Renagel® sevelamer hydrochloride

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 3).

<table>
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<tr>
<th>Renagel® (N=96)</th>
<th>Active-Control (N=96)</th>
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<tr>
<td>Phosphorus Baseline</td>
<td>7.5</td>
</tr>
<tr>
<td>Change from Baseline to Endpoint</td>
<td>-2.1</td>
</tr>
</tbody>
</table>

Eighty-one percent of Renagel patients and 72% 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

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

14.3 Active-Control, Parallel Study in Peritoneal Dialysis Patients

One hundred and forty-three patients on peritoneal dialysis who were hyperphosphatemic (serum phosphorus > 5.5 mg/dL) following a two-week phosphate binder washout period were randomized to receive Renagel® (N=98) 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 "RENA G EL 8 00" 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.


Do not use Renagel® after the expiration date on the bottle. (See USP controlled room temperature)

Protect from moisture.

17. PATIENT COUNSELING INFORMATION

17.1 Dosing Recommendations

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**INDICATIONS AND USE**

- **Renagel®** is a phosphate binder indicated for the control of serum phosphorus in patients with chronic kidney disease on dialysis.

**DOSE 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]

**DOSE FORMS AND STRENGTHS**

- Tablets: 800 mg and 400 mg [3]
- **CONTRAINDICATIONS**
- In patients with bowel obstruction. [4]

**WARNINGS AND PRECAUTIONS**

- Serious cases of dysphagia, bowel obstruction, and perforation have been associated with sevelamer use, some requiring hospitalization and surgery. [5,1]
Because clinical trials are conducted under widely varying conditions, adverse reactions observed in the clinical trials of a drug cannot be directly compared to rates in the general population.

In clinical trials, the most common reason for withdrawal from placebo or active treatments was death. The safety and efficacy of Renagel in CVD patients who are not on dialysis have not been established.

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<th>Table 1. Starting Dose for Dialysis Patients Not Taking a Phosphate Binder</th>
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<tr>
<td><strong>Serum Phosphorus</strong></td>
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<tr>
<td>5.5 mg/dL</td>
</tr>
<tr>
<td>7.0 mg/dL</td>
</tr>
<tr>
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</table>

Dosage Titration Table

- Serum Phosphorus
- Renagel® Dose
  - Increase 1 tablet per day at 2 week intervals
  - Maintain current dose
  - Decrease 1 tablet per week

- Calcium Acetate

5.2 Monitor Serum Chemistries

Bicarbonate and chloride levels should be monitored.

5.3 Gastrointestinal Adverse Events

Cases of diarrhea and opiate-like tablet retention have been reported in association with use of the tablet formulation of Renagel. Although the incidence is low, diarrhea is a common side effect of the drug. Consider using special dietary in patients with a history of swallowing disorders.

5.4 Other Contraindications

Patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders or swallowing problems, or major GI tract surgery were not included in the Renagel clinical studies.

5.5 Monitor Serum Chemistries

Bicarbonate and chloride levels should be monitored.

5.6 Monitor for Reduced Vitamins D, E, K (clotting factors) and Folic Acid Levels

In preclinical studies in rats and dogs, sevelamer hydrochloride reduced vitamin D, E, K ( clotting factors) and reduced folic acid levels at doses of 6–10 times the nonhuman dose. Use of vitamin D, E and K supplements is generally recommended in patients receiving Renagel to maintain normal levels of these nutrients.

5.7 Other Contraindications

There are no known drug-drug interactions between Renagel® and most concomitant drugs. During postmarketing experience, very rare cases of increased thyroxine-stimulating hormone (TSH) levels have been reported in patients co-administered levothyroxine sodium and sevelamer hydrochloride and levothyroxine. Closer monitoring of TSH levels is therefore recommended in these patients.

5.8 In Patients With Congestive Heart Failure

When administering an oral medication where a reduction in the bioavailability of that medication is desired, sevelamer hydrochloride should be administered 1 hour before or 2 hours after meals.

5.9 In Patients With Renal Impairment

In experimental animal models, sevelamer hydrochloride reduced absorption of fat-soluble vitamins. In pregnant rabbits given oral sevelamer hydrochloride by diet at 0.5, 3, or 10 mg/kg/day, there was no evidence of teratogenicity. In rabbits treated with oral sevelamer hydrochloride by diet at 30 mg/kg/day, there was no indication of fetal toxicity. Sevelamer hydrochloride has not been studied in pregnant women. It is not known whether sevelamer hydrochloride will pass into breast milk, although the drug is expected to appear in the breast milk of women taking the medication.

5.10 Prenatal and Milk Feeding

In a study on the potential for breast feeding in a nonhuman species (rabbit), animals were treated with oral sevelamer hydrochloride by diet at 40 mg/kg/day. There was no significant proteination in the nipples of the nursing dams. Neither the drug nor its metabolites were observed in the milk of nursing dams treated with oral sevelamer hydrochloride by diet at 40 mg/kg/day. In rabbits treated with oral sevelamer hydrochloride by diet at 120 mg/kg/day, the drug and its metabolites were observed in the milk of nursing dams treated with oral sevelamer hydrochloride by diet at 120 mg/kg/day. Sevelamer hydrochloride has not been studied in pregnant women. It is not known whether sevelamer hydrochloride will pass into breast milk, although the drug is expected to appear in the breast milk of women taking the medication.

6.2 Labor and Delivery

Use of sevelamer hydrochloride on labor and delivery in human is not known. It is not known whether sevelamer hydrochloride will pass into breast milk, although the drug is expected to appear in the breast milk of women taking the medication.

6.3 Pharmacodynamics

In a multiple dose study using an oral dose of 120 mg/kg/day of sevelamer hydrochloride, no significant changes were observed in the disposition and bioavailability of midazolam, diazepam, or lorazepam in rabbits given oral sevelamer hydrochloride by diet at 40 mg/kg/day.

6.4 Pediatric Use

Clinical studies of sevelamer hydrochloride in children have not been conducted in patients 18 years of age and older. Use of sevelamer hydrochloride in children is not recommended.

6.5 Geriatric Use

Clinical studies of sevelamer hydrochloride in geriatric patients have not been conducted. Use of sevelamer hydrochloride in elderly patients is not recommended.

6.6 Pregnancy

Because there are no adequately controlled clinical trials in pregnant women, sevelamer hydrochloride should not be used during pregnancy. Sevelamer hydrochloride may be excreted in breast milk, although it is not known whether it is present in breast milk. It is not known whether this drug is excreted in breast milk.

7.3 Monitoring Sevelamer Hydrochloride Levels

A blood test for monitoring the plasma concentration of sevelamer hydrochloride is available (Figure 1). This test is neither needed nor recommended as a guide to dosing since the drug is highly bound to plasma proteins, approximately 99%, and the unbound drug is not removed by dialysis.

7.4 Serum Chemistries

Serum electrolytes and phosphorus levels should be measured at baseline and approximately every 3 months during therapy. Use of sevelamer hydrochloride does not lower serum potassium levels. Serum calcium concentrations should be checked at least every 6 months. Sevelamer hydrochloride may cause a mild increase in serum creatinine levels. The increase-associated with sevelamer hydrochloride use, is not clinically significant and does not appear to be dose-dependent. Urine electrolyte excretion is not affected.

7.5 Metabolism

In 37 healthy subjects a single dose of 8 mg Renagel capsules did not alter the pharmacokinetics of a single dose of midazolam.

7.6 Ions

In 28 healthy subjects a single dose of 6 mg Renagel capsules did not alter the absorption of a single oral dose of 200 mg esomeprazole magnesium tablet.

7.10 Other Contraindications

There are no known drug-drug interactions between Renagel® and most concomitant drugs. During postmarketing experience, very rare cases of increased thyroxine-stimulating hormone (TSH) levels have been reported in patients co-administered levothyroxine sodium and sevelamer hydrochloride and levothyroxine. Closer monitoring of TSH levels is therefore recommended in these patients.

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8.1 Pregnancy

Sevelamer hydrochloride is not indicated for treatment of hyperphosphatemia in pregnant women. The long-term effects of sevelamer hydrochloride during pregnancy in humans are not known. Use of sevelamer hydrochloride during pregnancy should be avoided.

8.2 Labor and Delivery

Sevelamer hydrochloride is not indicated for treatment of labor and delivery in human patients.

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6.1 Clinical Trials Experience

In a study in 84 CKD patients on hemodialysis, a similar reduction in serum phosphate was seen with sevelamer capsules (approximately mg for mg) of Renagel and calcium acetate. Table 2 gives recommended starting doses for sevelamer hydrochloride in patients not taking a phosphate binder.

Table 2. Starting Dose for Dialysis Patients Taking a Phosphate Binder

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3. DOSAGE AND STRENGTHS

800 mg and 400 mg Tablets

1. IN INDIVIDUALS WITHRENAL INSUFFICIENCY

5.1 Gastrointestinal Adverse Events

Cases of diarrhea and osmotic diarrhea tablet retention have been reported in association with use of the tablet formulation of sevelamer hydrochloride. Consider using sevelamer suspension in patients with a history of swallowing disorders.

Cases of bowel obstruction, constipation, and ileus have occurred associated with the use of sevelamer hydrochloride. Patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders including diarrhea, irritable bowel syndrome, or major tract surgery were not included in the Renagel clinical trials.

5.2 Monitor Serum Cholesterol

Bilirubin and other liver enzymes should be monitored.

5.3 Monitor for Reduced Vitamins D, E, K ( clotting factors) and Folic Acid Levels

In preclinical studies in rats and dogs, sevelamer hydrochloride reduced vitamin D, E, and K levels. With high doses of 6-10 times the recommended human dose, in short-term clinical trials, there was no evidence of reduced vitamin D, E, or K levels and folic acid levels in rats. With high doses of 6-10 times the recommended human dose, no evidence was found for the reduction of vitamin D, E, or K levels in rats. With high doses of 6-10 times the recommended human dose, no effect was observed on vitamin D, E, or K levels in dogs.

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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.

17.2 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.

17.3 Contraindications

• In patients with bowel obstruction. (4)

7.4 Enalapril

• Medication would have a clinically significant effect on its 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. (7.7)

8.2 Labor and Delivery

• Coadministration with digoxin, warfarin, esmolol, metoprolol, and iron. (7)

7.5 Metoprolol

• When administering an oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its 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. (7.7)

7.6 Iron

• Cases of local impaction and, less commonly, leash, bowel obstruction, and bowel perforation have been reported. (9.2)

7.7 Other Concomitant Drug Therapy

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 1-800-847-0069 and or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

13 NONCLINICAL TOXICOLOGY

14 CLINICAL STUDIES

15 HOW SUPPLIED/STORAGE AND HANDLING

16 PATIENT COUNSELING INFORMATION

Revised: 05/2011

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