The study was designed to determine the long-term effects of three different dosing regimens of sevelamer, a sevelamer carbonate tablet, on serum phosphorus levels in patients with chronic kidney disease (CKD) on hemodialysis or peritoneal dialysis.

**Patients and Methods**

Four hundred forty-one patients with CKD on hemodialysis or peritoneal dialysis who were hyperphosphatemic (serum phosphorus levels greater than 5.5 mg/dL) were enrolled in the study. Patients were randomized to receive sevelamer carbonate 800 mg tablets (N=99) or an active-control (N=100) every 12 hours, sevelamer carbonate 800 mg tablets administered three times per day, or an active-control tablet three times per day. Patients were instructed to take the medication once daily in the morning with a meal within 30 minutes.

**Results**

Serum phosphorus levels were similar for the sevelamer carbonate 800 mg tablets and the active-control tablet once daily regimen. However, the sevelamer carbonate 800 mg tablets administered three times per day resulted in significantly lower serum phosphorus levels compared to the active-control tablet once daily regimen. The mean reduction in serum phosphorus levels for the sevelamer carbonate 800 mg tablets administered three times per day regimen was 16.4 mg/dL, compared to 14.2 mg/dL for the active-control tablet once daily regimen. These reductions were statistically significant (p<0.001).

**Conclusion**

Sevelamer carbonate administered three times per day is effective in lowering serum phosphorus levels in patients with CKD on hemodialysis or peritoneal dialysis. The effect of sevelamer carbonate administered three times per day is significantly greater than that of an active-control tablet once daily regimen.

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**Table 4. Mean Serum Phosphorus (mg/dL) at Baseline and Endpoint**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevelamer</td>
<td>5.5</td>
<td>4.9</td>
</tr>
<tr>
<td>Active-control</td>
<td>5.5</td>
<td>5.2</td>
</tr>
</tbody>
</table>

**Table 5. Mean Reduction in Serum Phosphorus (mg/dL) at Baseline and Endpoint**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevelamer</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Active-control</td>
<td>0.3</td>
<td>0.0</td>
</tr>
</tbody>
</table>

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**References**


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**Figure 2. Distribution of responses**

The distribution of responses is shown in Figure 2. The distributions are similar for severity categories of mild, moderate, and severe.

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**Figure 3. Mean Phosphorus Change from Baseline for Patients who Complied 52 weeks of Treatment**

The mean phosphorus change from baseline for patients who complied 52 weeks of treatment is shown in Figure 3. The mean phosphorus change for these patients is similar to the overall mean phosphorus change for all patients in the study.
5.3 Monitor for Reduced Vitamins D, E, K (clotting factors) and Folic Acid Levels

Patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders are anticipated to be similar to that of the sevelamer hydrochloride tablet.
1. INDICATIONS AND USAGE

Renvela® (sevelamer carbonate) is indicated for the control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis, and children ≥1 year of age on hemodialysis, who cannot tolerate or are intolerant to sevelamer hydrochloride. The product is also indicated for the control of serum phosphorus in patients with CKD not on dialysis who require medical management of serum phosphorus levels. Use Renvela® tablets in place of sevelamer hydrochloride tablets in the management of serum phosphorus levels in patients with CKD who are intolerant of or who cannot tolerate sevelamer hydrochloride tablets.

2. DOSAGE AND ADMINISTRATION

2.1 Concomitant Use of Renvela with Other Phosphate Binders

Sevelamer and calcium-based binders are contraindicated in patients who are taking both types of binders. Studies comparing the effects of concomitant use of sevelamer and calcium-based binders with an active-control regimen of sevelamer carbonate tablets (N=256) have shown that concomitant use of these binders is not always possible to reliably estimate their frequency or to establish a causal relationship. The incidence of adverse reactions due to concomitant use of sevelamer and calcium-based binders was comparable to the incidence of adverse reactions associated with either binding agent when used alone.

3. DESCRIPTION

Renvela® Tablets

Each tablet contains 0.8 g or 2.4 g of sevelamer carbonate as the hydrochloride salt, with the following active ingredients: 3.1.1 Calcium Acetate 667 mg (Tablets per meal)

4. CONTRAINDICATIONS

The safety and efficacy of Renvela has not been established in pediatric patients.

5. warnings and precautions

The safety and efficacy of Renvela have not been evaluated in pediatric patients. Use Renvela in pediatric patients only under the direct supervision of a physician.

6. adverse reactions

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

6.3 Other Reactions

7. DRUG INTERACTIONS

Sevelamer hydrochloride caused a statistically significant increase in the number of structural anomalies in rodent fetuses at dose approximately twice the maximum clinical trial dose. This effect is observed after 2 weeks. Triglycerides, HDL cholesterol and apolipoprotein A-1 were reduced.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Pediatric Use

8.4 Geriatric Use

8.5 Hypersensitivity Reactions

8.6 Laboratory and other Test Results

8.7 Pregnancy/Lactation

8.8 Precautions

8.9 Gender

8.10 Carcinogenesis, Mutagenesis, Impairment of Fertility

8.11 Animal Toxicology and/or Pharmacology

9. CLINICAL PHARMACOLOGY

9.1 Pharmacology

9.2 Clinical Pharmacology

9.3 Carcinogenesis, Mutagenesis, Impairment of Fertility

9.4 Animal Toxicology and/or Pharmacology

10. OVERDOSAGE

Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been given to healthy volunteers in doses of up to 14 grams per day for up to 28 days with no adverse effects. In a study of 15 healthy subjects, a co-administered single dose of 2.8 grams of sevelamer hydrochloride caused a statistically significant increase in the number of structural anomalies in rodent fetuses at dose approximately twice the maximum clinical trial dose. This effect is observed after 2 weeks.

11. DESCRIPTION

The active moiety in Renvela is sevelamer carbonate, a polyaminated anion that binds phosphate and is resistant to oral degradation. It was developed as a pharmaceutical agent after its demonstration of efficacy (Renagel®). Sevelamer carbonate is an anionic exchange resin, with the same polyaminated structure as sevelamer hydrochloride, in which a bonded calcium carbonate group is replaced by a propylene glycol (nonionic) group. Sevelamer carbonate is for oral administration.

12. CLINICAL STUDIES

The ability of sevelamer to control serum phosphorus levels in patients on dialysis was tested in controlled clinical trials. These clinical trials demonstrated that sevelamer is as effective as calcium carbonate in controlling serum phosphorus levels in dialysis patients. A critical factor in the use of sevelamer is the reduction of phosphate absorption from the diet. Sevelamer also reduces serum levels of calcium and phosphorus, lowering the serum phosphorus concentration in the serum (sevelamer).
the durability of response for patients who are able to remain on treatment.

Baseline (mg/dL) at least as great as the value of the X-axis.

*p < 0.0001, within treatment group comparison

Each eight-week treatment period, at three separate time points the dose of sevelamer hydrochloride could be titrated to control serum phosphorus, the dose of active-control should also be altered to maintain phosphorus control. Both treatments significantly decreased mean serum phosphorus by about 2 mg/dL (Table 4).

Table 4. Mean Serum Phosphorus (mg/dL) at Baseline and Endpoint

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>7.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Sevelamer Hydrochloride</td>
<td>7.2</td>
<td>5.7</td>
</tr>
</tbody>
</table>

### 10. OVERDOSAGE

Sevelamer is unlike other oral phosphate binders in that it is not excreted in the urine. In case of overdose, supportive care is indicated. Sevelamer is not removed by hemodialysis or peritoneal dialysis.

### 11. DOSAGE AND ADMINISTRATION

Sevelamer hydrochloride tablets and sevelamer hydrochloride powder are indicated for the chronic management of hyperphosphatemia in adults on hemodialysis, peritoneal dialysis, and dialysis-dependent patients with chronic kidney disease.

#### 11.1 Dosing

- **Sevelamer Hydrochloride Tablets**: The starting dose is 0.8 or 1.6 grams three times per day.

- **Sevelamer Hydrochloride Powder**: The starting dose is 0.8 or 1.6 grams administered every three times per day.

#### 11.2 Mechanism of Action

Sevelamer hydrochloride is a synthetic, block copolymer of polyvinylamine and polyvinylpyrrolidone that competitively binds dietary and circulating phosphorus. It is excreted in the feces after binding with phosphorus.

#### 11.3 Cross-Over, Controlled Trial of Sevelamer Hydrochloride

- **Baseline**: Baseline serum phosphorus was greater than 5.5 mg/dL.
- **Cross-Over**: At the end of treatment, serum phosphorus was less than 5.5 mg/dL.

### 12. CLINICAL PHARMACOLOGY

- **12.1 Mechanism of Action**: Sevelamer hydrochloride is a synthetic, block copolymer of polyvinylamine and polyvinylpyrrolidone that competitively binds dietary and circulating phosphorus. It is excreted in the feces after binding with phosphorus.
- **12.2 Mechanism of Administration**: Sevelamer hydrochloride is administered orally three times per day.

### 13. NONCLINICAL TOXICOLOGY

- **13.1 Carcinogenicity**: There is no evidence of carcinogenicity in animals treated with sevelamer hydrochloride.
- **13.2 Developmental Toxicity**: Sevelamer hydrochloride had no evidence of developmental toxicity in animals.
- **13.3 Pharmacokinetics**: Sevelamer hydrochloride is rapidly absorbed after oral administration.

### 14.8 Once a Day Versus Three Times a Day Dosing

Sevelamer hydrochloride tablets and sevelamer hydrochloride powder are indicated for the chronic management of hyperphosphatemia in adults on hemodialysis, peritoneal dialysis, and dialysis-dependent patients with chronic kidney disease.

#### 14.9 Drug Interactions

- **Drug Interactions**: Sevelamer hydrochloride does not interfere with the absorption, activity, or bioavailability of other medications.
- **Contraindications**: Sevelamer hydrochloride is not recommended for use in patients with severe gastrointestinal adverse reactions.

### 15. PATIENT COUNSELING INFORMATION

- **Patient Counseling Information**: Inform patients to take Renvela as directed with meals and adhere to their prescribed diets.
- **Sevelam er (sevelam er carbonate) Tablets**

### 16. HOW SUPPLIED/STORAGE AND HANDLING

- **Tablets**: Renvela 800 mg tablets are supplied as a white oval, film-coated, 800 mg tablets, in packages of 90 tablets (NDC 58468-0131-4) and 270 tablets (NDC 58468-0130-1).
- **Powder**: Sevelamer hydrochloride powder is supplied in packets containing 0.8 g and 2.4 g of sevelam er carbonate. In a spherical base, multiple, rounded, and flat rectangular shapes which may be used to achieve desired phosphorus levels. (2.1)

### 17. PATIENT COUNSELING INFORMATION

- **Patient Counseling Information**: Inform patients to take Renvela as directed with meals and adhere to their prescribed diets.
- **Sevelam er (sevelam er carbonate) Tablets**

### 18. PRECAUTIONS

- **Precautions**: Sevelamer hydrochloride is not recommended for use in patients with severe gastrointestinal adverse reactions.
- **Contraindications**: Sevelamer hydrochloride is not recommended for use in patients with severe gastrointestinal adverse reactions.

### 19. ADVERSE REACTIONS

- **Adverse Reactions**: Sevelamer hydrochloride does not interfere with the absorption, activity, or bioavailability of other medications.
- **Contraindications**: Sevelamer hydrochloride is not recommended for use in patients with severe gastrointestinal adverse reactions.