RENAMAX 800mg Film-Coated Tablet

NAME OF THE MEDICINAL PRODUCT
RENAMAX 800mg Film-coated Tablet

QUALITATIVE AND QUANTITATIVE COMPOSITION
RENAMAX 800mg: One film-coated tablet of RENAMAX contains 800mg of Sevelamer Carbonate.

PHARMACEUTICAL FORM
White to off-white, film-coated oval tablets, debossed with "X1" on one side and no debossing on the other side.

CLINICAL PARTICULARS
Therapeutic indications
RENAMAX is indicated for the control of hyperphosphatemia in adult patients receiving haemodialysis or peritoneal dialysis.

RENAMAX is also indicated for the control of hyperphosphatemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus ≥ 1.78 mmol/l.

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

Posology and method of administration
Because of the rapid disintegration of the carbonate salt tablet and its rapid reaction with the hydrochloric acid in the stomach, the dosing of RENAMAX is anticipated to be similar to that of the hydrochloride salt.

RENAMAX should be given three times a day with meals.

Patients Not Taking a Phosphate Binder
The recommended starting dose of RENAMAX is 800 to 1600 mg, which can be administered as one or two RENAMAX 800 mg Tablets, with meals based on serum phosphorus level. Table 1 provides recommended starting doses of RENAMAX for patients not taking a phosphate binder.

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

Serum Phosphorus	RENAMAX 800 mg
> 1.78 and < 2.42 mmol/L	1 tablet three times daily with meals
> 2.42 and < 2.91 mmol/L	2 tablets three times daily with meals
> 2.91 mmol/L	2 tablets three times daily with meals

Patients Switching from Sevelamer Hydrochloride

For patients switching from sevelamer hydrochloride, sevelamer carbonate should be prescribed on a gram per gram basis. Further titration to the desired phosphate levels may be necessary. The highest daily dose of sevelamer carbonate studied was 14 grams in CKD patients on dialysis.

Patients Switching from Calcium Acetate

In a study in 84 CKD patients on haemodialysis, a similar reduction in serum phosphorus was seen with equivalent doses (approximately mg for mg) of sevelamer hydrochloride and calcium acetate. Table 2 gives recommended starting doses of RENAMAX based on a patient's current calcium acetate dose.

Table 2. Starting Dose for Dialysis Patients Switching from Calcium Acetate to RENAMAX

Calcium Acetate 667 mg (Tablets per meal)	RENAMAX 800 mg (Tablets per meal)
1 tablet	1 tablet
2 tablets	2 tablets
3 tablets	3 tablets

Dose Titration for All Patients Taking RENAMAX

The dose should be increased or decreased by one tablet per meal at two-week intervals, as necessary, with the goal of controlling serum phosphorus within the target range of 1.13 mmol/L to 1.78 mmol/L.

Contraindications

RENAMAX is contraindicated in patients with bowel obstruction.

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

Special warnings and precautions for use

Gastrointestinal Adverse Events

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.

Cases of dysphagia and oesophageal 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, bleeding gastrointestinal ulcers, colitis, ulceration, necrosis, and perforation have also been reported with Sevelamer Carbonate use.

Inflammatory disorders may resolve upon Sevelamer Carbonate discontinuation. Treatment with Sevelamer Carbonate should be re-evaluated in patients who develop severe gastrointestinal symptoms.

Reductions 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.

Interaction with other medicinal products and other forms of interaction
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. 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 Enalapril Iron Metoprolol Warfarin	
Oral drugs that have demonstrated interaction with Sevelamer and are to be dosed separately from RENAMAX	
	Dosing Recommendations
Ciprofloxacin	Take at least 2 hours before or 6 hours after Sevelamer
Mycophenolate mofetil	Take at least 2 hours before Sevelamer

Pregnancy, lactation and other specific populations

Pregnancy:
Risk Summary

Sevelamer carbonate is not absorbed systemically following oral administration and maternal use is not expected to result in foetal exposure to the drug.

Clinical Considerations
Sevelamer carbonate may decrease serum levels of fat-soluble vitamins and folic acid in pregnant women. Consider supplementation.

Data
Animal data: 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 foetal 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).

Lactation:
Risk Summary
RENAMAX is not absorbed systemically by the mother following oral administration, and breastfeeding is not expected to result in exposure of the child to RENAMAX.

Clinical Considerations
Sevelamer carbonate may decrease serum levels of fat-soluble vitamins and folic acid in pregnant women. Consider supplementation.

Paediatric Use:
The safety and efficacy of RENAMAX has not been established in paediatric patients. RENAMAX is not recommended for use in children below the age of 18 years.

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.

Effects on ability to drive and use machines
RENAMAX has no or negligible influence on the ability to drive and use machines.

Undesirable effects
Clinical trials
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.

There are limited clinical trial data on the safety of Sevelamer Carbonate. However, because it contains the same active ingredient as the hydrochloride salt, the adverse event profiles of the two salts are expected to be similar. In a cross-over study in haemodialysis patients with treatment durations of eight weeks each and no washout, and another cross-over study in haemodialysis patients with treatment durations of four weeks each and no washout between treatment periods, the adverse reactions on sevelamer carbonate powder were similar to those reported for sevelamer hydrochloride.

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- comparator group (n=101). Overall adverse reactions among those treated with sevelamer hydrochloride occurring in >5% of patients included: vomiting (22%), nausea (20%), diarrhoea (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 8-52 weeks, the most common reason for withdrawal from sevelamer hydrochloride was gastrointestinal adverse reactions (3%-16%).

In 143 peritoneal dialysis patients studied for 12 weeks using sevelamer hydrochloride, most common adverse reactions were similar to adverse reactions observed in haemodialysis patients. The most frequently occurring treatment emergent serious adverse reaction was peritonitis (8 reactions in 8 patients [8%] in the sevelamer group and 2 reactions in 2 patients [4%] on active control). Thirteen patients (14%) in the sevelamer group and 9 patients (20%) in the active-control group discontinued, mostly for gastrointestinal adverse reactions.

Post marketing 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 causal relationship to drug exposure.

The following adverse reactions have been identified during post-approval use of sevelamer hydrochloride or sevelamer carbonate: hypersensitivity, pruritus, rash, abdominal pain, bleeding gastrointestinal ulcers, colitis, ulceration, necrosis, 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.

Overdose
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.

PHARMACOLOGICAL PROPERTIES

Mechanism of Action

RENAMAX contains 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).

Pharmacodynamic properties

In addition to effects on serum phosphate levels, sevelamer hydrochloride has been shown to bind bile acids in vitro and in vivo in experimental animal models. 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.

Pharmacokinetic properties

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.

<u>Drug Interactions In vivo</u>

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 (2.4-2.8 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 post marketing 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.

PHARMACEUTICAL PARTICULARS

List of excipients

Microcrystalline Cellulose (M105)
Purified Water
Silicon Dioxide (SYLOID 244 FP)
Zinc Stearate (PALMSTAR ZPR-2-V)
Opadry (06A190000) Clear (contains 39%w/w HPMC 2910/HYPROMELLOSE (USP, PhEur, JP, ChP), 39%w/w HPMC 2910/HYPROMELLOSE(USP, PhEur, JP, FCC), 22%w/w DI-ACETYLATED MONOGLYCERIDES (NF, FCC))

Incompatibilities

Not applicable

Shelf life

Refer to the outer carton

Special precautions for storage

Store at 30ºC. Protect from moisture.

Nature and contents of container

1 HDPE bottle with Polypropylene Child Resistant Closure of 30 Tablets

Special precautions for disposal

No special requirements.

Manufactured by:

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