NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Renvela 800mg film coated tablet

Renvela 1.6g powder for oral suspension

Renvela 2.4g powder for oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Renvela film-coated tablet contains 800 mg of sevelamer carbonate on an anhydrous basis.

Each Renvela sachet contains 1.6 g or 2.4 g of sevelamer carbonate for oral suspension on an anhydrous basis.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Renvela film-coated tablets: white oval film-coated tablets imprinted with “RENVELA 800” on one side and are blank on the other side.

Renvela powder for oral suspension: pale yellow powder free from foreign particles in a sachet.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Renvela is indicated for the management of hyperphosphataemia in adult patients with stage 4 and 5 chronic kidney disease.

4.2 DOSE AND METHOD OF ADMINISTRATION

Renvela is available as tablets or powder for oral suspension.

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

Renvela 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.

Renvela 1.6 or 2.4 g powder sachet must be taken three times per day with meals individually or in combination at a dosage based on individual patient requirements to control phosphate levels. The powder should be dispersed in water (40 ml for 1.6 g powder sachet and 60 ml for 2.4 g powder sachet) prior to administration. Multiple sachets may be mixed together, as long as the appropriate amount of water is used. Patients should drink the preparation within 30 minutes.

Starting dose

The recommended starting dose of Renvela is 2.4 to 4.8 g per day based on clinical needs and phosphorus level (Table 1). Renvela 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 Renvela. Serum phosphorus levels should be monitored to ensure optimal daily doses.

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

Calcium Carbonate (500mg*) (tablets per meal)	Renvela 800mg tablet (tablets per meal)	Renvela Powder (g per meal)
1 tablet	1	–
2 tablets	2	1.6
3 tablets	3	2.4

* elemental calcium of 200mg

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

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 Renvela should adhere to their prescribed diets.

Table 3 - Dose titration guideline 800mg tablets

Serum Phosphorus	Renvela 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 CONTRAINDICATION

Renvela is 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 Renvela 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 Renvela 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 Renvela is used in patients with these GI disorders.

Cases of serious inflammatory disorders of the GI tract (with complications including haemorrhage, perforation, ulceration, necrosis and colitis/cecal mass) with the presence of sevelamer crystals have been reported (Section 4.8 Undesirable Effects). Inflammatory disorders may resolve upon Renvela discontinuation. Treatment with Renvela 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 Renvela. Renvela 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 Renvela 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 Renagel 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 Renagel 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 Renvela treatment.

Swallowing and choking difficulties

Uncommon case reports of difficulty swallowing the Renvela 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 Renvela tablets are used in these patients. Consider using Renvela powder for oral suspension in patients with a history of difficulty swallowing.

Hypocalcaemia/hypercalcaemia

Patients with CKD may develop hypocalcaemia or hypercalcaemia. Renvela does 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 Renvela 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

Renvela is not indicated for the control of hyperparathyroidism. In patients with secondary hyperparathyroidism Renvela 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.

Instructions to Patients

The contents of Renvela 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).

Use in the elderly

No data available

Paediatric use

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

Effect on Laboratory Tests

No information available.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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 Renvela, decreased the bioavailability of ciprofloxacin by approximately 50% when co-administered with sevelamer hydrochloride in a single dose study. Consequently, Renvela should not be taken simultaneously with ciprofloxacin.

Reduced levels of ciclosporin, 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 ciclosporin, 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 Renvela to patients also taking these medications.

In interaction studies in healthy volunteers, sevelamer hydrochloride, which contains the same active moiety as Renvela, 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.

Renvela 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 Renvela, or the physician should consider monitoring blood levels.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy (Category B3)

The safety of Renvela has not been established in pregnant or lactating women. Renvela 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).

Breast-feeding

Oral administration of sevelamer hydrochloride to female rats throughout gestation and lactation did not have any adverse effects on offspring (see 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. Renvela tablets should be used during breastfeeding only if the potential benefit justifies the potential risks.

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on ability to drive and use machines have been performed.

4.8 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.

There are limited data on the safety of sevelamer carbonate powder, however based on the fact that it contains the same active ingredient as the sevelamer carbonate tablet, the adverse event profiles of the two formulations should be similar.

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	5.5	3.8
Muscle spasms	4.1	7.7
Pain in extremity		
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

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

During post- marketing experience, the following adverse events have been reported in patients receiving Renvela: Hypersensitivity, pruritus, rash, abdominal pain and uncommon cases of ileus, intestinal obstruction and intestinal perforation.

Cases of serious inflammatory disorders of the gastrointestinal tract (with complications including haemorrhage, perforation, ulceration, necrosis, colitis, and intestinal mass) associated with the presence of sevelamer crystals have been reported (see Section 4.4 Special Warnings and Precautions for Use).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at https://nzphvc.otago.ac.nz/reporting/

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 New Zealand National Poisons Information Centre (telephone 0800 POISON or 0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

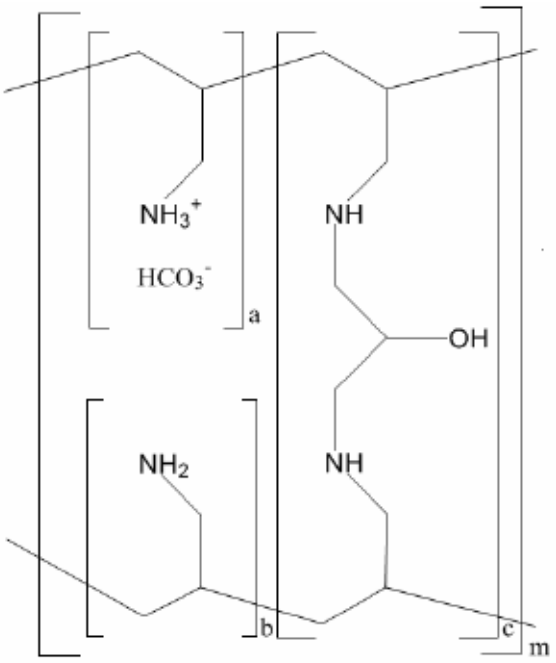
Pharmacotherapeutic group: Treatment of hyperphosphataemia. ATC code: V03A E02

Renvela contains 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

The structure is presented in Figure 1.

Figure 1 - 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

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 Registry Number

845273-93-0

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**.**

Renvela 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.

Renvela (sevelamer carbonate) was developed as a pharmaceutical alternative to sevelamer hydrochloride (Renagel). 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.

Renvela 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 efficacy and safety

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 Renagel and three clinical trials used Renvela.

The Renagel 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 Renvela 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 Renvela powder (N=31) and one randomized, parallel, open-label study using Renvela powder (N=144) dosed once daily or Renagel tablets (N=73) dosed three times daily for 24 weeks. Six of the active-controlled studies are described here (three Renagel and three Renvela studies). In all clinical studies patients were instructed to take sevelamer with meals.

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

In a cross-over study of sevelamer 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 Renagel for 8 weeks followed by calcium acetate for 8 weeks or calcium acetate for 8 weeks followed by Renagel for 8 weeks. Treatment periods were separated by a 2-week phosphate binder washout period. Patients started on Renagel 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. Renagel and calcium acetate both significantly decreased mean serum phosphorus by about 0.65 mmol/L (Table 6).

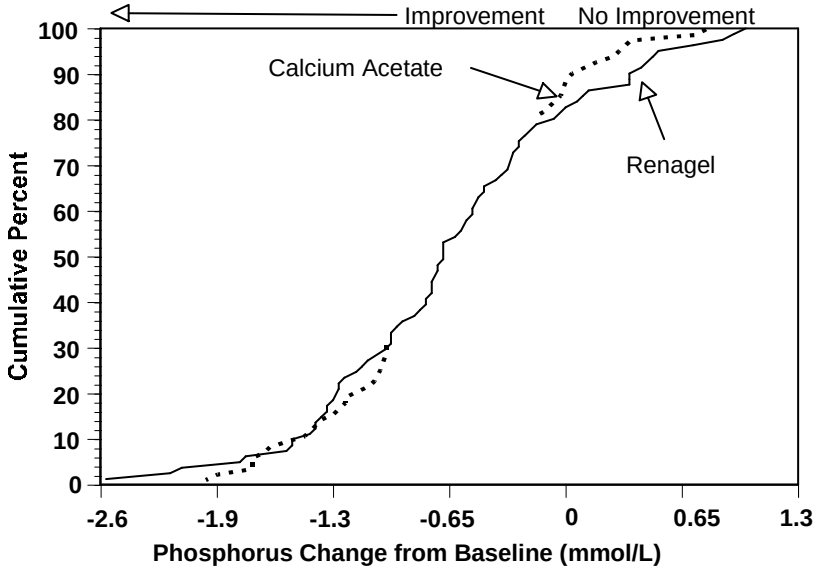
Table 6 - Mean serum phosphorus at baseline and endpoint

	Renagel (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 2 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 treatment. Not all patients achieve phosphorus control with sevelamer 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 (i.e. GTC-49-301-average actual daily dose 6.5 g/day) had a better rate of phosphorus response.

Figure 2 - 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 (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 ($p < 0.05$). Thus the risk of developing hypercalcaemia is less with Renagel compared to calcium acetate.

Mean LDL cholesterol and mean total cholesterol declined significantly on Renagel 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.

Renagel versus calcium in Haemodialysis Patients (GTC-49-301)

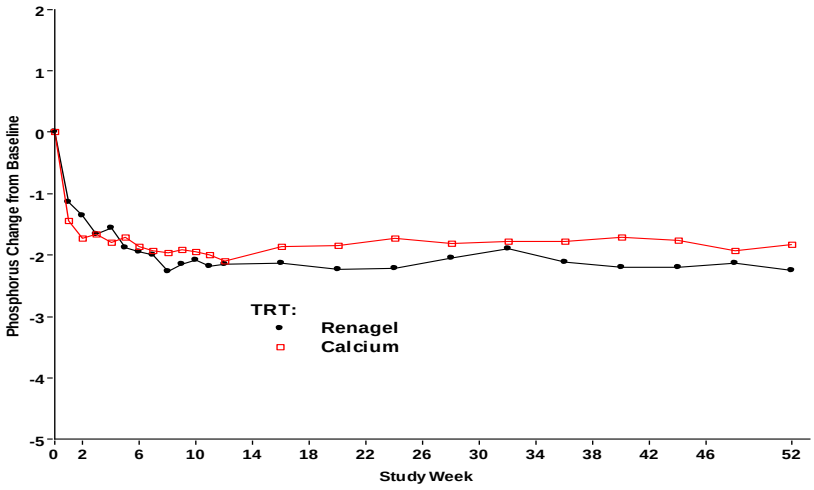
In a parallel study of Renagel and calcium acetate or calcium carbonate, two hundred ESRD patients on haemodialysis who were hyperphosphataemic (serum phosphorus >1.78 mmol/L) following a two-week phosphate binder washout period were randomised to receive Renagel 800 mg tablets (N=99) or calcium, either calcium acetate (N=54) or calcium carbonate (N=47). Seventy seven percent of Renagel 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 Renagel group was gastrointestinal adverse events. Calcium acetate and calcium carbonate produced comparable decreases in serum phosphorus. At week 52, using last observation carried - forward, Renagel and calcium both significantly decreased mean serum phosphorus (Table 7).

Table 7 - mean serum phosphorus at baseline and end of treatment (52 weeks)

Serum Phosphorus	Renagel (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 3, 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 3 - 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 (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 Renagel ($p<0.05$). Thus the risk of developing hypercalcaemia is less with Renagel compared to calcium salts.

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

Renagel 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 Renagel 800 mg tablets (N=97) or calcium acetate (N=46). Treatment for

12 weeks with Renagel 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 Renagel (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 Renagel (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 Renagel ($p=0.001$).

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

Cross-Over Study of Renvela 800 mg Tablets and Renagel 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 8 - 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 Renvela Powder and Renagel 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 9 - 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

Renvela Powder Once a Day versus Renagel 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. In dogs, >94% of [^{14}C-]-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

Renvela tablets: microcrystalline cellulose, sodium chloride, purified water and zinc stearate. The tablet coating contains; hypromellose and diacetylated monoglycerides. OPACODE WB monogramming ink NS‑78‑17715 BLACK is the tablet printing ink.

Each sachet of Renvela powder contains the following excipients: RB26 Genzyme N&A citrus cream FL PWD #24660 (PI-109424), propylene glycol alginate, sodium chloride, sucralose, and iron oxide yellow.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

36 months

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

Tablets

Renvela tablets are packaged in white high-density polyethylene bottles (HDPE), with a child resistant polypropylene cap and an induction seal.

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

Powder

Renvela powder is packaged in opaque, foil lined heat sealed sachets.

Renvela powder 1.6 g sachets are available in boxes of 15[§*], 60[*] or 90[*] count sachets.

Renvela powder 2.4 g sachets are available in boxes of 15[§*], 60[*] or 90[*] count sachets.

[§] Starter pack

* Presentations currently not-marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

sanofi-aventis new zealand limited
Level 8, 56 Cawley Street
Ellerslie, Auckland
New Zealand
Toll Free Number (medical information): 0800 283 684
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

30 July 2015

10 DATE OF REVISION OF THE TEXT

09 April 2020

SUMMARY OF CHANGES

Section changed	Summary of new information
Title; 2; 3; 4; 5; 6; 7; & 8	Editorial
4.4	Safety updates to Gastrointestinal disorders section in line with CCDSv8
4.8	Addition of Post-marketing experience to align with CCDSv8