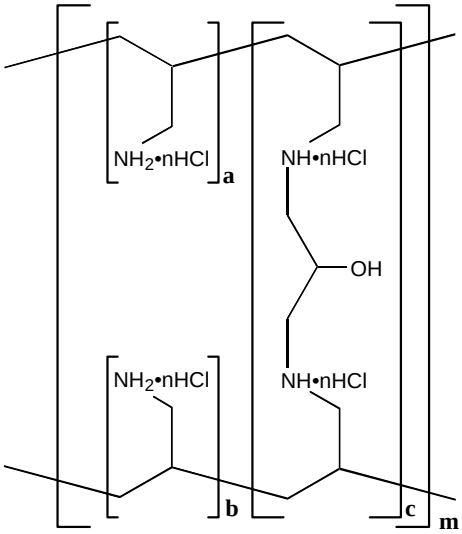
(logo) Renagel® Tablets
(sevelamer hydrochloride) 400 and 800 mg

(logo) Renagel® Capsules
(sevelamer hydrochloride) 403 mg
[se vel′ a mer]

DESCRIPTION

The active ingredient in Renagel* Tablets and Capsules is 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:

Chemical Structure of Sevelamer Hydrochloride



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.

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* Registered trademark of GelTex Pharmaceuticals, Inc.

Renagel® Tablets: Each film-coated tablet of Renagel contains either 800 mg or 400 mg of sevelamer hydrochloride on an anhydrous basis. The inactive ingredients are hydroxypropyl methylcellulose, diacetylated monoglyceride, colloidal silicon dioxide, and stearic acid. The tablet imprint contains iron oxide black ink.

Renagel® Capsules: 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.

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. All clinical studies were conducted with Renagel Capsules. *In vitro* studies have shown that the capsule and tablet formulations bind phosphate to a similar extent. 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.

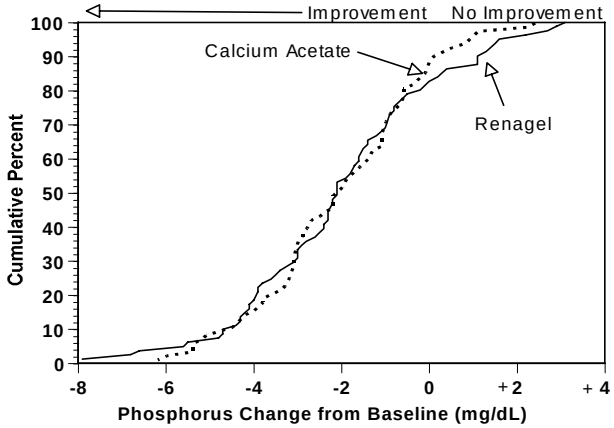

Figure 1. Cumulative percent of patients (Y-axis) attaining a phosphorus change from baseline at least as great as the value on the X-axis. A shift to the left of a curve indicates a better response.

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 is indicated for the reduction of serum phosphorus in patients with end-stage renal disease (ESRD). The safety and efficacy of Renagel 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 is contraindicated in patients known to be hypersensitive to sevelamer hydrochloride or any of its constituents.

PRECAUTIONS

General: The safety and efficacy of Renagel 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 is used in patients with these GI disorders.

Renagel does 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. Most (approximately 75%) patients in Renagel clinical trials received vitamin supplements, which is typical of patients on hemodialysis.

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. Because the contents of Renagel expand in water, tablets and capsules should be swallowed intact and should not be crushed, chewed, broken into pieces, or taken apart prior to administration.

Drug interactions: Renagel Capsules were studied in human drug-drug interaction studies with digoxin, warfarin, enalapril and metoprolol.

Digoxin: In 19 healthy subjects receiving 6 Renagel capsules three times a day with meals for 2 days, Renagel did not alter the pharmacokinetics of a single dose of digoxin.

Warfarin: In 14 healthy subjects receiving 6 Renagel capsules three times a day with meals for 2 days, Renagel did not alter the pharmacokinetics of a single dose of warfarin.

Enalapril: In 28 healthy subjects a single dose of 6 Renagel capsules did not alter the pharmacokinetics of a single dose of enalapril.

Metoprolol: In 31 healthy subjects a single dose of 6 Renagel capsules did not alter the pharmacokinetics of a single dose of metoprolol.

However, when administering any other oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on safety or efficacy, the drug should be administered at least one hour before or three hours after

Renagel, or the physician should consider monitoring blood levels of the drug. Patients taking anti-arrhythmic and anti-seizure medications were excluded from the clinical trials. Special precautions should be taken when prescribing Renagel to patients also taking these medications.

Carcinogenesis, mutagenesis, and 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 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 is administered to elderly patients.

Pediatric use: The safety and efficacy of Renagel has 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 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

Patients Not Taking a Phosphate Binder. The recommended starting dose of Renagel is 800 to 1600 mg, which can be administered as one to two Renagel® 800 mg Tablets, two to four Renagel® 400 mg Tablets, or two to four Renagel® Capsules with each meal based

on serum phosphorus level. Table 3 provides recommended starting doses of Renagel for patients not taking a phosphate binder.

Table 3. Starting Dose for Patients Not Taking a Phosphate Binder

SERUM PHOSPHORUS	RENAGEL® 800 MG	RENAGEL® 400 MG OR RENAGEL® CAPSULES
> 6.0 and < 7.5 mg/dL	1 tablet three times daily with meals	2 tablets or capsules three times daily with meals
≥ 7.5 and < 9.0 mg/dL	2 tablets three times daily with meals	3 tablets or capsules three times daily with meals
≥ 9.0 mg/dL	2 tablets three times daily with meals	4 tablets or capsules three times daily with meals

Patients Switching From Calcium Acetate. In a study in 84 ESRD patients on hemodialysis, a similar reduction in serum phosphorus was seen with equivalent doses (mg for mg) of Renagel Capsules and calcium acetate. Table 4 gives recommended starting doses of Renagel based on a patient's current calcium acetate dose.

Table 4. Starting Dose for Patients Switching From Calcium Acetate to Renagel

CALCIUM ACETATE 667 MG (TABLETS PER MEAL)	RENAGEL® 800 MG (TABLETS PER MEAL)	RENAGEL® 400 MG OR RENAGEL® CAPSULES (TABLETS OR CAPSULES PER MEAL)
1 tablet	1 tablet	2 tablets or capsules
2 tablets	2 tablets	3 tablets or capsules
3 tablets	3 tablets	5 tablets or capsules

Dose Titration for All Patients Taking Renagel. Dosage should be 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 tablet or capsule per meal at two week intervals as necessary. Table 5 gives a dose titration guideline. The average dose in Phase 3 clinical trials was four 403 mg capsules per meal. The maximum dose studied was 10 Renagel capsules per meal (the equivalent of 5 Renagel® 800 mg Tablets per meal or 10 Renagel® 400 mg Tablets per meal).

Table 5. Dose Titration Guideline

Serum Phosphorus	Renagel Dose
>6.0 mg/dL	Increase 1 tablet/capsule per meal at 2 week intervals
3.5-6.0 mg/dL	Maintain current dose
<3.5 mg/dL	Decrease 1 tablet/capsule per meal

Drug interaction studies have demonstrated that Renagel Capsules have no effect on the bioavailability of digoxin, warfarin, enalapril, or metoprolol. When administering any other 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, or the physician should consider monitoring blood levels of the drug. (See PRECAUTIONS: Drug interactions.)

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

HOW SUPPLIED

Renagel® 800 mg Tablets are supplied as oval, film-coated, compressed tablets, imprinted with “RENAGEL 800,” containing 800 mg of sevelamer hydrochloride on an anhydrous basis, hydroxypropyl methylcellulose, diacetylated monoglyceride, colloidal silicon dioxide, and stearic acid. Renagel® 800 mg Tablets are packaged in bottles of 180 tablets.

NDC 58468-0021-1 Bottle of 180 Tablets

Renagel® 400 mg Tablets are supplied as oval, film-coated, compressed tablets, imprinted with “RENAGEL 400,” containing 400 mg of sevelamer hydrochloride on an anhydrous basis, hydroxypropyl methylcellulose, diacetylated monoglyceride, colloidal silicon dioxide, and stearic acid. Renagel® 400 mg Tablets are packaged in bottles of 360 tablets.

NDC 58468-0020-1 Bottle of 360 Tablets

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

NDC 58468-4709-1 Bottle 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

Manufactured for GelTex Pharmaceuticals, Inc., Waltham, MA

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