INDICATIONS AND USAGE

Renagel® (sevelamer hydrochloride) Tablet for Oral use Initial U.S. Approval: 2000

Recent Major Changes

Contraindications (4) 03/2016

INDICATIONS AND USAGE

• Renagel® is a phosphate binder indicated for the control of serum phosphorus in patients with chronic kidney disease on dialysis. (1)

DOSAGE AND ADMINISTRATION

• Starting dose is one or two 800 mg or two to four 400 mg tablets three times per day with meals. (2)
• Adjust by one tablet per meal in two week intervals as needed to obtain serum phosphorus target (3.5 to 5.5 mg/dL). (2)

DOSAGE FORMS AND STRENGTHS

• Tablets: 800 mg and 400 mg (3)

CONTRAINDICATIONS

• Bowel obstruction. (4)
• Known hypersensitivity to sevelamer hydrochloride or to any of the excipients. (4)

ADVERSE REACTIONS

5.5 mg/dL Increase 1 tablet per meal at 2 week intervals

7.5 mg/dL 1 tablet three times daily

9.0 mg/dL 2 tablets three times daily

Serum Phosphorus

Renagel® 800 mg

Renagel® 400 mg

>5.5 and <7.5 mg/dL

1 tablet three times daily with meals

2 tablets three times daily with meals

≥7.5 and <9.0 mg/dL

2 tablets three times daily with meals

3 tablets three times daily with meals

≥9.0 mg/dL

2 tablets three times daily with meals

3 tablets three times daily with meals

Table 1: Starting Dose for Dialysis Patients Not Taking a Phosphate Binder

Dose Titration for All Patients Taking Renagel. Dosage should be adjusted based on the serum phosphorus concentration in a goal of lowering serum phosphorus to 5.5 mg/dL or less. The dose may be increased or decreased by one tablet per meal at two-week intervals as necessary. Table 3 gives a dose titration guideline. The average dose in a Phase 3 trial designed to lower serum phosphorus to 5.0 mg/dL or less was approximately three Renagel 800 mg tablets per meal. The maximum average daily Renagel dose studied was 13 grams.

Table 2: Starting Dose for Dialysis Patients Switching From Calcium Acetate to Renagel

<table>
<thead>
<tr>
<th>Calcium Acetate 667 mg (Tablets per meal)</th>
<th>Renagel® 800 mg (Tablets per meal)</th>
<th>Renagel® 400 mg (Tablets per meal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 tablet</td>
<td>1 tablet</td>
<td>2 tablets</td>
</tr>
<tr>
<td>2 tablets</td>
<td>2 tablets</td>
<td>3 tablets</td>
</tr>
<tr>
<td>3 tablets</td>
<td>3 tablets</td>
<td>5 tablets</td>
</tr>
</tbody>
</table>

Table 3: Dose Titration Guideline

<table>
<thead>
<tr>
<th>Serum Phosphorus</th>
<th>Renagel® Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5.5 mg/dL</td>
<td>Increase 1 tablet per meal at 2 week intervals</td>
</tr>
<tr>
<td>3.5–5.5 mg/dL</td>
<td>Maintain current dose</td>
</tr>
<tr>
<td>&lt;3.5 mg/dL</td>
<td>Decrease 1 tablet per meal</td>
</tr>
</tbody>
</table>

Patients Switching from Calcium Acetate. In a study in 84 CKD patients on hemodialysis, a similar reduction in serum phosphorus was seen with equal doses (approximately mg for mg) of Renagel and calcium acetate. Table 2 gives recommended starting doses of Renagel based on a patient's current calcium acetate dose.
5.3 Monitor for Reduced Vitamins

In preclinical studies in rats and dogs, sevelamer hydrochloride reduced vitamins D, E, and K (coagulation parameters) and folic acid levels at doses of 6 to 10 times the recommended human dose. In short-term clinical trials, there was no evidence of reduction in serum levels of vitamins. However, in a one-year clinical trial, 25-hydroxyvitamin D (normal range 10 to 55 ng/mL) fell from 39 ± 22 ng/mL to 34 ± 22 ng/mL (p < 0.01) with sevelamer hydrochloride treatment. Most (approximately 75%) patients in sevelamer hydrochloride clinical trials received vitamin supplements, which is typical on patients on dialysis.

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug can not be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a parallel design study of sevelamer hydrochloride with treatment duration of 52 weeks, adverse reactions reported for sevelamer hydrochloride (n=99) were similar to those reported for the active-control group (n=101). Overall adverse reactions among those treated with sevelamer hydrochloride occurring in >5% of patients included: vomiting (22%), nausea (20%), diarrhea (19%), dyspepsia (16%), abdominal pain (9%), flatulence (8%), and constipation (8%). A total of 27 patients treated with sevelamer and 10 patients treated with comparator withdrew from the study due to adverse reactions.

Based on studies of 8 to 52 weeks, the most common reason for withdrawal from Renagel was gastrointestinal adverse reactions (3%–16%).

In 143 peritoneal dialysis patients studied for 12 weeks, most adverse reactions were similar to adverse reactions observed in hemodialysis patients. The most frequently occurring treatment-emergent serious adverse reaction was peritonitis (6 reactions in 8 patients [8%] in the sevelamer group and 2 reactions in 2 patients [4%] in the active-control group). Thirteen patients (14%) in the sevelamer group and 9 patients (20%) in the active-control group discontinued, mostly for gastrointestinal adverse reactions. Patients on peritoneal dialysis should be closely monitored to ensure the reliable use of appropriate aseptic technique with prompt recognition and management of any signs and symptoms associated with peritonitis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of sevelamer hydrochloride (Renagel®): hypersensitivity, pruritus, rash, abdominal pain, fecal impaction and uncommon cases of ileus, intestinal obstruction, and intestinal perforation. Appropriate medical management should be given to patients who develop constipation or have worsening of existing constipation to avoid severe complications.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or to establish a causal relationship to drug exposure.

7. DRUG INTERACTIONS

There are no empirical data on avoiding drug interactions between Renagel® and most concomitant oral drugs. For oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy (e.g., cyclosporine, tacrolimus, levonorgestrel), consider separation of the timing of the administration of the two drugs [see Clinical Pharmacology (12.2)]. The separation of administration depends upon the absorption characteristics of the medication concomitantly administered, such as the time to reach peak systemic levels and whether the drug is an immediate-release or an extended-release product. Where possible consider monitoring clinical responses and/or blood levels of concomitant drugs that have a narrow therapeutic range.

Table 4: Sevelamer Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral drugs for which sevelamer did not alter the pharmacokinetics when administered concomitantly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>Dosing Recommendations: Take at least 2 hours before or 6 hours after sevelamer</td>
</tr>
<tr>
<td>Enalapril</td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td></td>
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<tr>
<td>Warfarin</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral drugs that have demonstrated interaction with sevelamer and are to be dosed separately from Renagel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>Dosing Recommendations: Take at least 2 hours before or 6 hours after sevelamer</td>
</tr>
</tbody>
</table>

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: The effect of Renagel on the absorption of vitamins and other nutrients has not been studied in pregnant women. Requirements for vitamins and other nutrients are increased in pregnancy. In pregnant rats given doses of Renagel during organogenesis, reduced or irregular ossification of fetal bones, probably due to a reduced absorption of fat-soluble vitamin D, occurred. In pregnant rabbits given oral doses of Renagel by gavage during organogenesis, an increase of early resorptions occurred [see Nonclinical Toxicology (13.1)].

11. DESCRIPTION

The active ingredient in Renagel Tablets is sevelamer hydrochloride, a polymeric amine that binds phosphate and is meant for oral administration. Sevelamer hydrochloride is poly(allylamine hydrochloride) crosslinked with epichlorohydrin in which 40% 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 Hydrolphilic, but insoluble in water. The structure is represented in Figure 1.

Figure 1: Chemical Structure of Sevelamer Hydrochloride

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.

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 hypromellose, diacetylated monoglyceride, colloidal silicon dioxide, and stearic acid. The tablet imprint contains iron oxide black ink.

12. CLINICAL PHARMACOLOGY

Patients with chronic kidney disease (CKD) on dialysis 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 × P) exceeds 55 mg²/dL², there is an increased risk that ectopic calcification will occur. Hyperphosphatemia plays a role in the development of secondary hyperparathyroidism in renal insufficiency.

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 CKD who are on dialysis.

12.1 Mechanism of Action

Renagel contains sevelamer hydrochloride, a non-absorbed binding crosslinked polymer. It contains multiple amines separated by one carbon from the polymer backbone. These amines exist in a protonated form in the intestine and interact with phosphate molecules.
through ionic and hydrogen bonding. By binding phosphate in the dietary tract and decreasing absorption, sevelamer hydrochloride lowers the phosphate concentration in the serum.

12.2 Pharmacodynamics

In addition to effects on serum phosphate levels, sevelamer hydrochloride has been shown to bind bile acids in vitro and in vivo in experimental and clinical models. Bile acid binding by ion exchange resins is a well-established method of lowering blood cholesterol. Because sevelamer binds bile acids, it may interfere with normal fat absorption and thus may reduce absorption of fat-soluble vitamins such as A, D, and K. In clinical trials of sevelamer hydrochloride, both the mean total and LDL cholesterol declined by 15% to 31%. This effect is observed after 2 weeks. Triglycerides, HDL cholesterol, and albumin did not change.

12.3 Pharmacokinetics

A mass balance study using 14C-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.

Drug Interactions

In vivo

Sevelamer carbonate has been studied in human drug-drug interaction studies (9.6 grams once daily with a meal) with warfarin and digoxin. Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been studied in human drug-drug interaction studies (2.8 grams single dose or three times daily with meals or two times daily without meals) with ciprofloxacin, digoxin, enalapril, iron, metoprolol, mycophenolate mofetil and warfarin.

Co-administered single dose of 2.8 grams of sevelamer hydrochloride in fasted state decreased the bioavailability of ciprofloxacin by approximately 50% in healthy subjects. Co-administered administration of sevelamer and mycophenolate mofetil in adult and pediatric patients decreased the mean MPA Cmax and AUC0-12h, by 36% and 26%, respectively. Sevelamer carbonate or sevelamer hydrochloride did not alter the pharmacokinetics of a single dose of enalapril, digoxin, iron, metoprolol and warfarin when coadministered. During postmarketing experience, cases of increased thyroid stimulating hormone (TSH) levels have been reported in patients coadministered sevelamer hydrochloride and levothyroxine. Reduction in concentrations of cyclosporine and tacrolimus leading to dose increases has also been reported in transplant patients when coadministered with sevelamer hydrochloride without any clinical consequences (e.g., graft rejection). The possibility of an interaction cannot be excluded with these drugs.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Rats were given oral doses of 100, 500, or 1000 mg/kg/day of sevelamer hydrochloride by gavage (human equivalent doses less than the maximum clinical trial dose of 13 g). In pregnant rabbits during organogenesis, reduced or irregular ossification of fetal bones, probably due to a reduced absorption of fat-soluble vitamin D, occurred in mid and high-dose groups (human equivalent dose twice the maximum clinical trial dose of 13 g). Oxidative stress was observed in experimental animal models. Bile acid binding by ion exchange resins is a well-established method of lowering blood cholesterol. Because sevelamer binds bile acids, it may interfere with normal fat absorption and thus may reduce absorption of fat-soluble vitamins such as A, D, and K.

14 CLINICAL STUDIES

14.1 Active-Control, Parallel Study in Hemodialysis Patients

Two hundred CKD patients on hemodialysis who were hyperphosphatemic (serum phosphorus >5.5 mg/dL) following a two-week phosphate-binder washout period were randomized to receive Renagel 800 mg tablets (N=99) or an active control (N=101). The two treatments produced similar decreases in serum phosphorus. At week 52, using last observation carried forward, Renagel and active control both significantly decreased mean serum phosphorus (Table 6).

14.2 Active-Control, Parallel Study in Peritoneal Dialysis Patients

Average daily Renagel dose at the end of treatment was 4.9 g (range of 0.0 to 12.6 g).

14.3 Active-Control, Parallel Study in Peritoneal Dialysis Patients

Eighty-four CKD patients on hemodialysis who were hyperphosphatemic (serum phosphorus >5.5 mg/dL) following a two-week phosphate-binder washout period, received Renagel and active control for eight weeks each in random order. Treatment periods were separated by a two-week phosphate-binder washout period. Patients started on treatment three times per day with meals. Over each eight-week treatment period, at three separate time points the dose of Renagel could be titrated up 1 capsule or tablet per meal (3 per day) to control serum phosphorus, the dose of active control could also be altered to attain phosphate control. Both treatments significantly decreased mean serum phosphorus by about 2 mg/dL (Table 5).

Table 5: Mean Serum Phosphorus (mg/dL) at Baseline and Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Renagel® (N=81)</th>
<th>Active-Control (N=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Endpoint</td>
<td>6.4</td>
<td>5.9</td>
</tr>
</tbody>
</table>

*p<0.0001, within treatment group comparison

The distribution of responses is shown in Figure 2. The distributions are similar for sevelamer hydrochloride and active control. The median response is a reduction of about 2 mg/dL in both groups. About 50% of subjects have reductions between 1 and 3 mg/dL.

Figure 2: Percentage of Patients (Y-axis) Attaining a Phosphorus Reduction from Baseline (mg/dL) at Least as Great as the Value of the X-axis.

Average daily Renagel dose at the end of treatment was 6.5 g (range of 0.8 to 13 g).

Figure 3: Mean Phosphorus Change from Baseline for Patients who Completed 52 Weeks of Treatment.

Sixty-one percent of Renagel patients and 73% of the control patients completed the full 52 weeks of treatment.

Figure 3, a plot of the phosphorus change from baseline for the completers, illustrates the durability of response for patients who are able to remain on treatment.

Figure 3: Mean Phosphorus Change from Baseline for Patients who Completed 52 Weeks of Treatment

Table 6: Mean Serum Phosphorus (mg/dL) and Ion Product at Baseline and Change from Baseline to End of Treatment

<table>
<thead>
<tr>
<th></th>
<th>Renagel® (N=84)</th>
<th>Active-Control (N=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphorus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.5</td>
<td>7.3</td>
</tr>
<tr>
<td>Change from Baseline</td>
<td>-2.1</td>
<td>-1.8</td>
</tr>
<tr>
<td>Ca × Phosphorus Ion Product</td>
<td>70.5</td>
<td>68.4</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from Baseline</td>
<td>-19.4</td>
<td>-14.2</td>
</tr>
</tbody>
</table>
were randomized to receive Renagel® (N=97) or active control (N=46) open label for 12 weeks. Average daily Renagel dose at the end of treatment was 5.9 g (range 0.8 to 14.3 g). There were statistically significant changes in serum phosphorus (p<0.001) for Renagel (-1.6 mg/dL from baseline of 7.5 mg/dL), similar to the active control.

16 HOW SUPPLIED/STORAGE AND HANDLING
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, hypromellose, diacetylated monoglyceride, colloidal silicon dioxide, and stearic acid. Renagel® 800 mg Tablets are packaged in bottles 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, hypromellose, diacetylated monoglyceride, colloidal silicon dioxide, and stearic acid. Renagel® 400 mg Tablets are packaged in bottles of 360 tablets.

1 Bottle of 180 ct 800 mg Tablets (NDC 58468-0021-1)
1 Bottle of 360 ct 400 mg Tablets (NDC 58468-0020-1)

Storage Store at 25°C (77°F); excursions permitted to 15°C–30°C (59°F–86°F).
Do not use Renagel® after the expiration date on the bottle.
[See USP controlled room temperature]
Protect from moisture.

17 PATIENT COUNSELING INFORMATION
Dosing Recommendations
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.

Adverse Reactions
Renagel may cause constipation that if left untreated may lead to severe complications. Patients should be cautioned to report new onset or worsening of existing constipation promptly to their physician.

Manufactured By:

Genzyme Ireland Ltd.

For: Genzyme Corporation

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Cambridge, MA 02142 USA

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