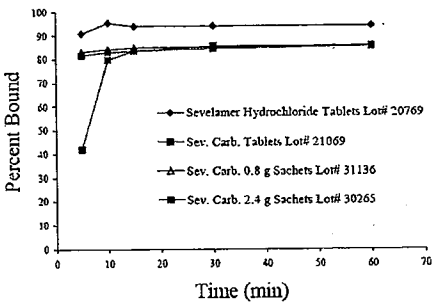


Figure 1. Phosphate biding profile at 2.5 mM.

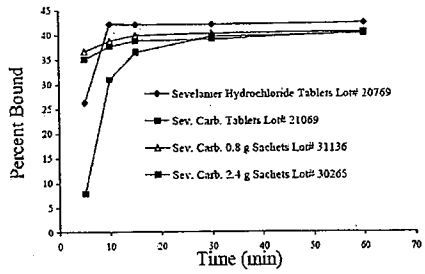


Figure 2. Phosphate biding profile at 38.7 mM.

Considering these non-physiologic binding and kinetic studies, there are differences between the formulation in their ability to bind phosphate.

Medical/Statistical:

There were two studies submitted in support of the powder. One study (#301) compared a once daily regimen to the standard regimen utilizing the hydrochloride salt. The second study (#205) was a crossover study comparing sevelamer hydrochloride tablets to the carbonate salt of sevelamer as a powder.

Study GD3-199-301 (# 301) consisted of a screening phase, a 2 week washout phase, and a 24 week randomized phase. Subjects were to have had phosphorus (phosphate levels) of between 3 and 6.5 mg/dL (inclusive), and an iPTH measurement $\leq$

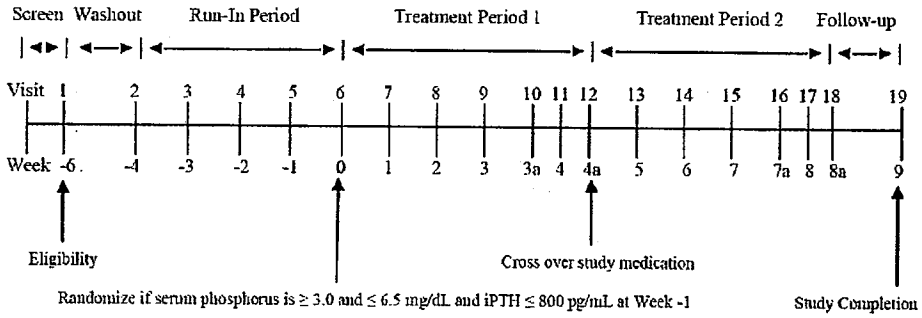
800 ng/L prior to the washout phase and have serum phosphorus levels of > 5.5 after the washout period. Subjects were randomized in a 2:1 ratio to the carbonate powder formulation QD : the hydrochloride tablet divided TID. For the QD dosing, the dose was administered with the largest daily meal, for the TID dosing, the drug was divided equally and administered with each meal. There were 217 patients enrolled, 144 were allocated to the once daily dose and 73 to the TID hydrochloride salt. Although the sponsor specified that the primary endpoint is non-inferiority to serum phosphate levels[1], the true metric of importance is change in phosphate levels from washout. This timing of this measurement with respect to dose was not specified and therefore, the magnitude of the effect at the interdosing interval is probably substantially less than the measured effect.

Both regimens started treatment at a dose of 4.8 g/day either as a single dose or divided TID. At the end of the study, the total daily dose for the safety set was 6.2 ± 2.6 g/day of sevelamer carbonate powder QD and 6.7 ± 3.0 g/day of sevelamer hydrochloride tablets TID.

The result listed in the table below show that disposition of patients as well as the effects on phosphate and the calcium-phosphate product. Not only were the effects on serum phosphorus and calcium-phosphate product less in the QD dosing group but the numbers of subjects who discontinued treatment during the 24 week observation period was substantially greater for the once daily regimen. The most frequent reason for discontinuation among those who were allocated to the QD dosing regimen were related to the administration of study drug: gagging or bad taste, N= 5; nausea, N= 4; vomiting, worsening hyperphosphatemia, bloatedness, renal transplantation, cerebrovascular accident, rectal bleeding and S. aureua central line infection; each N=1.

[1] The primary metric was time average serum concentration. This value is the sum of the mid-interval phosphate levels multiplied by the duration of that interval. Each of these values normalized for the duration of the interval are summed for the entire study with the average value during the study determined.

Figure 1: Study SVCARB00205 phases.



Those eligible for enrollment were > 18 years old who were taking, as monotherapy, sevelamer hydrochloride as their phosphate binder and had two consecutive laboratory values of their serum phosphorous between 3 and 7 mg/dl, inclusive and had an iPTH of ≤ 900 pg/mL. Eligible subjects were also required to have serum phosphorus after washout of > 5.5 mg/dL as well as serum phosphorus between 3.5 and 6,5 mg/dL at time of randomization. They were excluded form participation if they had confounding medical conditions.

The sponsor specified as the primary endpoint was the control of phosphate levels in the per protocol population. The most appropriate endpoint, however, is the equivalence of drug effect. That is the effect that the phosphate-binder has on decreasing phosphate levels. In this study the best estimate of pre-drug effect is the phosphate levels at week -4. It should be noted that this measurement, because of "regression to the mean" effect, probably overstates the phosphate levels after washout and consequently overstates the phosphate-binding capacity of the two binders.

I have not included the sponsor's analysis to define equivalence, since the metric used is irrelevant. The distribution of paired valued comparing change from washout while on powder to change from washout is shown below. There were sufficient differences between the treatments that would make titration in a reasonable number of individuals likely.

Table 3: Distribution of difference in phosphate levels powder minus tablet

	< -2	-2 to <-1	-1 to +1	>1 to 2	>2
number	2	4	18	2	1

Since there is an inability to titrate these subjects with the finer doses of the powder, use of this formulation creates problems.

DMETS comments:

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 [redacted] 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 '[redacted] for Oral Suspension' which is inconsistent with the USP definition of this type of pharmaceutical dosage form which is 'for Oral Suspension'. b(4)

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 [redacted] 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. b(4)

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 [redacted] 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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/s/

Abraham Karkowsky
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