# Sevela Film Coated Tablet 800 mg
# (Sevelamer Carbonate 800mg)

## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

Sevelamer Carbonate is indicated for the control of hyperphosphatemia in adult patients receiving haemodialysis or peritoneal dialysis.

Sevelamer Carbonate should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxyvitamin D3 or one of its analogues to control the development of renal bone disease.

## 2 DOSAGE AND ADMINISTRATION

Due to the rapid reaction of the drug with hydrochloric acid in stomach, the dosage of Sevelamer Carbonate tablet is expected to be similar with hydrochloride.

### 2.1 General Dosing Information

The drug should be taken 3 times daily with meals.

*D*ose for Adult Patients Not Taking a Phosphate Binder: The recommended starting dose of Sevelamer Carbonate is 0.8 to 1.6 g with meals based on serum phosphorus level. Table 1 provides recommended starting doses of Sevelamer Carbonate for adult patients not taking a phosphate binder.

**Table 1. Starting Dose for Adult Dialysis Patients Not Taking a Phosphate Binder**

| Serum Phosphorus | **Sevelamer Carbonate tablet 800 mg** |
|---|---|
| > 5.5 and < 7.5 mg/dL | 1 tablet each time, three times daily with meals |
| ≥ 7.5 mg/dL | 2 tablets each time, three times daily with meals |

*Switching from Sevelamer Hydrochloride Tablets:* For adult patients switching from Sevelamer Hydrochloride tablets to Sevelamer Carbonate tablets or powder, use the same dose in grams. To achieve the target phosphate concentration, further adjusting of dose may be necessary. For CKD patients on dialysis treatment, the highest daily dose of the used Sevelamer Carbonate in the study is 14 grams.

*Switching from Calcium Acetate:* A research performing on 84 of CKD patients on dialysis indicated that equivalent dose (approximate mg to mg) of Sevelamer Hydrochloride and Calcium Acetate showed similar decreasing serum phosphorus levels. Table 2 gives recommended starting doses of Sevelamer Carbonate based on a patient's current calcium acetate dose.

**Table 2. Starting Dose for Dialysis Patients Switching from Calcium Acetate to Sevelamer Carbonate**

| **Calcium Acetate 667 mg (Tablets per meal)** | **Sevelamer Carbonate 800 mg (Tablets per meal)** |
|---|---|
| 1 tablet | 1 tablet |
| 2 tablets | 2 tablets |
| 3 tablets | 3 tablets |

*Adjusting doses for all patients using this product:* Sevelamer Carbonate dose by 0.8 g three times per day with meals at two-week intervals as necessary to achieve target serum phosphorus levels (3.5 mg/ dL to 5.5 mg/dL).

Sevelamer Carbonate tablet should be swallowed entirely and should not be grinded, chewed to fragments or split.

## 3 DOSAGE FORMS AND STRENGTHS

Film-coated Tablets: 800 mg off-white to white oval shaped film-coated tablet, "CH86" on one side and no word on the other side.

## 4 CONTRAINDICATIONS

Sevelamer carbonate is contraindicated in patients with hypophosphatemia and bowel obstruction.

Sevelamer carbonate is contraindicated in patients with known hypersensitivity to sevelamer carbonate, or to any of the excipients.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Gastrointestinal Adverse Events

Cases of dysphagia and esophageal tablet retention have been reported in association with use of the tablet formulation of sevelamer, some requiring hospitalization and intervention. Consider using Sevelamer suspension in patients with a history of swallowing disorders. Cases of bowel obstruction and perforation have also been reported with sevelamer use.

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

Use with caution in patients with these GI disorders.

### 5.2 Monitoring Serum Chemical Substances

Serum bicarbonate and chloride concentration should be monitored.

### 5.3 Monitoring in Vitamins D, E, K (clotting factors) and Folic Acid Levels

In preclinical studies in rats and dogs, sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, reduced vitamins D, E, and K (coagulation parameters) and folic acid levels at doses of 6-10 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 were receiving vitamin supplements.

It is recommended that CKD patients not on dialysis are given Vitamin D supplements (approximately 400 IU of native vitamin D daily) which can be part of a multivitamin preparation to be taken apart from their dose of sevelamer carbonate. In patients undergoing peritoneal dialysis, additional monitoring of fat-soluble vitamins and folic acid is recommended, since vitamin A, D, E, and K levels were not measured in a clinical study in these patients.

## 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 cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of sevelamer (as either carbonate and hydrochloride salts) has been investigated in numerous clinical trials involving a total of 969 haemodialysis patients with treatment duration of 4 to 50 weeks (724 patients treated with sevelamer hydrochloride and 245 with sevelamer carbonate), 97 peritoneal dialysis patients with treatment duration of 12 weeks (all treated with sevelamer hydrochloride) and 128 patients with CKD not on dialysis with treatment duration of 8 to 12 weeks (79 patients treated with sevelamer hydrochloride and 49 with sevelamer carbonate).

The most frequently occurring (≥5% of patients) adverse reactions were all in the gastrointestinal disorders system organ class. Most of these adverse reactions were mild to moderate in intensity.

Adverse reactions are listed by frequency in the table below. The reporting rate is classified as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from available data).

| |
|---|
| *Very common:* Nausea, vomiting, upper abdominal pain, constipation |
| *Common:* Diarrhoea, dyspepsia, flatulence, abdominal pain |
| *Not known:* Pruritis, rash, intestinal obstruction, ileus/subileus, and intestinal perforation |

### 6.2 Postmarketing Experience

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

The following adverse reactions have been identified during post-approval use of sevelamer hydrochloride, which has the same active moiety as sevelamer carbonate: pruritus, rash, abdominal pain, faecal 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.

During post-marketing experience, hypersensitivity has been reported in patients receiving Sevelamer Carbonate.

## 7 DRUG INTERACTIONS

There are no empirical data on avoiding drug interactions between Sevelamer Carbonate 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, levothyroxine), consider separation of the timing of the administration of the two drugs *[see Clinical Pharmacology (12.3)]*. The duration of separation 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 3. Sevelamer Drug Interactions**

| **Oral drugs for which sevelamer did not alter the pharmacokinetics when administered concomitantly** | |
|---|---|
| Digoxin<br>Enalapril<br>Iron<br>Metoprolol<br>Warfarin | |
| **Oral drugs that have demonstrated interaction with sevelamer and are to be dosed separately from Sevelamer Carbonate** | |
| | **Dosing Recommendations** |
| Ciprofloxacin | Take at least 2 hours before or 6 hours after sevelamer |
| Mycophenolate mofetil | Take at least 2 hours before sevelamer |

Patients taking anti-arrhythmic medications for the control of arrhythmias and anti-seizure medications for the control of seizure disorders were excluded from the clinical trials. Special precautions should be taken when prescribing Sevelamer Carbonate to patients also taking these medications.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy category C: There are no enough and great active-control group study for the pregnant women.

Sevelamer is recommended for the pregnant women only when the potential fetal benefit is more than possible risk. How sevelamer hydrochloride influences the absorption of vitamins and other nutrients in pregnant women has not been studied. During pregnancy, the demand of vitamins and other nutrients would increase.

In pregnant rats given specific doses of sevelamer hydrochloride 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 doses approximately equal to 3-4 times the maximum clinical trial dose of 13 g). In pregnant rabbits given oral doses of sevelamer hydrochloride by gavage during organogenesis, an increase of early resorptions occurred in the high-dose group (human equivalent dose twice the maximum clinical trial dose). *[see NonClinical Toxicology (13.2)]*.

### 8.2 Lactation

It is unknown whether sevelamer is excreted in human breast milk.

The non-absorbed nature of sevelamer indicates that excretion of sevelamer in breast milk is unlikely. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Sevelamer Carbonate should be made taking into account the benefit of breast-feeding to the child and the benefit of Sevelamer Carbonate therapy to the woman.

### 8.3 Labor and Delivery

In animal studies, related influence for labor and delivery has not been observed in the treatment of sevelamer hydrochloride. The influence on labor and delivery in the treatment of sevelamer carbonate is unknown. *[see NonClinical Toxicology (13.1)]*. Consider supplementation.

### 8.4 Paediatric Use

The safety and efficacy of Sevelamer Carbonate has not been established.

### 8.5 Geriatric Use

Clinical studies of Sevelamer Carbonate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose
selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

## 9 OVERDOSAGE

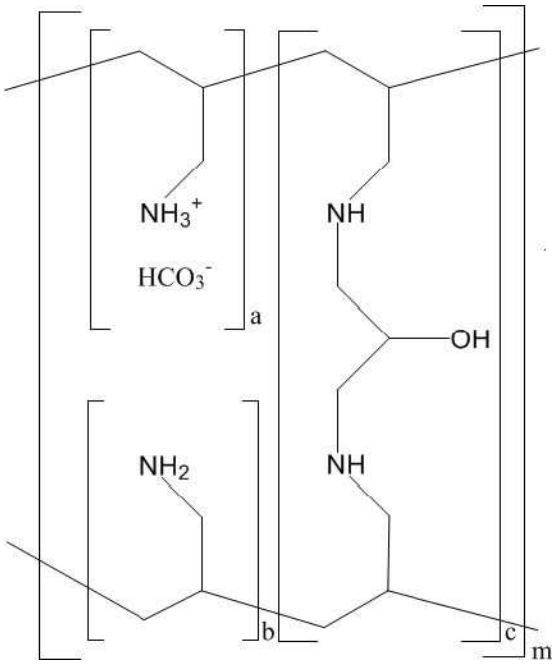
There are no adverse reactions when applying sevelamer hydrochloride (contains the same active ingredient as sevelamer carbonate) to healthy volunteers at a daily dose of 14 mg for 8 days. In CKD patients on dialysis, the maximum dose studied was 14 grams of sevelamer carbonate and 13 grams of sevelamer hydrochloride. There are no reports of overdosage with sevelamer carbonate or sevelamer hydrochloride in patients. Since sevelamer is not absorbed, the risk of systemic toxicity is low.

## 10 DESCRIPTION

The active ingredient is Sevelamer Carbonate, a polymeric amine that binds phosphate and is meant for oral administration. It was developed as a pharmaceutical alternative to sevelamer hydrochloride. Sevelamer Carbonate is an anion exchange resin, with the same polymeric structure as sevelamer hydrochloride, in which carbonate replaces chloride as the counterion. While the counterions differ for the two salts, the polymer itself, the active moiety involved in phosphate binding, is the same.

Sevelamer Carbonate is known chemically as poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane) carbonate salt. Sevelamer Carbonate is hygroscopic, but insoluble in water. The structure is represented in Figure 1.

**Figure 1: Chemical Structure of Sevelamer Carbonate**




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

## 11 EXCIPIENTS

Microcrystalline Cellulose, Sodium Chloride, Magnesium Stearate, Silicon Dioxide, Purified Water, Stearic Acid, HPMC and PEG.

## 12 CLINICAL PHARMACOLOGY

In CKD patients, phosphorus would remain in the body and develop as hyperphosphatemia. When the product of serum calcium and phosphorus (Ca **x** P) is more than 55 $mg^2/dL^2$, the risk of ectopic calcification would increase.

Hyperphosphatemia is one of the causes that induces secondary hyperparathyroidism in renal dysfunction.

Treatments of hyperphosphatemia include reducing the phosphate intake in the meals, using phosphate binder to inhibit intestine absorption of phosphate and removing phosphate by dialysis. For CKD patients on dialysis, administration of sevelamer carbonate with meals has been proved to control serum phosphorus levels.

### 12.1 Mechanism of Action

Sevelamer carbonate, a non-absorbed phosphate binding crosslinked polymer, free of metal and calcium. 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 gastrointestinal tract and decreasing absorption, sevelamer carbonate lowers the phosphate concentration in the serum (serum phosphorus).

### 12.2 Pharmacodynamics

In addition to effects on serum phosphorus levels, sevelamer hydrochloride has been shown to bind bile acids in vitro and in vivo in experimental animal models. Binding bile acids by ion exchange resin is a widely accepted method to lower serum 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 15-31%; the clinical significance of this finding, which was observed after 2 weeks, is unclear. Triglycerides, HDL cholesterol and albumin did not change.

### 12.3 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.

*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 moiety as sevelamer carbonate, has been studied in human drug-drug interaction studies (2.4 - 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.

Concomitant administration of sevelamer and mycophenolate mofetil in adult and paediatric patients decreased the mean MPA $C_{max}$ and $AUC_{0-12h}$ 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 co-administered.

During postmarketing experience, cases of increased thyroid stimulating hormone (TSH) levels have been reported in patients co-administered sevelamer hydrochloride and levothyroxine. Reduction in concentrations of cyclosporine and tacrolimus leading to dose increases has also been reported in transplant patients when co-administered with sevelamer hydrochloride without any clinical consequences (for example, 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 sevelamer hydrochloride by diet at 0.3, 1, or 3 g/kg/day. There was an increased incidence of urinary bladder transitional cell papilloma in male rats of the high dose group (human equivalent dose twice the maximum clinical trial dose of 13 g). Mice received dietary administration of sevelamer hydrochloride at doses of up to 9 g/kg/day (human equivalent dose 3 times the maximum clinical trial dose). There was no increased incidence of tumors observed in mice.

In an *in vitro* mammalian cytogenetic 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 the fertility of male or female rats in a dietary administration study in which the females were treated from 14 days prior to mating through gestation and the males were treated for 28 days prior to mating. The highest dose in this study was 4.5 g/kg/day (human equivalent dose 3 times the maximum clinical trial dose of 13 g).

### 13.2 Developmental toxicity

In pregnant rats given dietary doses of 0.5, 1.5, or 4.5 g/kg/day of sevelamer hydrochloride 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 doses approximately equal to 3-4 times the maximum clinical trial dose of 13 g). In pregnant rabbits given oral doses of 100, 500, or 1000 mg/kg/day of sevelamer hydrochloride by gavage during organogenesis, an increase of early resorptions occurred in the high-dose group (human equivalent dose twice the maximum clinical trial dose).

## 14 CLINICAL STUDIES

The ability of sevelamer to control serum phosphorus in CKD patients on dialysis was predominantly determined from the effects of the hydrochloride salt to bind phosphate. Six clinical trials used sevelamer hydrochloride and three clinical trials used sevelamer carbonate. The sevelamer hydrochloride studies include one double-blind, placebo-controlled 2-week study (sevelamer N=24); two open-label, uncontrolled, 8-week studies (sevelamer N=220) and three active-controlled open-label studies with

treatment durations of 8 to 52 weeks (sevelamer N=256). The sevelamer carbonate studies include one double-blind, active-controlled, cross-over study with two 8-week treatment periods using sevelamer carbonate tablets (N=79), one open-label, active-controlled, cross-over study with two 4-week treatment periods using sevelamer carbonate powder (N=31) and one randomized, parallel, open-label study using sevelamer carbonate powder (N=144) dosed once daily or sevelamer hydrochloride tablets (N=73) dosed three times daily for 24 weeks. Four of the active-controlled studies are described here (one sevelamer carbonate and three sevelamer hydrochloride studies).

### 14.1 Cross-Over Study of Sevelamer Carbonate 800 mg Tablets and Sevelamer Hydrochloride 800 mg Tablets

Stage 5 CKD patients on haemodialysis were entered into a five-week sevelamer hydrochloride run-in period and 79 patients received, in random order, sevelamer carbonate 800 mg tablets and sevelamer hydrochloride 800 mg tablets for eight weeks each, with no intervening washout. Study dose during the crossover period was determined based on the sevelamer hydrochloride dose during the run-in period on a gram per gram basis. The phosphorus levels at the end of each of the two cross-over periods were similar. Average actual daily dose was 6 g/day divided among meals for both treatments. A portion of the patients who completed the cross-over portion of the study were entered into a two-week washout period. During the two-week washout period, patients were instructed not to take any phosphate binders; forty (40) patients completed the washout period and confirmed the activity of sevelamer in this study.

### 14.2 Sevelamer Hydrochloride Versus Active-Control, Cross-Over Study in Haemodialysis Patients

Eight-four CKD patients on haemodialysis who were hyperphosphatemic (serum phosphorus >6.0 mg/dL) following a two-week phosphate binder washout period were randomized in a cross-over design to receive in random order sevelamer hydrochloride and active-control for eight weeks each. 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 sevelamer hydrochloride could be titrated up to control serum phosphorus, the dose of active-control could also be altered to attain phosphorus control. Both treatments significantly decreased mean serum phosphorus by about 2 mg/dL (Table 4).

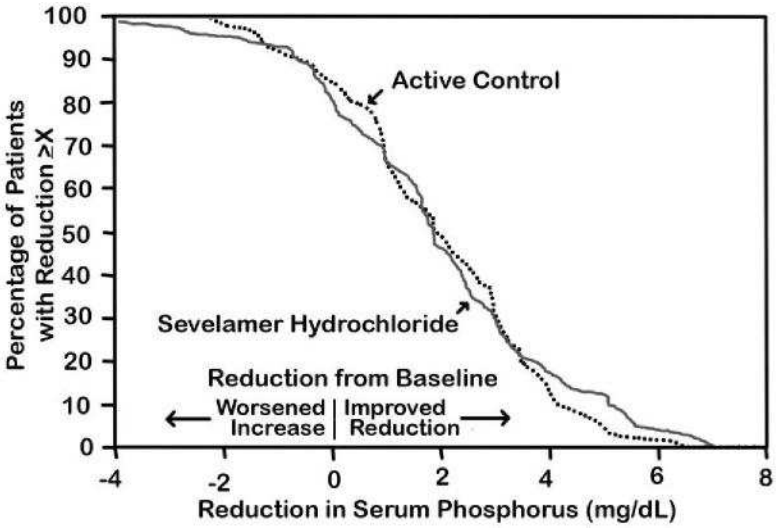
**Table 4. Mean Serum Phosphorus (mg/dL) at Baseline and Endpoint**

| | **Sevelamer Hydrochloride (N = 81)** | **Active Control (N = 83)** |
|---|---|---|
| Baseline at End of Washout | 8.4 | 8.0 |
| Endpoint | 6.4 | 5.9 |
| 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

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 sevelamer hydrochloride dose at the end of treatment was 4.9 g (range from 0.0 to 12.6 g).

### 14.3 Sevelamer Hydrochloride Versus Active-Control in Haemodialysis Patients

Two hundred CKD patients on haemodialysis who were hyperphosphatemic (serum phosphorus >5.5 mg/dL) following a two-week phosphate binder washout period were randomized to receive sevelamer hydrochloride 800 mg tablets (N=99) or an active control (N=101). At week 52, using last-observation carried-forward, sevelamer and active-control both significantly decreased mean serum phosphorus (Table 5).

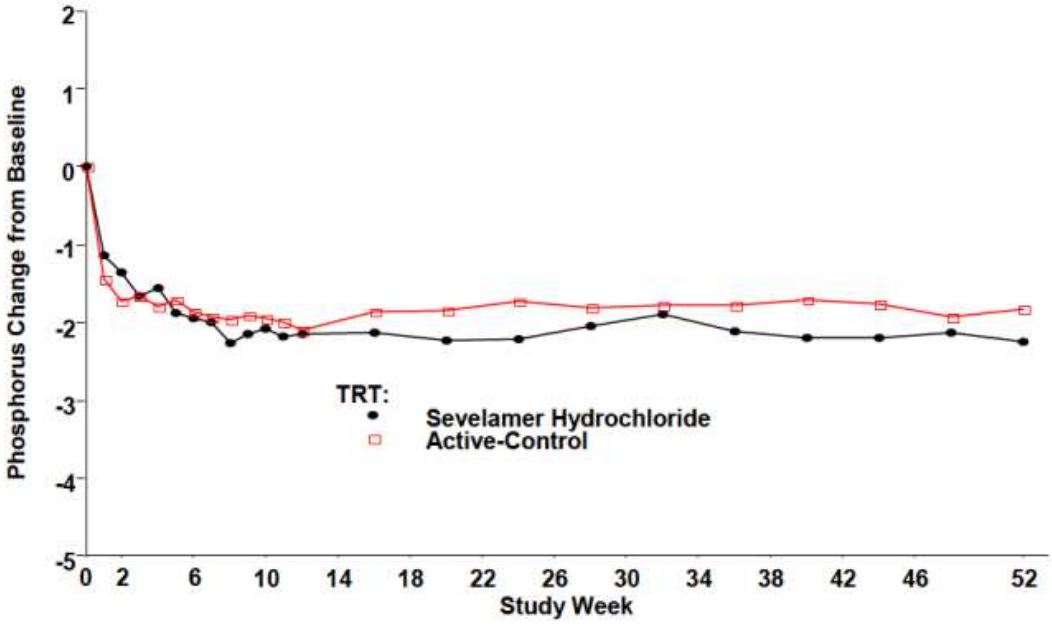
**Table 5: Mean Serum Phosphorus (mg/dL) and Ion Product at Baseline and Change from Baseline to End of Treatment**

| | **Sevelamer HCl (N = 94)** | **Active Control (N = 99)** |
|---|---|---|
| Phosphorus | | |
| Baseline | 7.5 | 7.3 |
| Change from Baseline at Endpoint | -2.1 | -1.8 |
| Ca × Phosphorus Ion Product | | |
| Baseline | 70.5 | 68.4 |
| Change from Baseline at Endpoint | -19.4 | -14.2 |

61% of sevelamer hydrochloride patients and 73% of the control patients completed the full 52 weeks of treatment.

Figure 3, a plot of 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 sevelamer hydrochloride dose at the end of treatment was 6.5 g (range of 0.8 to 13 g).

### 14.4 Sevelamer Hydrochloride Versus Active-Control 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 sevelamer hydrochloride (N=97) or active-control (N=46) open label for 12 weeks. Average daily sevelamer hydrochloride dose at the end of treatment was 5.9 g (range 0.8 to 14.3 g).

Thirteen patients (14%) in the sevelamer group and 9 patients (20%) in the active-control group discontinued, mostly for gastrointestinal adverse reactions. There were statistically significant changes in serum phosphorus ($p<0.001$) for sevelamer hydrochloride (-1.6 mg/dL from baseline of 7.5 mg/dL), similar to the active-control.

### 14.5 An Open Label, Dose Titration Study of Sevelamer Carbonate Tablets Dosed Three Times A Day In Hyperphosphatemic Chronic Kidney Disease Patients Not On Dialysis

An open-label, single-arm, dose titration study was conducted with sevelamer carbonate tablets in hyperphosphatemic CKD patients not on dialysis. The study included a washout period for those on binder, an 8-week treatment period followed by a post-treatment washout period for all patients. All patients were supplemented with a daily dose of 400 IU of native vitamin D to be taken separately from the dose of sevelamer carbonate. Sevelamer carbonate tablets were dosed three times per day and mean serum phosphorus level decreased from 2.0 nmol/L (6.2 mg/dL) at baseline to 1.6 mmol/L (4.8 mg/dL) at the end of treatment. The decrease in serum phosphorus level was statistically significant [mean 0.5 mmol/L (1.4 mg/dL), $p<0.001$]. During the post-treatment washout period, there was a statistically significant increase in mean serum phosphorus levels of 0.6 mmol/L (1.7 mg/dL) ($p<0.001$) confirming the efficacy of sevelamer carbonate in hyperphosphatemic CKD patients not on dialysis.

## 15 PACKAGING

The tablets are packed in PVC/Aluminium blisters placed in carton boxes containing 100 and 500 tablets.

## 16 STORAGE

Store below 30°C, protect from light.

## 17 SHELF LIFE

2 years from date of manufacture.

## 18 NAME AND ADDRESS OF MANUFACTURER

Chen Ho Pharmaceuctical Co., Ltd. Sinying Plant
No. 23, Singong Road, Jiafeng Vill., Sinying Dist., Tainan City,
730 Taiwan, R.O.C.