# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

**Application Number: 020926**

**Trade Name: RENAGEL CAPSULES 403 MG**

**Generic Name: SEVELAMER HYDROCHLORIDE**

**Sponsor: GELTEX PHARMACEUTICALS, INC**

**Approval Date: 10/30/98**

**Indication(s): THE REDUCTION OF SERUM PHOSPHOROUS PATIENTS WITH ENDSTAGE RENAL DISEASE WHO ARE ON DIALYSIS**

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION: 020926

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| Final Printed Labeling | X | | | |
| Medical Review(s) | X | | | |
| Chemistry Review(s) | X | | | |
| EA/FONSI | X | | | |
| Pharmacology Review(s) | X | | | |
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| Microbiology Review(s) | | | | X |
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| Bioequivalence Review(s) | | | | X |
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# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number: 020926**

## APPROVAL LETTER

October 30, 1998

NDA 20-926

GelTex Pharmaceuticals, Inc.
Attention: Ms. Martha Carter
Vice President, Regulatory Affairs
Nine Fourth Avenue
Waltham, MA 02451

Dear Ms. Carter:

Please refer to your new drug application (NDA) dated November 3, 1997, received November 3, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Renagel (sevelamer hydrochloride) Capsules, 403 mg.

We acknowledge receipt of your submissions dated December 10 and 19, 1997; and January 21, February 13, March 13, July 16, August 4, September 2 and 30, and October 1(9), 5(2), 8(2), 9(2), 20, and 30, 1998. The user fee goal date for this application is November 3, 1998.

This new drug application provides for the use of Renagel (sevelamer hydrochloride) Capsules for the reduction of serum phosphorus in patients with end stage renal disease who are on hemodialysis.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted October 30, 1998, immediate container and carton labels submitted October 9, 1998). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-926." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitment made in your October 8, 1998, submission in which Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of the commitment in your

annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments should be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301)827-6392.

Sincerely,

/S/

Florence Houn, M.D., M.P.H.
Deputy Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 020926

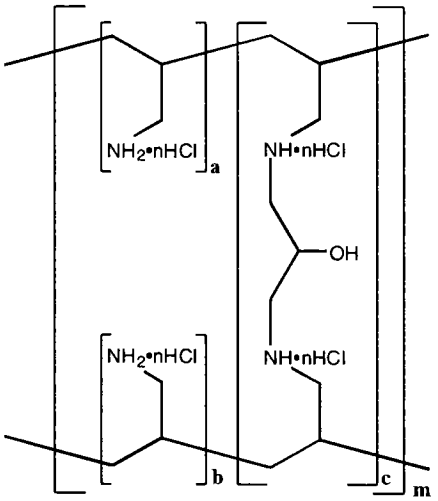
## FINAL PRINTED LABELING

## 2.1 PACKAGE INSERT

**(LOGO) Renagel® Capsules**
**(sevelamer hydrochloride) 403 mg**

**Renagel® Capsules**
**(sevelamer hydrochloride)**
**[se vel′ a mer]**
**DESCRIPTION**

Renagel* Capsules contain sevelamer hydrochloride, a polymeric phosphate binder intended for oral administration. Sevelamer hydrochloride is poly(allylamine hydrochloride) crosslinked with epichlorohydrin in which forty percent of the amines are protonated. It is known chemically as poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane) hydrochloride. Sevelamer hydrochloride is hydrophilic, but insoluble in water. The structure is represented below:




a, b = number of primary amine groups a + b = 9
c = number of crosslinking groups c = 1
n = fraction of protonated amines n = 0.4
m = large number to indicate extended polymer network

The primary amine groups shown in the structure are derived directly from poly(allylamine hydrochloride). The crosslinking groups consist of two secondary amine groups derived from poly(allylamine hydrochloride) and one molecule of epichlorohydrin.
Each hard-gelatin capsule of Renagel contains 403 mg of sevelamer hydrochloride on an anhydrous basis. The inactive ingredients are colloidal silicon dioxide and stearic acid. The capsule and imprint contain titanium dioxide and indigo carmine ink.

## CLINICAL PHARMACOLOGY

Patients with end-stage renal disease (ESRD) retain phosphorus and can develop hyperphosphatemia. High serum phosphorus can precipitate serum calcium resulting in ectopic calcification. When the product of serum calcium and phosphorus concentrations (Ca x P) exceeds 66, there is an increased risk that ectopic calcification will occur. Hyperphosphatemia plays a role in the development of secondary hyperparathyroidism in renal insufficiency. An increase in parathyroid hormone (PTH) levels is characteristic of patients with chronic renal failure. Increased levels of PTH can lead to osteitis fibrosa, a bone disease. A decrease in serum phosphorus may decrease serum PTH levels.

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* Registered trademark of GelTex Pharmaceuticals, Inc.

Treatment of hyperphosphatemia includes reduction in dietary intake of phosphate, inhibition of intestinal phosphate absorption with phosphate binders, and removal of phosphate with dialysis. Renagel taken with meals has been shown to decrease serum phosphorus concentrations in patients with ESRD who are on hemodialysis. Since Renagel does not contain aluminum, it does not cause aluminum intoxication.

Renagel treatment also results in a lowering of low-density lipoprotein (LDL) and total serum cholesterol levels.

**Pharmacokinetics:** A mass balance study using $^{14}C$-sevelamer hydrochloride in 16 healthy male and female volunteers showed that sevelamer hydrochloride is not systemically absorbed. No absorption studies have been performed in patients with renal disease.

**Clinical trials:** The ability of Renagel Capsules to lower serum phosphorus in ESRD patients on hemodialysis was demonstrated in three Phase 2 studies with treatment duration ranging from 2 to 12 weeks and two Phase 3 studies with treatment duration of 8 weeks. Four of the 5 studies were open-label dose-titration studies. One of the Phase 2 studies was a placebo-controlled study. The Phase 3 crossover study, described below, had a control arm. About half the patients from these studies (N=192) were treated with Renagel Capsules in a long-term open-label extension study of 44 weeks.

**Cross-over study of Renagel Capsules and calcium acetate:** Eighty-four ESRD patients on hemodialysis who were hyperphosphatemic (serum phosphorus >6.0 mg/dL) following a two-week phosphate binder washout period were randomized to receive either Renagel Capsules for eight weeks followed by calcium acetate for eight weeks or calcium acetate for eight weeks followed by Renagel Capsules for eight weeks. Treatment periods were separated by a two-week phosphate binder washout period. Patients started on Renagel Capsules or calcium acetate tablets three times per day with meals. Over each eight-week treatment period, at three separate time points the dose of either agent could be titrated up 1 capsule or tablet per meal (3 per day) to control serum phosphorus. Renagel Capsules and calcium acetate both significantly decreased mean serum phosphorus by about 2 mg/dL (Table 1).

Table 1. Mean Serum Phosphorus (mg/dL) at Baseline and Endpoint

| | Renagel (N=81) | Ca Acetate (N=83) |
|---|---|---|
| Baseline at End of Washout | 8.4 | 8.0 |
| Change from Baseline at Endpoint (95% Confidence Interval) | -2.0* (-2.5, -1.5) | -2.1* (-2.6, -1.7) |

*$p<0.0001$, within treatment group comparison

Figure 1 illustrates that the proportion of patients achieving a given level of serum phosphorus lowering is comparable between the two treatment groups. For example, about half the patients in each group had a decrease of at least 2 mg/dL at endpoint.

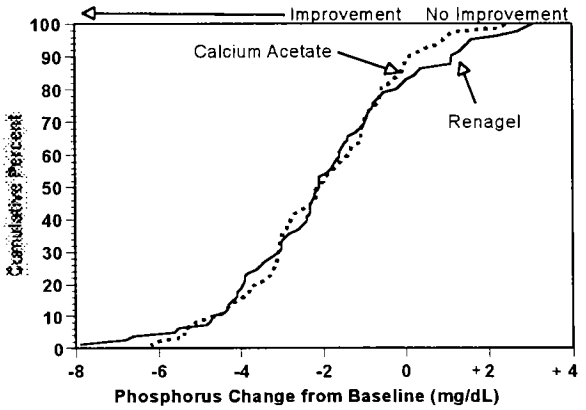


**Figure 1. Cumulative percent of patients (Y-axis) attaining a phosphorus change from baseline at least as great as the value on the X-axis. A shift to the left of a curve indicates a better response.**

Average daily consumption at the end of treatment was 4.9 g sevelamer hydrochloride (range of 0.0 to 12.6 g) and 5.0 g of calcium acetate (range of 0.0 to 17.8 g). During calcium acetate treatment, 22% of patients developed serum calcium ≥ 11.0 mg/dL on at least one occasion versus 5% for Renagel ($p < 0.05$). Thus the risk of developing hypercalcemia is less with Renagel Capsules compared to calcium acetate.
Mean LDL cholesterol and mean total cholesterol declined significantly on Renagel Capsules treatment (-24% and -15%, respectively). Neither LDL nor total cholesterol changed on calcium acetate treatment. Triglycerides, high-density lipoprotein (HDL) cholesterol, and albumin did not change on either treatment. Similar reductions in serum phosphorus and LDL cholesterol were observed in an eight-week open-label, uncontrolled study of 172 end stage renal disease patients on hemodialysis.

## INDICATIONS AND USAGE

Renagel Capsules are indicated for the reduction of serum phosphorus in patients with end-stage renal disease (ESRD). The safety and efficacy of Renagel Capsules in ESRD patients who are not on hemodialysis have not been studied. In hemodialysis patients, Renagel decreases the incidence of hypercalcemic episodes relative to patients on calcium acetate treatment.

## CONTRAINDICATIONS

Renagel is contraindicated in patients with hypophosphatemia or bowel obstruction. Renagel Capsules are contraindicated in patients known to be hypersensitive to sevelamer hydrochloride or any of its constituents.

## PRECAUTIONS

**General:** The safety and efficacy of Renagel Capsules in patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders, or major GI tract surgery have not been established. Consequently, caution should be exercised when Renagel Capsules are used in patients with these GI disorders.

Renagel Capsules do not contain calcium or alkali supplementation; serum calcium, bicarbonate, and chloride levels should be monitored.
In preclinical studies in rats and dogs, sevelamer hydrochloride reduced vitamin D, E, K, and folic acid levels at doses of 6-100 times the recommended human dose. In clinical trials, there was no evidence of reduction in serum levels of vitamins in patients who were supplemented with multivitamins.
**Information for the patient:** The prescriber should inform patients to take Renagel with meals and adhere to their prescribed diets. Instructions should be given on concomitant medications that should be dosed apart from Renagel Capsules. Because the contents of Renagel Capsules expand in water, capsules should not be taken apart prior to administration and should not be chewed.
**Drug interactions:** No drug-drug interaction studies were performed in humans. There is a possibility that sevelamer hydrochloride may bind concomitantly-administered drugs and decrease their bioavailability. When administering any oral drug for which alteration in blood levels could have a clinically significant effect on safety or efficacy, the drug should be administered at least one hour before or three hours after Renagel Capsules. Patients taking anti-arrhythmic and anti-seizure medications were excluded from the clinical trials. Special precautions should be taken when prescribing Renagel Capsules to patients also taking these medications.
**Carcinogenesis, mutagenesis, impairment of fertility:** Long-term studies in animals to evaluate carcinogenic potential have not been completed. In an *in vitro* mammalian cytogenetics test with metabolic activation, sevelamer hydrochloride caused a statistically significant increase in the number of structural chromosome aberrations. Sevelamer hydrochloride was not mutagenic in the Ames bacterial mutation assay. Sevelamer hydrochloride did not impair fertility in male or female rats.
**Pregnancy:**
**Pregnancy Category C**
In rats, at doses of 1.5 and 4.5 g/kg/day (approximately 15 and 45 times the recommended human dose based on mg/kg), sevelamer hydrochloride caused reduced or irregular ossification of fetal bones, probably due to a reduced absorption of fat-soluble vitamin D. In rabbits, sevelamer hydrochloride slightly increased prenatal mortality due to an increased incidence of early resorptions at a dose of 1 g/kg/day (approximately 10 times the recommended human dose based on mg/kg). Requirements for vitamins and other nutrients are increased in pregnancy. The effect of Renagel Capsules on the absorption of vitamins and other nutrients has not been studied in pregnant women. There are no adequate and well-controlled studies in pregnant women or nursing mothers.
**Geriatric use**: There is no evidence for special considerations when Renagel Capsules are administered to elderly patients.
**Pediatric use**: The safety and efficacy of Renagel Capsules have not been established in pediatric patients.

## ADVERSE REACTIONS

In a placebo-controlled study with a treatment duration of two weeks, the adverse events reported for Renagel Capsules (N=24) were similar to those reported for placebo (N=12). In a cross-over study with treatment durations of eight weeks each, the adverse events reported for Renagel Capsules (N=82) were similar to those reported for calcium acetate (N=82) (Table 2).

Table 2. Treatment-Emergent Adverse Events ≥ 10% from a Cross-Over Trial of Renagel Capsules versus Calcium Acetate for Eight Weeks of Treatment (N=82)

| | Renagel | Ca Acetate |
|---|---|---|
| Adverse Event | N (%) | N (%) |
| Any | 64 (78) | 65 (79) |
| Body As A Whole | 36 (44) | 38 (46) |
| Headache | 8 (10) | 9 (11) |
| Infection | 12 (15) | 9 (11) |
| Pain | 11 (13) | 13 (16) |
| Cardiovascular | 24 (29) | 29 (35) |
| Hypertension | 7 (9) | 8 (10) |
| Hypotension | 9 (11) | 10 (12) |
| Thrombosis | 8 (10) | 5 (6) |
| Digestive | 28 (34) | 23 (28) |
| Diarrhea | 13 (16) | 8 (10) |
| Dyspepsia | 9 (11) | 3 (4) |
| Vomiting | 10 (12) | 4 (5) |
| Respiratory | 8 (10) | 18 (22) |
| Cough Increased | 3 (4) | 9 (11) |

In a long-term, open-label extension trial, adverse events possibly related to Renagel Capsules and which were not dose-related, included nausea (7%), constipation (2%), diarrhea (4%), flatulence (4%), and dyspepsia (5%).

## OVERDOSAGE

Renagel Capsules have been given to normal healthy volunteers in doses of up to 14 grams, the equivalent of thirty-five 403 mg capsules, per day for eight days with no adverse effects. There are no reported overdosages of Renagel in patients. Since Renagel is not absorbed, the risk of systemic toxicity is low.

## DOSAGE AND ADMINISTRATION

The recommended starting dose of Renagel is two to four capsules with each meal depending on the severity of hyperphosphatemia.

| Starting Dose | |
|---|---|
| Serum Phosphorus | Renagel Capsules |
| >6.0 and <7.5 mg/dL | 2 capsules, three times a day |
| ≥7.5 and <9.0 mg/dL | 3 capsules, three times a day |
| ≥9.0 mg/dL | 4 capsules, three times a day |

The dosage should be gradually adjusted based on the serum phosphorus concentration with a goal of lowering serum phosphorus to 6.0 mg/dL or less. The dose may be increased or decreased by one capsule per meal as necessary. The average dose in clinical trials was three to four capsules per meal. The maximum daily dose studied was 30 Renagel Capsules.

There is a possibility that sevelamer hydrochloride may bind concomitantly-administered drugs and decrease their bioavailability. When administering any oral drug for which alteration in blood levels could have a clinically significant effect on safety or efficacy, the drug should be administered at least one hour before or three hours after Renagel Capsules.

Do not use Renagel Capsules after the expiration date on the bottle.

## HOW SUPPLIED

Renagel® Capsules are supplied as hard-gelatin capsules, axially imprinted with "G403," containing 403 mg of sevelamer hydrochloride on an anhydrous basis, 4.6 mg of colloidal silicon dioxide, and 4.6 mg of stearic acid. Renagel Capsules are packaged in bottles of 200 capsules.

NDC 58468-4709-1 Bottles of 200 Capsules

## STORAGE

Store at 25°C (77°F): excursions permitted to 15-30°C (59-86°F).
[See USP controlled room temperature]
Protect from moisture.
Rx Only

Licensed from: GelTex Pharmaceuticals, Inc.

Distributed by: (logo)
Genzyme Corporation
One Kendall Square
Cambridge, MA 02139
USA
Tel. (800) 847-0069

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