HEALOL SEVELAMER

1. NAME OF THE MEDICINAL PRODUCT

HEALOL SEVELAMER (Sevelamer carbonate 800 mg film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 800 mg sevelamer carbonate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White or off-white oval film coated tablet, debossed with "XH" on one side and "800" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HEALOL SEVELAMER is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis.

HEALOL SEVELAMER is also indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease (CKD) not on dialysis with serum phosphorus ≥ 1.78 mmol/l.

HEALOL SEVELAMER should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy Vitamin D_3 or one of its analogues to control the development of renal bone disease.

4.2 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 HEALOL SEVELAMER is anticipated to be similar to that of the hydrochloride salt.

HEALOL SEVELAMER should be given three times a day with meals.

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

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

Serum Phosphorus	HEALOL SEVELAMER 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 hemodialysis, 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 HEALOL SEVELAMER based on a patient's current calcium acetate dose.

Table 2. Starting Dose for Dialysis Patients Switching From Calcium Acetate to HEALOL SEVELAMER

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

Dose Titration for All Patients Taking HEALOL SEVELAMER. 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.

4.3 Contraindications

HEALOL SEVELAMER is contraindicated in patients with bowel obstruction.

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

4.4 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 HEALOL SEVELAMER clinical studies.

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, bleeding gastrointestinal ulcers, colitis, ulceration, necrosis, and perforation have also been reported with sevelamer use.

Inflammatory disorders may resolve upon HEALOL SEVELAMER discontinuation. Treatment with HEALOL SEVELAMER 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.

4.5 Interaction with other medicinal products and other forms of interaction

There are no empirical data on avoiding drug interactions between HEALOL SEVELAMER 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 fromseparately	
HEALOL SEVELAMER	
Ciprofloxacin Mycophenolate mofetil	**Dosing Recommendations** Take at least 2 hours before or 6 hours after sevelamer Take at least 2 hours before sevelamer

4.6 Use in specific populations

Pregnancy

Risk Summary

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

Clinical Considerations

Sevelamer carbonate may decrease serum levels of fat soluble vitamins and folic acid in pregnant women [see Clinical Pharmacology (12.2)]. 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 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).

Lactation

Risk Summary

Sevelamer carbonate is not absorbed systemically by the mother following oral administration, and breastfeeding is not expected to result in exposure of the child to Sevelamer carbonate.

Clinical Considerations

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

Pediatric Use

The safety and efficacy of HEALOL SEVELAMER has not been established in pediatric patients. HEALOL SEVELAMER is not recommended for use in children below the age of 18 years.

Geriatric Use

Clinical studies of HEALOL SEVELAMER 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.

4.7 Undesirable effects

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.

There are limited clinical trial data on the safety of HEALOL SEVELAMER. 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 hemodialysis patients with treatment durations of eight weeks each and no washout, and another cross-over study in hemodialysis 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%), 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 8-52 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 hemodialysis 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.

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 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.

4.8 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

HEALOL SEVELAMER contain 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).

5.2 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 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.

5.3 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 (2.4-2.8 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 pediatric patients decreased the mean MPA C_{max} and $AUC_{0\text{-}12h}$ 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Mannitol
Crospovidone
Hydroxypropyl cellulose
Colloidal silicon dioxide
Talc
Glyceryl Dibehenate

Film-coating:
Opadry® 06A590025-CN

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30℃.
Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

HDPE bottles with a polypropylene cap and a foil induction seal.
Each bottle contains 180 tablets.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Healol Pharmaceuticals Sdn. Bhd.
74, 74-1, 74-2, 74-3, Pusat Bandar Wangsa Maju, Jalan Wangsa Delima 6 (1/27F), Seksyen 5 Wangsa Maju, 53300 Kuala Lumpur, Malaysia.

8. MARKETING AUTHORISATION NUMBER(S)

MAL26076039AZ

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of revision: 18/08/2026

HEALOL SEVELAMER
Sevelamer carbonate
film coated tablets
800 mg

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示意图
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客户名称	山东新华制药股份有限公司		
产品名称	新华Sevelamer carbonate说明书		
成品尺寸	279*306mm		
追溯码			
材质工艺	60g白卡 印刷、裁切		
制版单号	24C-5-017改5	日期	2026.8.19
制作人员	冯盼盼	校对	杨倩倩

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