AUSTRALIAN PRODUCT INFORMATION
SEVELAMER APOTEX (SEVELAMER CARBONATE) TABLETS

1 NAME OF THE MEDICINE

Sevelamer carbonate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SEVELAMER APOTEX film-coated tablets contain 800 mg of sevelamer carbonate on an anhydrous basis.

For the full list of excipients see section **6.1 List of Excipients**

3 PHARMACEUTICAL FORM

White to off-white, oval film-coated tablets imprinted with “R789” on one side and are blank on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the management of hyperphosphataemia in adult patients with stage 4 and 5 chronic kidney disease.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Sevelamer carbonate is available as tablets.

Note that powder for oral suspension can be available from other brand/s.

It is recommended to continue monitoring serum phosphorus levels in patients when switching between sevelamer carbonate tablets and powder.

Sevelamer carbonate should be taken in conjunction with a prescribed diet for the management of hyperphosphatemia.

Sevelamer carbonate 800 mg tablets must be taken three times per day with meals at a dosage based on individual patient requirements to control phosphate levels. Tablets should be swallowed intact and should not be crushed, chewed, or broken into pieces prior to administration. Patients should swallow the tablets whole with water.

Starting dose

The recommended starting dose of sevelamer carbonate is 2.4 to 4.8 g per day based on clinical needs and phosphorus level (Table 1). Sevelamer carbonate must be taken three times per day with meals.

Table 1 - Starting dose for patients not taking a phosphate binder

Serum Phosphorus	Total daily dose taken over three meals per day
> 1.78 and < 2.42 mmol/L	2.4 g
≥ 2.42	4.8 g

For patients previously on calcium based phosphate binders, Table 2 below provides guidance on switching to sevelamer carbonate. Serum phosphorus levels should be monitored to ensure optimal daily doses.

Table 2 - Starting dose for patients switching from calcium carbonate to sevelamer carbonate

Calcium Carbonate (500 mg*) (tablets per meal)	Sevelamer carbonate 800 mg tablet (tablets per meal)
1 tablet	1
2 tablets	2
3 tablets	3

* elemental calcium of 200 mg

Titration and Maintenance

Serum phosphorus levels must be monitored and the dose of sevelamer carbonate titrated every 2- 4 weeks until an acceptable serum phosphorus level is reached, with regular monitoring thereafter. The dose may be increased or decreased by one tablet per meal at two week intervals as necessary (Table 3). Patients taking sevelamer carbonate should adhere to their prescribed diets.

Table 3 - Dose titration guideline 800 mg tablets

Serum Phosphorus	Sevelamer Carbonate Dose
> 1.78 mmol/L	Increase 1 tablet per meal at 2 week intervals
1.13 – 1.78 mmol/L	Maintain current dose
< 1.13 mmol/L	Decrease 1 tablet per meal

In clinical practice, treatment will be continuous based on the need to control serum phosphorus levels and the daily dose is expected to be an average of approximately 6 g per day.

4.3 CONTRAINDICATIONS

Sevelamer carbonate tablets are contraindicated in patients:

- known to be hypersensitive to sevelamer carbonate or any of the other components of the tablet
- with hypophosphataemia
- with bowel obstruction

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

The safety and efficacy of sevelamer carbonate have not been established in adult patients with chronic kidney disease not on dialysis with serum phosphorus < 1.78 mmol/L.

The safety and efficacy of sevelamer carbonate in patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders, severe constipation or major GI tract surgery have not been established. Consequently, caution should be exercised when sevelamer carbonate is used in patients with these GI disorders.

Cases of serious inflammatory disorders of the GI tract (including serious complications such as bleeding, perforation, ulceration, necrosis and colitis) with the presence of sevelamer crystals have been reported. Sevelamer carbonate should be re-evaluated in patients who develop severe gastrointestinal symptoms.

Intestinal obstruction and ileus/subileus

In very rare cases, intestinal obstruction and ileus/subileus have been observed in patients during treatment with sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate. Constipation may be a preceding symptom. Patients who are constipated should be monitored carefully while being treated with sevelamer carbonate. Sevelamer carbonate treatment should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal symptoms.

Fat-soluble vitamins

Depending on dietary intake and the nature of chronic kidney disease, dialysis patients may develop low vitamin A, D, E and K levels. It cannot be excluded that sevelamer carbonate can bind fat-soluble vitamins contained in ingested food. Therefore, in patients not taking these vitamins, monitoring vitamin A, D and E levels and assessing vitamin K status through the measurement of thromboplastin time should be considered and these vitamins should be supplemented if necessary. 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.

In clinical trials, there was no evidence of reduction in serum levels of vitamins with the exception of a one year clinical trial in which sevelamer hydrochloride treatment was associated with reduction of 25 - hydroxyvitamin D (normal range 10 to 55 µg/mL) from 39 ± 22 µg/mL to 34 ± 22 µg/mL ($p < 0.01$). Most patients in sevelamer hydrochloride clinical trials received vitamin supplements, which is typical of patients on haemodialysis. Indirect evidence of a reduction in vitamin K levels (an increase in haemorrhage corrected by vitamin K supplementation) was also seen in animals.

Folate deficiency

There is at present insufficient data to exclude the possibility of folate deficiency during long term sevelamer carbonate treatment.

Swallowing and choking difficulties

Uncommon case reports of difficulty swallowing the sevelamer carbonate tablet have been reported. Many of these cases involved patients with contributing co-morbid conditions affecting the ability to swallow including swallowing disorders or oro-esophageal abnormalities. Caution should be exercised when sevelamer carbonate tablets are used in these patients.

Hypocalcaemia/hypercalcaemia

Patients with CKD may develop hypocalcaemia or hypercalcaemia. Sevelamer carbonate tablets do not contain calcium. Serum calcium levels should be monitored and elemental calcium should be given as a supplement in case of hypocalcaemia.

Metabolic acidosis

Patients with chronic kidney disease are predisposed to metabolic acidosis. As part of good clinical practice, monitoring of serum bicarbonate levels is therefore recommended.

Peritonitis

Patients receiving dialysis are subject to certain risks for infection specific to dialysis modality. Peritonitis is a known complication in patients receiving peritoneal dialysis and in a clinical study with sevelamer hydrochloride, a greater number of peritonitis cases were reported in the sevelamer group than in the control group. Patients on peritoneal dialysis should be closely monitored to ensure the correct use of appropriate aseptic technique with the prompt recognition and management of any signs and symptoms associated with peritonitis.

Anti-arrhythmic and anti-seizure medicinal products

Caution should be exercised when prescribing sevelamer carbonate to patients also taking antiarrhythmic and anti-seizure medicinal products (see section **4.5 Interactions with other medicines and other forms of interactions**).

Hypothyroidism

Closer monitoring of patients with hypothyroidism co-administered with sevelamer carbonate and levothyroxine is recommended (see section **4.5 Interactions with other medicines and other forms of interactions**).

Hyperparathyroidism

Sevelamer carbonate is not indicated for the control of hyperparathyroidism. In patients with secondary hyperparathyroidism sevelamer carbonate should be used within the context of a multiple therapeutic approach, which could include calcium as supplements, 1,25 - dihydroxy Vitamin D3 or one of its analogues to lower the intact parathyroid hormone (iPTH) levels.

Use in the elderly

No data available.

Paediatric use

The safety and effectiveness of sevelamer carbonate in patients below the age of 18 years have not been established.

Effects on laboratory tests

No data available.

Instructions to patients

The contents of sevelamer carbonate tablets expand in water thus tablets should be swallowed intact and should not be crushed, chewed or broken into pieces prior to administration (see section **4.2 Dose and method of administration**).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interaction studies have not been conducted in patients on dialysis.

In interaction studies in healthy volunteers, sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, decreased the bioavailability of ciprofloxacin by approximately 50% when co-administered with sevelamer hydrochloride in a single dose study. Consequently, sevelamer carbonate should not be taken simultaneously with ciprofloxacin.

Reduced levels of cyclosporin, mycophenolate mofetil and tacrolimus have been reported in transplant patients when co-administered with sevelamer hydrochloride without any clinical consequences (i.e. graft rejection). The possibility of an interaction cannot be excluded and a close monitoring of blood concentrations of cyclosporin, mycophenolate mofetil and tacrolimus should be considered during the use of combination and after its withdrawal.

During post-marketing experience, very rare cases of increased TSH levels have been reported in patients co-administered sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate and levothyroxine. Closer monitoring of TSH levels is therefore recommended in patients receiving both medications.

During post-marketing experience, very rare cases of increased phosphate levels have been reported in patients taking proton pump inhibitors co-administered with sevelamer carbonate.

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

In interaction studies in healthy volunteers, sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, had no effect on the bioavailability of digoxin, warfarin, enalapril or metoprolol.

In 14 healthy subjects receiving 2.4 g of sevelamer hydrochloride three times a day with meals for two days sevelamer did not alter the pharmacokinetics of a single dose of warfarin. In 14 healthy subjects receiving 9.6 grams of sevelamer carbonate once daily with a meal, sevelamer did not alter the pharmacokinetics of a single dose of warfarin.

In 19 healthy subjects receiving 2.4 grams of sevelamer hydrochloride three times a day with meals for 2 days, sevelamer did not alter the pharmacokinetics of a single dose of digoxin. In 18 healthy subjects receiving 9.6 grams of sevelamer carbonate once daily with a meal, sevelamer did not alter the pharmacokinetics of a single dose of digoxin.

Sevelamer carbonate is not absorbed and may affect the bioavailability of other medicinal products. When administering any medicinal product where a reduction in the bioavailability could have a clinically significant effect on safety or efficacy, the medicinal product should be administered at least one hour before or three hours after sevelamer carbonate, or the physician should consider monitoring blood levels.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data from the effect of sevelamer on fertility in humans. Sevelamer hydrochloride administered orally to male and female rats prior to and throughout mating, at doses up to 4.5 g/kg/day (more than 15 times the maximum tested human dose on a mg/kg basis for a 50 kg person) did not alter mating or fertility.

Use in pregnancy

Category B3

The safety of sevelamer carbonate has not been established in pregnant or lactating women. Sevelamer carbonate should only be given to pregnant or lactating women if clearly needed and after careful risk/benefit analysis has been conducted for both the mother and foetus or infant.

Studies in animals have shown minimal reproductive toxicity when sevelamer was administered to rats at high doses.

There was no evidence of teratogenicity in rabbits or rats following oral administration of sevelamer hydrochloride during the period of organogenesis at respective doses 1.5 and 4.5 g/kg/day (5 and 15 times respectively on a mg/kg basis for a 50 kg human). In rats receiving doses of 1.5 and 4.5 g/kg/day during organogenesis, there was reduced or irregular ossification of foetal bones at exposures of 5 and 15 times the maximum tested human dose. In rabbits receiving 1 g/kg/day during organogenesis, there was an increase in early resorptions leading to a reduction in the number of live foetuses per liter at an exposure 3.3 times the maximum recommended human dose.

Oral administration of sevelamer hydrochloride to female rats throughout gestation and lactation at doses of 0.1 - 1 g/kg/day (exposure 0.3 - 3.3 times the maximum recommended human dose) did not affect the birth or growth of their offspring or their postnatal development.

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 less than 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).

Use in lactation

Oral administration of sevelamer hydrochloride to female rats throughout gestation and lactation did not have any adverse effects on offspring (see Use in Pregnancy).

No adequate and controlled studies have been conducted using sevelamer in nursing mothers. 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. Sevelamer carbonate tablets should only be used during breastfeeding if the potential benefit justifies the potential risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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 treatment with sevelamer hydrochloride and 49 with sevelamer carbonate). The safety profile of sevelamer carbonate in patients not on dialysis was similar to the safety profile of the drug in patients on dialysis.

Data possibly or probably related to sevelamer from these studies are listed below by frequency. The reporting rate is classified as very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 0.1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 4 below provides a tabulated list of adverse reactions in CKD patients on haemodialysis (Study GD3-163-201). Patients received sevelamer carbonate 800 mg tablets and sevelamer hydrochloride 800 mg tablets for eight weeks each with meals. Adverse reactions occurring in ≥ 5% of patients are listed by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT).

Table 4 - Treatment Emergent AEs (All Causality) Occurring in ≥ 5% of Patients during Either Treatment Regimen in Study GD3-163-201

System Organ Class Preferred Term	Sevelamer Carbonate Tablets TID (N = 73) Patients %	Sevelamer Hydrochloride Tablets TID (N = 78) Patients %
Gastrointestinal Disorders		
Nausea	9.6	12.8
Vomiting	8.2	10.3
Diarrhoea	2.7	6.4
Gastro-oesophageal reflux disease	1.4	5.1
General Disorders and Administration Site Conditions		
Fatigue	1.4	5.1
Infections and Infestations		
Urinary tract infection	8.2	1.3
Injury, Poisoning and Procedural Complications		
Arteriovenous fistula site complication	6.8	1.3
Arteriovenous fistula site haemorrhage	5.5	2.6
Arteriovenous fistula thrombosis	4.1	11.5
Investigations		
Carbon dioxide decreased	5.5	5.1
Metabolism and Nutrition Disorders		
Hypercalcaemia	8.2	2.6
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	5.5	3.8
Pain in extremity	4.1	7.7
Nervous System Disorders		
Dizziness	8.2	3.8
Headache	4.1	5.1
Respiratory, Thoracic and Mediastinal Disorders		
Cough	5.5	3.8

The most frequently occurring (≥ 2% of patients) undesirable effects possibly or probably related to sevelamer were mainly in the gastrointestinal disorders system organ class (Table 5). Most of these adverse reactions were mild to moderate in intensity.

Table 5 - Adverse Reactions in Studies GD3-163-201 (N = 73), SVCARB00205 (N = 31), and SVCARB00105 (N = 49) in CIOMS format

System Organ Class	Common (≥ 1/100 to < 1/10)
Gastrointestinal Disorders	Nausea
	Constipation
	Vomiting
	Abdominal pain upper
	Diarrhoea
	Dyspepsia
	Flatulence
Investigations	Carbon dioxide decreased

POST-MARKETING EXPERIENCE

During post- marketing experience, the adverse events (listed by frequency) in Table 6 have been reported in patients receiving sevelamer carbonate although no direct relationship to sevelamer carbonate could be established:

Table 6 - Summary of post-marketing adverse events

System Organ Class	Preferred Term
Gastrointestinal disorders	*Not known:* Abdominal pain, ileus, intestinal obstruction and intestinal perforation
Skin and Subcutaneous Tissue Disorders	*Not known:* Hypersensitivity, Pruritus, rash

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems and contact Apotex Medical Information Enquiries/Adverse Drug Reaction Reporting on 1800 195 055.

4.9 OVERDOSE

In CKD patients on dialysis, the maximum dose studied was 14.4 grams of sevelamer carbonate and 13 grams of sevelamer hydrochloride. Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been given to normal healthy volunteers in doses of up to 14.4 grams per day for 8 days with no adverse effects.

There are no reported cases of overdose with sevelamer carbonate or sevelamer hydrochloride in patients. Since sevelamer is not absorbed, the risk of systemic toxicity is low.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Patients with end-stage renal disease (ESRD) retain phosphorus and can develop hyperphosphataemia. High serum phosphorus can precipitate serum calcium resulting in ectopic calcifications. When the product of serum calcium and phosphorus concentrations (Ca x P) exceeds 4.46 $(mmol/L)^2$, there is an increased risk that ectopic calcification will occur. Hyperphosphataemia plays a role in the development of secondary hyperparathyroidism in renal insufficiency. An increase in parathyroid hormone (PTH) levels is characteristic of patients with chronic renal failure. Increased levels of PTH can lead to the bone disease osteitis fibrosa. A decrease in serum phosphorus may decrease serum PTH levels**.**

Sevelamer contains multiple amines separated by one carbon from the polymer backbone, which become partially protonated in the intestine and interact with phosphorus molecules through ionic and hydrogen bonding. By binding phosphorus in the gastrointestinal tract and decreasing absorption, sevelamer lowers the phosphorus concentration in the serum.

Sevelamer decreases the incidence of hypercalcaemic episodes as compared to patients using calcium based phosphate binders alone, probably because the product itself does not contain calcium.

Sevelamer carbonate 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 counter ion. While the counter ions differ for the two salts, the polymer itself, the active moiety, is the same.

Sevelamer treatment also results in a lowering of low density lipoprotein (LDL) and total serum cholesterol levels by increasing faecal excretion of bile acids. 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, both the mean total-cholesterol and LDL- cholesterol declined by 15-39%. This effect is observed after 2 weeks. Triglycerides, HDL cholesterol and albumin did not change.

Clinical trials

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 hydrochloride N = 220) and three active- controlled open-label studies with treatment durations of 8 to 52 weeks (sevelamer hydrochloride 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. Six of the active-controlled studies are described here (three sevelamer hydrochloride and three sevelamer carbonate studies). In all clinical studies patients were instructed to take sevelamer with meals.

Sevelamer hydrochloride versus calcium acetate, Cross-Over Study in Haemodialysis Patients (GTC-36- 301)

In a cross-over study of sevelamer hydrochloride and calcium acetate, 84 ESRD patients on haemodialysis who were hyperphosphataemic (serum phosphorus > 1.94 mmol/L) following a 2-week phosphate binder washout period were randomised to receive either sevelamer hydrochloride for 8 weeks followed by calcium acetate for 8 weeks or calcium acetate for 8 weeks followed by sevelamer hydrochloride for 8 weeks. Treatment periods were separated by a 2-week phosphate binder washout period. Patients started on sevelamer hydrochloride capsules or calcium acetate tablets 3 times per day with meals. Over each 8-week treatment period, at three separate time points the dose of either agent could be titrated up one capsule or tablet per meal (3 per day) to control serum phosphorus. Sevelamer hydrochloride and calcium acetate both significantly decreased mean serum phosphorus by about 0.65 mmol/L (Table 7).

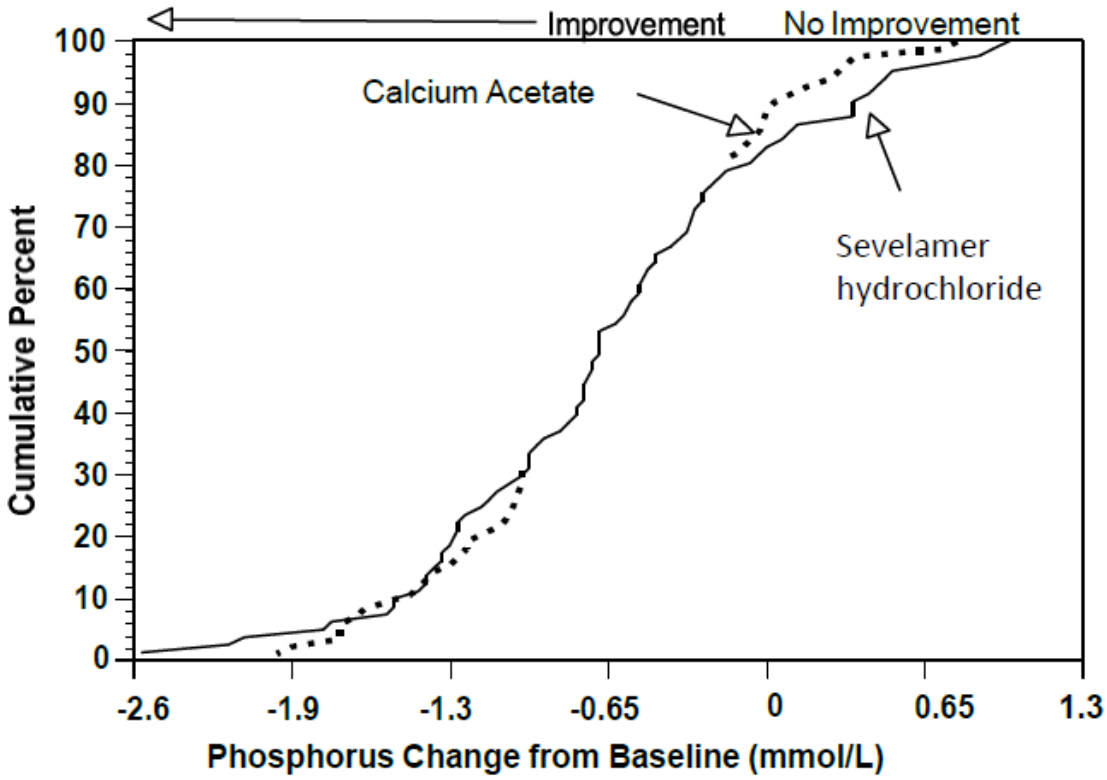
Table 7 - Mean serum phosphorus at baseline and endpoint

	Sevelamer hydrochloride (n = 81)	**Ca Acetate (N = 83)**
Baseline at End of Washout	2.7 mmol/L	2.6 mmol/L
Change from Baseline at Endpoint (95% Confidence Interval)	- 0.65 mmol/L* (-0.81, -0.48)	- 0.68 mmol/L* (-0.84, -0.55)

*p < 0.0001, within treatment group comparison

Figure 1 illustrates that the proportion of patients achieving a given level of serum phosphorus lowering is comparable between the two treatment groups. For example, about half the patients in each group had a decrease of at least 0.65 mmol/L at endpoint. Successful control of serum phosphorus in chronic kidney disease patients is multifactorial including reduction of dietary phosphate intake, removal of phosphate with dialysis and inhibition of intestinal phosphate absorption with phosphate binders. As seen in Figure 2, some of the patients in GTC-36-301 did not respond to sevelamer hydrochloride treatment. Not all patients achieve phosphorus control with sevelamer hydrochloride alone, especially at the doses administered in this study (average actual daily dose 4.3 g/day). Later studies which employed higher doses of sevelamer hydrochloride (i.e. GTC-49-301-average actual daily dose 6.5 g/day) had a better rate of phosphorus response.

Figure 1 - Cumulative percent of patients (y-axis) attaining a phosphorus change from baseline at least as great as the value of the x-axis. A shift to the left of a curve indicates a better response.



Average daily consumption at the end of treatment was 4.9 g sevelamer hydrochloride (range of 0.0 to 12.6 g) and 5.0 g of calcium acetate (range of 0.0 to 17.8 g). During calcium acetate treatment, 22% of patients developed serum calcium ≥ 2.75 mmol/L on at least one occasion versus 5% for sevelamer hydrochloride ($p < 0.05$). Thus the risk of developing hypercalcaemia is less with sevelamer hydrochloride compared to calcium acetate.

Mean LDL cholesterol and mean total cholesterol declined significantly on sevelamer hydrochloride capsules treatment (-24% and -15% respectively). Neither LDL nor total cholesterol changed on calcium acetate treatment. Triglycerides, high-density lipoprotein (HDL) cholesterol, and albumin did not change on either treatment.

Similar reductions in serum phosphorus and LDL cholesterol were observed in an 8-week open - label, uncontrolled study of 172 end-stage renal disease patients on haemodialysis.

Sevelamer hydrochloride versus calcium in Haemodialysis Patients (GTC-49-301)

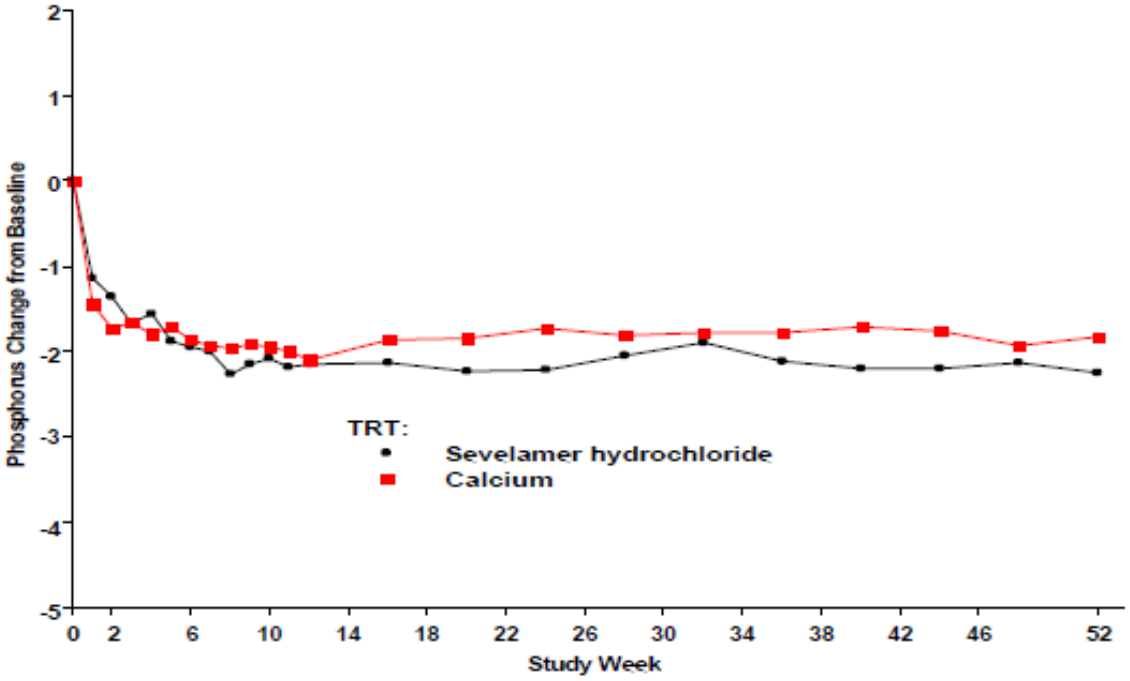
In a parallel study of sevelamer hydrochloride and calcium acetate or calcium carbonate, two hundred ESRD patients on haemodialysis who were hyperphosphataemic (serum phosphorus > 1.78 mmol/L) following a two-week phosphate binder washout period were randomised to receive sevelamer hydrochloride 800 mg tablets (N = 99) or calcium, either calcium acetate (N = 54) or calcium carbonate (N = 47). Seventy seven percent of sevelamer hydrochloride patients (N = 76) and 80% of the calcium patients (N = 81) completed the full 52 weeks of treatment with the major reason for dropout in the sevelamer hydrochloride group was gastrointestinal adverse events. Calcium acetate and calcium carbonate produced comparable decreases in serum phosphorus. At week 52, using last observation carried - forward, sevelamer hydrochloride and calcium both significantly decreased mean serum phosphorus (Table 8).

Table 8 - mean serum phosphorus at baseline and end of treatment (52 weeks)

Serum Phosphorus	Sevelamer hydrochloride (N = 76)	Calcium (N = 81)
Baseline	2.38 mmol/L	2.33 mmol/L
Change from baseline at 52 weeks	-0.72 mmol/L	-0.64 mmol/L
Mean serum phosphorus levels at 52 weeks	1.67 mmol/L	1.68 mmol/L

Figure 2, 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 2 - mean phosphorus change from baseline for patients who completed 52 weeks of treatment



Average daily consumption at the end of the treatment was 6.5 g of sevelamer hydrochloride (range of 0.8 to 13 g) or approximately eight 800 mg tablets (range of 1 to 16 tablets), 4.6 g of calcium acetate (range of 0.7 to 9.5 g) and 3.9 g of calcium carbonate treatment, 34% of patients in the calcium group developed serum calcium corrected for albumin ≥ 2.75 mmol/L on at least one occasion versus 7% for sevelamer hydrochloride ($p < 0.05$). Thus the risk of developing hypercalcaemia is less with sevelamer hydrochloride compared to calcium salts.

Mean LDL cholesterol and mean total cholesterol declined significantly ($p < 0.05$) on sevelamer hydrochloride treatment (-32% and -20%, respectively) compared to calcium (+0.2% and -2%, respectively) triglycerides, HDL cholesterol, and albumin did not change.

Sevelamer hydrochloride versus calcium acetate in Peritoneal Dialysis Patients (REN-003-04)

In a parallel study of sevelamer hydrochloride or calcium acetate in peritoneal dialysis patients, one hundred and forty three patients on peritoneal dialysis who were hyperphosphatemic (serum phosphorus ≥ 1.78 mmol/L) following a two-week phosphate binder washout period were randomized to receive sevelamer hydrochloride 800 mg tablets (N = 97) or calcium acetate (N = 46). Treatment for 12 weeks with sevelamer was non-inferior to calcium acetate in reducing serum phosphorus. There were statistically significant changes in serum phosphorus ($p < 0.001$) from baseline for both the sevelamer hydrochloride (0.52 mmol/L from 2.42 mmol/L) and calcium acetate (-0.58 mmol/L from 2.35 mmol/L) groups.

Average daily consumption at the end of treatment was 5.9 g for sevelamer hydrochloride (range of 0.8 to 14.3 g) and 4.3 g for calcium acetate (range of 1.7 to 9.0 g). During calcium acetate treatment, 18% of patients had a serum calcium corrected for albumin ≥ 2.75 mmol/L at the end of the study versus 2% for sevelamer hydrochloride ($p = 0.001$).

There appeared to be a trend for a decrease from baseline for total, LDL, and non-HDL cholesterol levels in patients receiving sevelamer hydrochloride. The long term impact of sevelamer hydrochloride on cardiovascular related morbidity and mortality is unclear.

Cross-Over Study of Sevelamer carbonate 800 mg Tablets and Sevelamer hydrochloride 800 mg Tablets (GD3-163-201)

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 cross-over 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. Forty of those completing the cross-over portion of the study were entered into a two-week washout period during which patients were instructed not to take any phosphate binders; this confirmed the activity of sevelamer in this study.

Table 9 - Mean time weighted serum phosphorous levels

Serum phosphorous	Sevelamer carbonate (n = 56)	Sevelamer hydrochloride (n = 56)	Geometric LSM Ratio (Carb/HCl)	90% CI ratio
Arithmetic mean ± SD mmol/L	1.5 ± 0.3	1.5 ± 0.3	0.99	0.95, 1.03

Cross-Over Study of Sevelamer carbonate Powder and Sevelamer hydrochloride Tablets (SVCARB00205)

Stage 5 CKD patients on haemodialysis were entered into a four-week sevelamer hydrochloride run-in period and 31 patients received, in random order, sevelamer carbonate powder and sevelamer hydrochloride tablets for four weeks each with no intervening washout. Study dose during the cross-over 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 6.0 g/day divided among meals for sevelamer carbonate powder and 6.4 g/day divided among meals for sevelamer hydrochloride tablets.

Table 10 - Mean time weighted serum phosphorous levels

Serum phosphorous	Sevelamer carbonate (n = 21)	Sevelamer hydrochloride (n = 21)	Geometric LSM Ratio (Carb/HCl)	90% CI ratio
Arithmetic mean ± SD mmol/L	1.6 ± 0.5	1.7 ± 0.4	0.95	0.87, 1.03

Sevelamer carbonate Powder Once a Day versus Sevelamer hydrochloride Tablet Three Times a Day Dosing (GD3-199- 301)

Stage 5 CKD patients on haemodialysis with a serum phosphate level of > 1.78 mmol/L after washout from baseline therapies were randomized in a 2:1 ratio to receive either sevelamer carbonate powder once-daily (N = 144) or sevelamer hydrochloride as a tablet with the dose divided three times per day (N = 73) for 24 weeks. The initial dose for the two groups was 4.8 g/day. At the end of the study, the total daily dose was 6.2 g/day of sevelamer carbonate powder once daily and 6.7 g/day of sevelamer hydrochloride tablets three times per day. A greater percentage of subjects on the once daily dose than three times per day regimen discontinued therapy prematurely, 35% versus 15%. The reasons for discontinuation were largely driven by adverse events and withdrawal of consent in the once daily dosing regimen. Serum phosphate levels and calcium-phosphate product were better controlled on the three times per day regimen than on the once daily regimen. Mean serum phosphorus decreased 0.66 mmol/L for sevelamer carbonate powder once daily and 0.96 mmol/L for sevelamer hydrochloride tablets three times per day.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Pharmacokinetic studies have not been carried out with sevelamer carbonate in humans. Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, is not absorbed from the gastrointestinal tract. A mass balance study using ^{14}C-sevelamer hydrochloride in 16 healthy male and female volunteers showed that sevelamer is not systemically absorbed. No absorption studies have been performed in patients with renal disease.

Excretion

In dogs, > 94% of [14C-]- sevelamer carbonate was excreted in the faeces within 24 hours and ≤ 0.07% was recovered in urine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

In an *in vitro* mammalian cytogenetics 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. Based on the available evidence, sevelamer hydrochloride is considered unlikely to be genotoxic *in vivo* following oral administration.

Carcinogenicity

Sevelamer hydrochloride was administered in the diet to rats and mice for two years. In mice and female rats, there was no increase in the incidence of tumours. In male rats, there was an increased incidence of transitional cell papillomas and transitional cell carcinomas in the urinary bladder at a dose of 3 g/kg/day, which is 10 times the maximum daily human dose (mg/kg basis) for a 50 kg person examined in clinical trials.

To investigate the mechanism of action of proliferative effects (development of urinary bladder transitional cell papilloma) noted previously in the rat study of sevelamer hydrochloride, sevelamer carbonate was administered to male rats by dietary admixture for a period of 13 weeks at nominal dose-levels of 250, 1000 or 4500 mg/kg/day followed by 6 week treatment free period. Sevelamer carbonate was well tolerated at all dose-levels. No treatment-related changes were seen in the macroscopic or microscopic examinations. The urine of the mid and high dose sevelamer carbonate groups contained significant levels of calcium oxalate crystals. Immunohistochemical analyses did not identify increased cell proliferation in the urinary bladder or kidneys. This study did not replicate the proliferative changes observed in the urinary tract in a previous study of sevelamer hydrochloride.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Mannitol
- crospovidone
- hyprolose
- silicon dioxide
- zinc stearate
- Opadry AMB complete film coating system OY-B-29000 Translucent (ARTG PI No. 106232)
- OPACODE monogramming ink S-1-17823 BLACK (ARTG PI No. 12108)

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not refrigerate. Protect from moisture. Keep the container tightly closed.

6.5 NATURE AND CONTENTS OF CONTAINER

SEVELAMER APOTEX tablets are packaged in white high-density polyethylene bottles (HDPE), with a child resistant polypropylene cap.

SEVELAMER APOTEX tablets are available in pack sizes of 30[§*], 180 and 270[*].

§ Starter pack

* Presentations currently not-marketed.

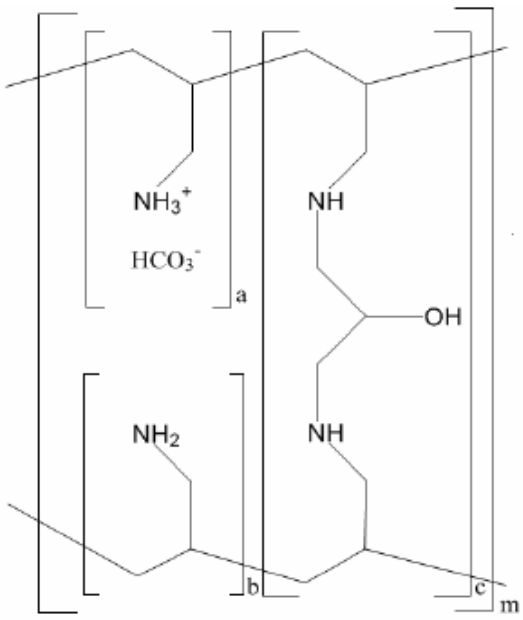
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Sevelamer carbonate tablets contain sevelamer, a non-absorbed phosphate binding cross-linked polymer, free of metal and calcium. Sevelamer is a white to off-white powder comprising of a partial carbonate salt with approximately 40% amine carbonate and 60% free base. Sevelamer carbonate is amorphous, hygroscopic and hydrophilic, but insoluble in water with a pH range of 8-10.5 as a 1% aqueous slurry.

Chemical structure



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

The primary amine groups shown in the structure are derived directly from poly (allylamine hydrochloride). The cross - linking groups consist of two secondary amine groups derived from poly (allylamine hydrochloride) and one molecule of epichlorohydrin.

Molecular Formula: $(C_3H_7N.nH_2CO_3)_{810z}$ $(C_9H_{18}N_2O.nH_2CO_3)_{95z}$ where z = a large number

Chemical Name: poly (allylamine-*co-N,N'*-diallyl-1,3-diamino-2-hydroxypropane) carbonate salt.

CAS number 845273-93-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

9 November 2018

10 DATE OF REVISION

9 July 2019

Summary table of changes

Section Changed	Summary of new information
All	Reformatted product information; minor editorial changes
8	Addition of Distributor address