CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020926

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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Clinical Pharmacology and Biopharmaceutics Review

NDA:	**20-926**
Sevelamer HCl Capsules (RenaGel®)	
Submission Date:	**3 November 1997** **19 December 1997**
Sponsor:	**GelTex Pharmaceuticals**
Type of Submission:	**New Drug Application**
Reviewer:	**Michael J. Fossler**

Synopsis

Sevelamer HCl (RenaGel®) is a hydrophilic, but insoluble polymer proposed for the treatment of hyperphosphatemia in patients with end-stage renal failure. The drug acts locally in the GI tract to bind dietary phosphate, where it is then excreted in the feces. Renagel® will be marketed as 403 mg capsules. The initial starting dose is 2-4 capsules with each meal, depending upon the severity of the hyperphosphatemia being experienced by the patient. The dose is then adjusted, based on serum phosphate levels, with the goal of therapy being a serum phosphate of ≤ 6.0 mg/dl.

A single radiolabeled mass-balance study was performed to show that sevelamer was not absorbed to any significant extent. In 20 normal volunteers, no significant radioactivity was detected in the urine or blood at any time during the study. About 99% of the administered dose of radioactivity was recovered in the feces, Since the purpose of the compound is to bind dietary phosphate, the compound should be given with meals. No food effect studies were performed.

No drug interaction studies were performed. Since the compound is an insoluble binding compound, the possibility exists that sevelamer might reduce the bioavailability of other concomitantly-administered drugs. In the clinical trials, patients were instructed to take other medications 2 hours before or 4 hours after ingesting sevelamer. The firm will be asked to commit to performing drug interaction studies with drugs typically taken by ESRD patients, with particular emphasis paid to those drugs which are used in the treatment of diabetes and hypertension, and those drugs labeled to be taken with food.

Since the compound is insoluble both in water and organic solvents, there is no proposed dissolution method. Rather, the firm proposes the use of the disintegration test and an *in vitro* phosphate binding assay for quality control purposes. The disintegration specification is

Recommendations

The clinical pharmacology and biopharmaceutics portion of NDA 20-926 is approved, provided that the firm make the indicated labeling changes. The proposed disintegration and in vitro PO_4 binding specifications are acceptable. Please send the **Labeling Comments** and **Comments to the Firm** to the Sponsor.

Table of Contents

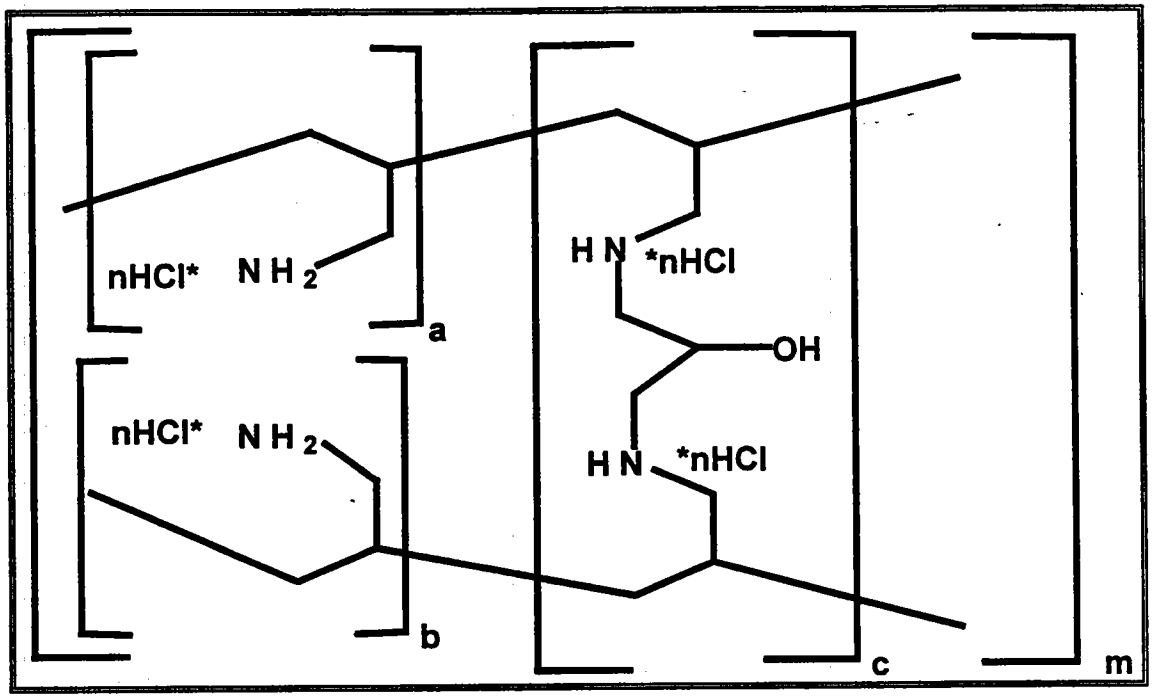
I. Background

GelTex Pharmaceuticals has submitted NDA 20-926 in support of RenaGel® (sevelamer HCl) capsules. The proposed indication is for the control of hyperphosphatemia in patients with end-stage renal failure. The drug works locally in the GI tract to bind phoshates found in food.

RenaGel will be marketed as 403 mg capsules. The initial starting dose is 2-4 capsules with each meal, depending on the severity of the hyperphosphatemia. The dose is then adjusted based on serum phospahe levels, with the target serum phosphate being ≤ 6.0 mg/dL.

Sevelamer $((C_3H7 \bullet nHCl)_{812}(C_9H_{18}N_2O \bullet nHCl)_{94z}$ (where z= a large number) is poly(allyamine HCl) crosslinked with epichlorohydrin to form a hydrophilic polymer. It is insoluble in water and organic solvents. The structure is depicted in Figure 1.

Figure 1: Structure of sevelamer HCl. a,b = 9 = number of primary amines, c = 1 = number of crosslinks, n = 0.4 = fraction of protonated amines, and m= a large number to indicate an extended polymer



III. Bioavailability and Bioequivalence

Absolute and Relative Bioavailability

The ^{14}C metabolism study (see **IV. Metabolism, below**) showed that the polymer is not absorbed to any detectable extent.

Effect of Food

Since the compound is not absorbed, no food effect studies were performed. Since the purpose of the compound is to bind dietary phosphate, RenaGel® should be given with meals.

IV. Metabolism

In vitro

No studies were performed

In vivo

A ^{14}C-metabolism study was performed to confirm that sevelamer is not systemically absorbed. Twenty male (5 age 19-40, 5 age >65) and female (5 age 19-40, 5 age >65) volunteers were dosed with 2.3 g sevelamer TID with meals for 28 days prior to the study. On the day of the study, each subject was dosed with labeled sevelamer (2.3g, 100 mCi) after a 10 hour fast. Unlabeled drug was given at lunch and dinner. Plasma, urine, and feces were collected up to 96 hours post-dose. All samples were analyzed for radioactivity by liquid scintillation spectrometry after oxidation.

The results are shown in Table 2. No radioactivity above background was detected in the plasma of any subject at any time during the study. On two occasions (in two subjects), trace amounts of radioactivity were detected in urine, but as they were each less than 0.1% of the dose, they are mostly likely the result of contamination.

Table 2: Results of Study WGTC-10-801a. Values in the table are listed as % of administered dose, unless otherwise noted

Analyte	Mean±SD (range)
Whole Blood ‡	0.0±0.0 (na)
Urine	0.01%±0.01% (0.0% - 0.02%)
Feces	99.4%±7.1% (81.5% - 112%)

‡ng drug per g of blood

V. Pharmacokinetics

No pharmacokinetics information is available for sevelamer.

VI. Special Populations

Gender, Age

In the metabolism study, no differences were seen between young and elderly men and women in the elimination of sevelamer.

VII. Drug Interactions

In vitro

No studies were performed.

In vivo

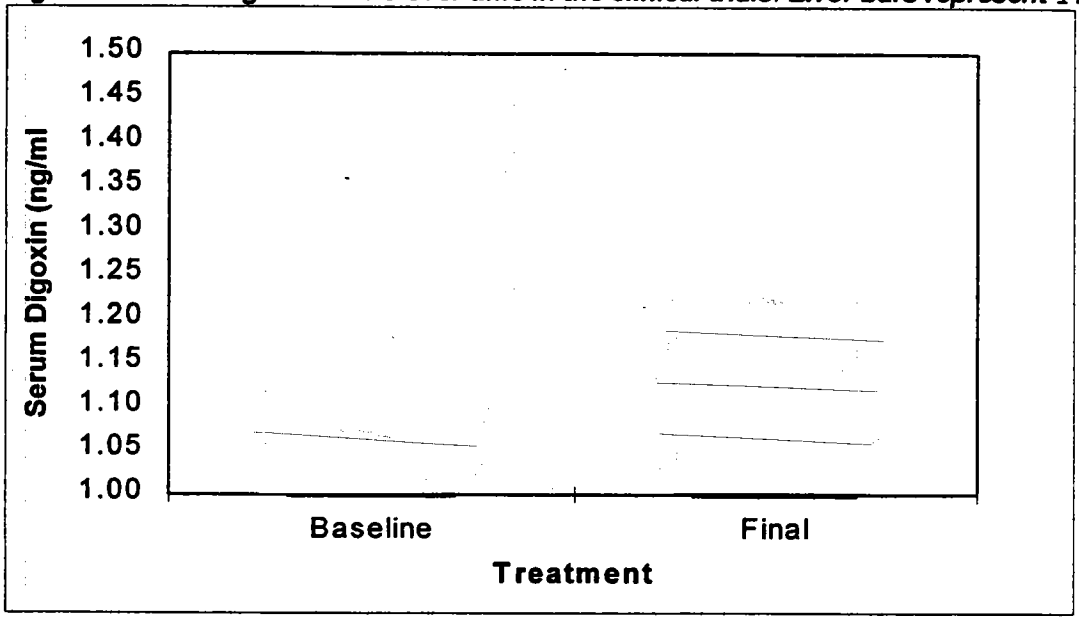
No studies were performed in humans. Some single-dose studies in beagles were performed, but these, aside from the fact that they were performed in a different species, were not adequately designed, as they only used a single dose of both Renagel and the interacting compounds.

Since the compound is not absorbed, the only conceivable mechanism by which sevelamer could interact with concomitantly-administered compounds is by interfering with their absorption (i.e., by

binding). This appears to be a likely mechanism, similar to what is seen with cholestyramine and colestipol, which are also hydrophilic, non-absorbable polymers.

In the pivotal clinical trials, patients taking either digoxin or warfarin were monitored closely. Digoxin was monitored by serial plasma samples over time, and warfarin was monitored by measuring serial prothrombin times. The results are depicted in Figures 2 (digoxin) and 3 (warfarin). Although it appears that sevelamer has no effect on the absorption of either compound, these data are misleading in that these patients were instructed to take these medications 2 hours before or 4 hours after RenaGel administration[1]. Thus, these data do not show a lack of interaction, but they suggest that dosing other medications 2 hours before or 4 hours after RenaGel may be sufficient to prevent a decrease in absorption. Further study of the drug-adsorbing properties of RenaGel will be recommended.

Figure 2: Serum digoxin levels over time in the clinical trials. Error bars represent ±1 SEM.



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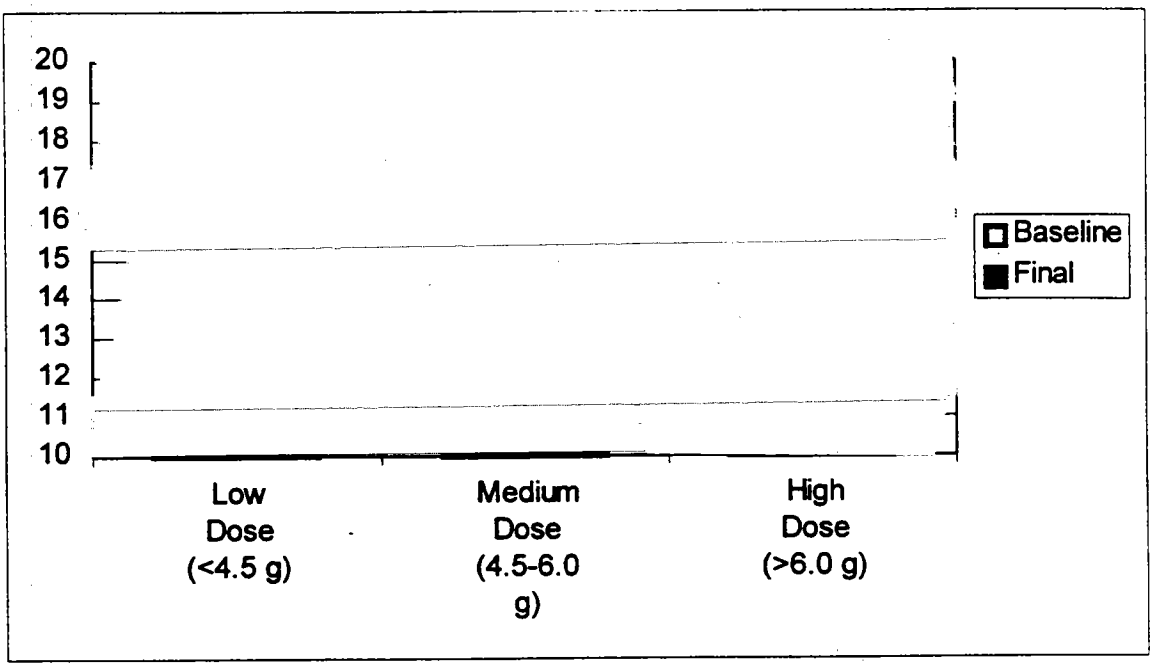
[1] **The firm was sufficiently concerned about the possibility of a binding interaction between sevelamer and other drugs that it wrote these dosing recommendations into the protocols.**

Figure 3: Baseline and final prothrombin times in patients on anticoagulation therapy in the RenaGel trials.



VIII. Pharmacokinetic/Pharmacodynamic Relationships

Not applicable.

IX. Dosage and Administration

In the package insert, the recommended dose of Renagel is 2-4 capsules with meals, with the dose being adjusted until the serum phosphorus is ≤ 6.0 mg/dL. The average number of capsules used in the clinical trials was 3-4 capsules per meal.

X. Formulation

The to-be-marketed formulation is listed in Table 3.

Table 3: Market Formulation.

Ingredient	Amount per capsule
Sevelamer HCl	
Stearic Acid	
Colloidal Silicon Dioxide	

XI. Reviewer Comments

1. The firm has not performed any drug interaction studies in humans for this application. Although some animal studies were performed, these are not sufficient for labeling purposes. The *post hoc* analyses of digoxin and warfarin can not be used as evidence of a lack of drug interaction, since the patients were instructed to take these medications 2 hours before or 4 hours after RenaGel administration. The firm will be asked to commit to performing drug interaction studies with drugs typically taken by ESRD patients, with particular emphasis paid to those drugs which are used in the treatment of diabetes and hypertension, and those drugs labeled to be taken with food.

N.B: At the briefing held on 9/28/98, it was decided that *in vitro* drug interaction studies might provide more useful information on the drug-binding capabilities of sevelamer. The interim guidance titled *Cholestyramine Powder In Vitro Bioequivalence* was suggested as a basis for designing the *in vitro* studies. Equilibrium and kinetic binding studies should be carried out at pH 1, 4, and 7. Concentrations of interacting drug and sevelamer used should be as close as possible to what might be observed clinically. The experimental plan should be reviewed by the Agency prior to initiation of these studies. If no interactions exist *in vitro*, then it may be assumed that no interactions will be seen clinically. If significant *in vitro* binding of drug is seen, then *in vivo* studies will be needed to confirm the interaction. The above was conveyed verbally by the reviewer to Lisa D'Attanasio (GelTex Pharmaceuticals) in a telephone conversation on 9/29/98.

XII. Comments to firm

None at this time.

XIII. Labeling Comments

Drug Interactions: No studies were performed. Because of the possibility that sevelamer may bind concomitantly-administered drugs and decrease their bioavailability, other medications should not be ingested within 2 hours before or 4 hours after Renagel administration. Patients should be closely monitored for reduced clinical efficacy of the concomitantly-administered agent.

XIV. Signatures

/S/ 9/29/98

Michael J. Fossler, Pharm.D., Ph.D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

/S/ 10/1/98

FT initialed by Hae-Young Ahn, Ph.D., Team Leader

version: Final

Briefing held 9/28/98. Present: Lesko, Ahn, Hunt, Reynolds, Madani, Hylton, Mehta, Kim, Strong, Fossler

CC: NDA 20-926 (orig., 1 copy), HFD-510(Schneider, Hedin), HFD-850(Lesko), HFD-870(M. Chen, Fossler, Ahn), HFD-340(Vish), Central Document Room (Barbara Murphy)

2/27/98

Recommendation Code: AP

Study Summary

Study GTC-10-801: Absorption of ^{14}C-Renagel in Healthy Young and Old Male and Female Volunteers

Sponsor: GelTex Pharmaceuticals

Study Site:

Objective: To assess the absorption of Renagel in healthy young and old male and female volunteers

Study Design: Open Label, Parallel design in 20 male and female volunteers. Starting on Day -28 and continuing through day -1, each subject received 5 x 465 mg Renagel capsules with each meal for a total of 6.975 g daily.

On Day 0 of the study, the subjects received a single 2.325 g capsule of 14C-labeled sevelamer. The subjects then received non-labeled doses of sevelamer at lunch and dinner on day 0, and continuing TID with meals until 4 days post-labeled dose.

Blood samples were drawn at 0, 4, 8, 12, 24, 48, 72, and 96 hours post-labeled dose.

Urine and feces were collected at 0 (pre-dose) 0-24, 24-48, 48-72, and 72-96 hours post-labeled dose.

Results:

Analyte	Mean±SD (range)
Whole Blood ‡	0.0±0.0 (na)
Urine	0.01%±0.01% (0.0% - 0.02%)
Feces	99.4%±7.1% (81.5% - 112%)

Conclusions:

1) > 99% of the administered dose was recovered in the feces of each subject
2) No detectable radioactivity found in the blood or urine of any subject

Reviewer Comments

In general, the study is well-designed. There is a question of the variability of the assay, making it at least theoretically possible that some of the compound might be absorbed, although it is impossible to say for certain how much. The clinical significance of this is unknown.

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