Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Sevelamer carbonate

Proprietary Product Name: Renvela / Sevelamer Carbonate Winthrop/ Sevelamer Carbonate Sanofi

Sponsor: Sanofi Aventis Australia Pty Ltd

October 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
AE	Adverse event
APD	Automated Peritoneal Dialysis
AV	Arteriovenous
CAPD	Continuous Ambulatory Peritoneal Dialysis
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CER	Clinical Evaluation Report
CHMP	Committee on Human Medicinal Products
CKD	Chronic kidney disease
CMI	Consumer Medicines Information
EMA	European Medicines Agency
ESRD	End-stage renal disease
ET	Early termination
EU	European Union
FMD	Flow mediated dilation
GFR	Glomerular filtration rate
GI	Gastrointestinal
HCl	Hydrochloride
HDL	High density lipoprotein
KDOQI	Kidney Disease Outcomes Quality Initiative
LDL	Low density lipoprotein
LV	Left ventricular
MedDRA	Medical Dictionary of Regulatory Activities
mg	Milligram
mL	Milliliter
mmol	Millimol
NSAIDS	Non-steroidal Anti-inflammatory Drugs
PD	Peritoneal dialysis
PI	Product Information
PT	Preferred Term

Abbreviation	Meaning
PTH	Parathyroid hormone
QD	Once daily
RDPLF	French Peritoneal Dialysis Registry
RMP	Risk Management Plan
SAE	Serious adverse event
SCB	Sevelamer carbonate
SHC	Sevelamer hydrochloride
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TDS	Three times daily
URR	Urea Reduction ratio

I. Introduction to product submission

Submission details

Type of submission:	New Chemical Entity (new salt of an existing active)
Decision:	Approved
Date of decision:	14 April 2015
Active ingredient(s):	Sevelamer carbonate
Product name(s):	Renvela/Sevelamer Carbonate Winthrop/Sevelamer Carbonate Sanofi
Sponsor's name and address:	Sanofi Aventis Australia Pty Ltd 12-24 Talavera Road, Macquarie Park, NSW, 2113
Dose form(s):	Film coated tablets and Powder for oral suspension
Strength(s):	800 mg (tablets) and 1.6 g and 2.4 g (powder for oral suspension
Container(s):	High Density Polyethylene (HDPE) bottles (tablets) or Surlyn (Ionomer Resin)/Aluminium (Al)/polyethylene (PE)/ Polyethylene Terephthalate (PET) laminate sachets in cartons (powder for oral suspension)
Pack size(s):	30, 180 and 270 tablets and 15, 60 and 90 sachets (powder for oral suspension)]
Approved therapeutic use:	*Renvela/Sevelamer Carbonate Winthrop/ Sevelamer Carbonate Sanofi is indicated for the management of hyperphosphataemia in adult patients with Stage 4 and 5 chronic kidney disease.*
Route(s) of administration:	Oral (PO)
Dosage:	Sevelamer Carbonate Sanofi 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. Sevelamer Carbonate Sanofi 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. For starting dose and maintenance titration please see PI (Attachment 1).
ARTG number (s):	220889, 220890, 220892, 220886, 220893, 220888, 220894, 220887 and 220891

Product background

This AusPAR describes the application by the sponsor to register sevelamer carbonate, an alternative sevelamer salt to the currently registered sevelamer hydrochloride.

The sponsor has proposed that sevelamer carbonate be indicated for

> *The management of hyperphosphataemia in adult patients with Stage 4 and stage 5 chronic kidney disease.*

The proposed indication is identical to the approved indication for sevelamer hydrochloride (Renagel, Genzyme Australia, a subsidiary of Sanofi). Sevelamer hydrochloride is registered as 400 mg and 800 mg tablets but not as a powder for solution.

Chronic kidney disease (CKD) is associated with hyperphosphataemia in its later stages, when a significant degree of renal function has been lost. Continued phosphate ingestion, reduced bone uptake of phosphate or increased release of phosphate from high bone turnover results in hyperphosphataemia. Hyperphosphataemia can result in significant pathology including secondary hyperparathyroidism, renal osteodystrophy, arterial calcification and increased morbidity and mortality. The goal of therapy with phosphate binding agents is to limit the absorption of dietary intestinal phosphate that results from an adequate protein intake to prevent hyperphosphataemia.

Sevelamer is a non-absorbed phosphate cross-linked polymer, free of metal and calcium. Sevelamer salts become ionised in the stomach, releasing their anions (carbonate or hydrochloride). The protonated amines of sevelamer bind phosphate ions in the gut and the sevelamer-phosphate complexes transit the gut and are not absorbed. Sevelamer also binds bile salts and has previously been shown to reduce serum lipids.

The first sevelamer salt developed was sevelamer hydrochloride. Data from clinical trials suggested that treatment with sevelamer hydrochloride may be associated with hyperchloraemia and/or reduction in serum bicarbonate with the potential to increase the acidaemia in patients with pre-existing metabolic acidosis. This is because, upon ionisation, the hydrochloride ion is liberated from the amine groups attached to the polymer backbone. The protonated amines are non-specific anion binders and may also bind bicarbonate in the gut.

In sevelamer carbonate a carbonate counter ion replaces the hydrochloride counter ion of sevelamer hydrochloride. The sponsor stated that sevelamer carbonate was developed to mitigate this risk while maintaining the same phosphate binding properties of the original polymer. Hence, sevelamer carbonate was developed for use in patients experiencing acid-base balance problems, for which sevelamer hydrochloride is contraindicated.

The sponsor has proposed two dosage forms of sevelamer carbonate: a film coated tablet and a powder for reconstitution to an oral suspension. The sponsor proposes a starting dose of 2.4 to 4.8 g per day based on clinical needs and the phosphorus level and sevelamer carbonate must be taken three times per day with meals. Additional dosing instructions are provided for patients not taking a phosphate binder and those switching from calcium acetate to sevelamer and for dose titration of sevelamer based on serum phosphorous levels with the goal of lowering serum phosphorus.

The rationale for development of the oral powder for suspension was to provide an alternative dosage form for patients with difficulty with or a dislike for swallowing tablets or who have a high pill burden. The sponsor considers the clinical development program for sevelamer carbonate a continuation of the development program for sevelamer hydrochloride.

Besides the general guidelines, there are specific guidelines adopted by the TGA relevant to this submission,:

- Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev1)
- Clinical Requirements for Locally Applied, Locally Acting Products, containing Known Constituents (pp 193 – 198 of Rules 1998(3C) – 3CC12a

Regulatory status

Sevelamer carbonate has not been previously considered by the TGA's Advisory Committee on Prescription Medicines (ACPM).

Renagel was registered on 30 June 2005 (AUST R 101553 and 101550).

Table 1 summarises the international regulatory status of Renvela.

Table 1: International regulatory status

Country	Presentations	Submission Date	Status (Approved; Review Ongoing; Withdrawn; Rejected)
European Union	800mg film-coated tablets 1.6g powder for oral suspension 2.4g powder for oral suspension	5 March 2008	Approved 10 June 2009 Renvela is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis. Renvela is also indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus > 1.78 mmol/L. Renvela should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy Vitamin D3 or one of its analogues to control the development of renal bone disease
United States of America	800 mg film-coated tablets	20 December 2006	Approved 19 October 2007 Renvela (sevelamer carbonate) is indicated for the control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis
	0.8 g powder for oral suspension 2.4 g powder for oral suspension	31 March 31 2008	Approved 12 August 2009 Renvela (sevelamer carbonate) is indicated for the control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis
Canada	800 mg film-coated tablets	27 June 2008	Approved 8 July 2010 Control of serum phosphorus in adult patients with chronic kidney disease (CKD) on dialysis.

Note the 0.8 g powder for oral suspension is approved in the US.

In the USA, sevelamer carbonate (Renvela) 800 mg tablets were first approved on 29 October 2007 for the control of serum phosphorus in patients with CKD on dialysis, and 0.8 g and 2.4 powders for oral suspension formulations were subsequently approved for that indication on 12 August 2009.

In the EU, sevelamer 800 mg film coated tablets and 1.6 g and 2.4 g powder for oral suspension formulations were approved on 5 March 2008.

In the EU, sevelamer carbonate (Renvela) is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis and for the control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus > 1.78 mmol/L. The EU indications state that sevelamer carbonate (Renvela) should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy Vitamin D3 or one of its analogues to control the development of renal bone disease

Sevelamer carbonate has also been approved in Canada (8 July 2009; 800 mg film-coated tablets), Switzerland (10 November 2011; 800 mg film-coated tablets and 2.4 g powder for oral suspension) and Singapore (6 November 2009; 800 mg film-coated tablets). An application to register sevelamer carbonate in New Zealand has not yet been submitted.

Product Information

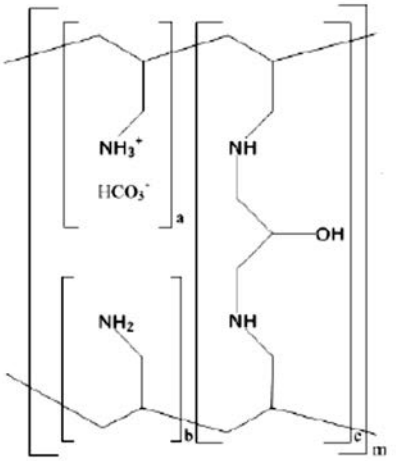
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Drug substance (active ingredient)

The drug substance, sevelamer carbonate, has the following structure (Figure 1):

Figure 1: Chemical structure of sevelamer carbonate



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

The active pharmaceutical ingredient (API) and finished product are made by the same Genzyme Ltd sites as those used to make the finished product and sevelamer hydrochloride used in the Renagel products, which are also registered to the same sponsor. While the anions differ for the two salts, the polymer, which is the active moiety responsible for binding of phosphate, is the same. The replacement of hydrochloride with carbonate mitigates the potential worsening of pre-existing metabolic acidosis.

The polymer is a high molecular weight, water-insoluble synthetic phosphate binder cross-linked poly(allylamine) cross-linked with epichlorhydrin as 1,3-2-diamino-2-hydroxypropyl linkages. The cross-linking groups consist of two secondary amine groups derived from the starting material poly(allylamine) hydrochloride and epichlorhydrin. A portion of the amine is present as the carbonate salt at similar levels to sevelamer hydrochloride.

Sevelamer carbonate is a phosphate binding anionic exchange resin that is not absorbed from the gastrointestinal tract. The polymeric backbone includes multiple amines separated by one carbon. Upon ingestion, the tablets readily disintegrate. The polymer's amines become protonated in the stomach releasing the salt anions. The protonated amines (cationic) of sevelamer bind to negatively charged phosphate anions via ionic and hydrogen bonding in the intestine and the complexed phosphate is excreted faecally. The net effect is the reduction in the amount of phosphate available for absorption and reduced serum phosphorous. Phosphate is preferentially bound because it is polyvalent. Binding phosphate in the gastrointestinal (GI) tract consequently lowers serum phosphate levels.

The drug substance specification includes tests and limits for soluble oligomers, residual cross-linker and monomer identified as related substances. Limits for impurities are the same as those applied to the API in the existing Renagel products.

Drug product

The proposed products are an immediate-release film-coated tablet and powder for oral suspension.

Tablets

The manufacturing process for the tablets involves conventional wet granulation of screened API with microcrystalline cellulose and sodium chloride in purified water in a high shear granulator. The wet mix is blended with zinc stearate and compressed into tablet cores before film coating, imprinting with black ink and packaging.

Excipients are conventional. Tablets are white oval film-coated tablets imprinted with 'RENVELA 800' on one side and are blank on the other side.

The tablet assay limits do not comply with Therapeutic Goods Order (TGO) No. 78. A Section 14 (S14) exemption was granted for the Renagel sevelamer hydrochloride products in this regard. An S14 exemption has been sought for the proposed tablets in this regard, with justification based on indirect method of determination, the basis that the API is polymeric in nature and the basis that the limits are the same as those in draft European Pharmacopeia (EP) and US Pharmacopeia (USP) monographs.

The stability data provided supports a shelf life of 3 years when stored below 25ºC with the conditions '*Do not refrigerate. Protect from moisture. Keep container tightly closed/airtight in the proposed packaging'*.

Powder for oral suspension

The manufacturing process for the proposed powder for oral suspension products involves combining the API with flavour, sweetener and colour excipients. An 'overfill' has been declared to allow withdrawal of label claim. The proposed products are direct scales.

Excipients are conventional. The powder for suspension is a pale yellow powder. The presentation strengths are distinguished by the labelling.

The stability data provided supports a shelf life of 3 years when stored below 25^{0}C with the conditions '*Do not refrigerate. Protect from moisture'*.

Biopharmaceutics

Sevelamer carbonate is a phosphate binding anionic exchange resin that is not systemically or locally absorbed, so satisfies the requirements under Section 15.3 of Guidance 15 of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM)[1], as an absolute bioavailability study cannot be performed on the molecule.

Comparative in vitro equilibrium studies and equivalency kinetic phosphate binding studies of the two carbonate and hydrochloride salts (consistent with the FDA guidance for Sevelamer[2]), were used to demonstrate equivalence between the phosphate binding capacity of sevelamer hydrochloride (Renagel) and sevelamer carbonate (Renvela) to

[1] http://www.tga.gov.au/guidance-15-biopharmaceutic-studies
[2] http://www.fda.gov/downloads/Drugs/.../Guidances/ucm089621.pdf

enable the clinical data previously evaluated for Renagel to support the present submission.

A summary of the pivotal equilibrium and kinetic studies (TR-2527-07-SC) compared sevelamer hydrochloride tablets (800 mg), sevelamer carbonate tablets (800 mg) and sevelamer carbonate powder [0.8 g (not proposed for registration), 1.6 g and 2.4 g sachets] for phosphate binding under varying physiologically relevant conditions that may be encountered in the GI tract included varying phosphate concentrations with and without acid pre-treatment.

Equilibrium studies

Equilibrium binding studies compared sevelamer hydrochloride tablets (800 mg), sevelamer carbonate tablets, and sevelamer carbonate powder for oral suspension (0.8 g, 1.6 g, and 2.4 g sachets) under conditions of constant time with varying concentrations of phosphate, with and without acid pre-treatment. Eight different concentrations of phosphate salt solution were used with a fixed amount of sevelamer hydrochloride or sevelamer carbonate. The following physiologically relevant phosphate concentrations were used: 1, 2.5, 5, 7.5, 10, 14.5, 30, and 38.7 mM potassium dihydrogen orthophosphate (KH_2PO_4). The binding affinity constant (k_1) and the binding capacity constant (k_2) were calculated from an eight point binding isotherm. Linear regression of every calibration curve produced an r^2 value > 0.99. The bound and unbound phosphate concentrations and the % phosphate bound were calculated for all test articles.

The equilibrium studies concluded equivalent phosphate binding with and without acid pre-treatment. No significant differences in equilibrium binding capacity (k_2) was apparent for acid pre-treated and non-treated tablets and powder. Variation in apparent binding affinity constants (k_1) was explained by slight interference of the carbonate ion with the study media as increasing carbonate ion concentration caused a linear decline in affinity constants. This was not considered significant, given that both forms of sevelamer will be protonated after exposure to stomach fluids and will be similarly protonated salts of cross-linked poly(allylamine hydrochloride).

Kinetic studies

Kinetic studies were provided to demonstrate that the phosphate binding of sevelamer hydrochloride 800 mg tablets, sevelamer carbonate 800 mg tablets and sevelamer carbonate powder (0.8 g, 1.6 g and 2.4 g sachets) was similarly rapid and independent of initial phosphate concentration.

Phosphate binding was reached in approximately 15 mins and indicate that incubation time is sufficient to ensure maximum binding. The report considers that the time over which the differences are seen to be short, compared to the overall time in the GI tract. Given this, no significant differences between in vivo phosphate binding are expected. The results show phosphate binding in tablet and powder form to be similarly rapid and comparable on mass basis.

Clinical studies

The dossier also refers to clinical studies performed on sevelamer hydrochloride as well as clinical studies conducted with sevelamer carbonate. The two main studies and their findings are summarised in relation to phosphorous binding and other studies are listed below.

Study GD3-163-201 was conducted to show equivalence in controlling serum phosphorous between sevelamer hydrochloride tablets and sevelamer carbonate tablets when administered 3 times a day with meals.

Serum phosphorous levels were measured in 79 subjects (40 randomised to carbonate/HCl and 39 to the HCl/carbonate treatment periods) dosed for 8 weeks with one of two treatments and 8 weeks with the other treatment after a 5-week phosphate binder run-in period. The original study did not include a 2-week washout. After implementation during the study only 47 entered the washout and 40 subjects completed the washout.

The mean serum phosphorous levels were 1.49 ± 0.3 mmol/L for sevelamer carbonate treatment and 1.52 ± 0.3 mmol/L for sevelamer HCl treatment. The geometric least square mean ratio was 0.99 with a 90% confidence interval (CI) of 0.95 - 1.03 (that is, within the 80 to 125% range) indicating that sevelamer carbonate and sevelamer HCl are equivalent in controlling serum phosphorous. Regression analyses for dose groups also showed 90% CIs for daily dose of no more than (NMT) 4.8 g, for the range 4.8 to 9.6 g and for doses > 9.6 g. This indicates phosphorous binding equivalency, regardless of dose group.

Regression analysis in the washout and p value showed those on higher prescribed doses had greater increases in serum phosphorous during the washout, confirming dose level is a reasonable marker of hyperphosphataemia. Other parameters including lipids (low-density lipoprotein (LDL) cholesterol and high density lipoprotein (HDL) cholesterol and triglycerides) were measured.

Study SVCARB00205 was conducted to show equivalence in controlling serum phosphorous between sevelamer hydrochloride tablets and sevelamer carbonate powder for oral suspension when administered 3 times a day with meals.

This was a 6 period study: 2 week screening and wash-out period, 4 week sevelamer HCl tablet run-in period, 4 week treatment period (Period 1), a second 4 week treatment period (Period 2 when the alternative study medication was taken) and 1 week follow-up. The treatment sequences were:

- Sevelamer carbonate powder dosed three times a day (TDS) with meals for 4 weeks followed by sevelamer HCl tablets dosed TDS with meals for 4 weeks.
- Sevelamer HCl tablets dosed TDS with meals for 4 weeks followed by sevelamer carbonate powder dosed TDS with meals for 4 weeks.

Mean prescribed doses were 7.7 ±3.1 g/day sevelamer carbonate powder and 7.8 ± 3.0 g/day sevelamer HCl tablets. Compliance between treatments was similar (81 to 83%). The mean serum phosphorous levels was 1.6 ± 0.5 mmol/L for the sevelamer carbonate powder treatment and 1.7 mmol/L for the sevelamer HCl tablet treatment. The geometric least square mean ratio was 0.95 with 90% CI of 0.87 to 1.03 (within the 80 to 125% range).

Mean serum calcium (albumin-adjusted) phosphorous was 3.7 ± 1.1 $mmol^2/L^2$ during sevelamer carbonate treatment and 3.7 ± 0.8 $mmol^2/L^2$ for sevelamer HCl treatment. No statistically significant difference in serum calcium (albumin-adjusted) phosphorous was observed between the treatments. The geometric least square mean ratio was 0.98 with a 90% CI of 0.88 to 1.09, that is, within the 80 to 125% range). Other parameters including lipids (LDL cholesterol and HDL cholesterol and triglycerides) were measured.

Study GD3-199-301 was conducted in haemodialysis patients comparing a once daily dose with TDS. Results from this study did not demonstrate non inferiority between the 2 dosing regimens; however, results from the once daily dosing suggested clinically meaningful reductions from baseline in serum phosphorous and a high clinical response rate.

Study SVCARB00105 was conducted to show that sevelamer carbonate tablets, dosed TDS with meals in controlling serum phosphorous levels in CKD patients not on dialysis had a similar safety and efficacy profile in the dialysis population.

Advisory committee considerations

The application was not considered by the TGA's Pharmaceutical Subcommittee of the Advisory Committee on Prescription Medicines (ACPM).

Quality summary and conclusions

The sponsor has provided satisfactory responses to the issues raised by the quality evaluator.

Registration is recommended with respect to chemistry, quality control and biopharmaceutic aspects.

III. Nonclinical findings

Introduction

All nonclinical studies, except one, were conducted according to Good Laboratory Practice (GLP). The nonclinical submission provides sufficient evidence to enable assessment of sevelamer carbonate.

Pharmacokinetics/Pharmacology

The absorption study for sevelamer carbonate confirmed that the sevelamer polymer is minimally absorbed. The majority is excreted in the faeces within 24 hours. This is consistent with data for sevelamer hydrochloride. Therefore, further studies of pharmacokinetics were not required.

Previous studies had shown increased calcium deposition in the glandular stomach of rats following cessation of sevelamer hydrochloride treatment. A safety pharmacology study was performed to characterise calcium deposition during recovery. This demonstrated that the deposition of calcium occurred within 3 days of cessation and that frequency and severity of calcium deposits decreased with time. The deposition of calcium is likely related to the large fluctuations in serum calcium levels following cessation of sevelamer hydrochloride administration. The transient nature indicates minimal safety concern.

Toxicology

As sevelamer is not absorbed systemically, relative blood volumes, metabolic rate and clearance rates are not relevant to dose comparisons between experimental animals and humans. Therefore, direct comparisons have been made between doses on an mg/kg basis as a means of expressing relative exposures. A 50 kg human was used to make the comparison, with an average dose of 6 g/day and expected maximum dose of 14.4 g/day based on the highest dose tested in clinical trials.

Acute toxicity

Single doses of 10, 15 and 20 g/kg were administered to Sprague-Dawley (SD) rats over 24 hours, with a 2 week recovery period. No adverse effects were observed. Therefore, the No observable adverse effect level (NOAEL) was set at 20 g/kg/day. The exposure ratio is 167 for the average dose in humans and 69 for the expected maximum dose.

Repeat dose toxicity

In the pivotal studies for sevelamer hydrochloride, the main toxicological findings were dose-dependent reductions in serum vitamins, lipids and/or folic acid. These studies were conducted for 6 months in rats (0.6, 3.0 and 6.0 g/kg/day, Study GT-01-TX-6) and 12 months in dogs (0.2, 0.6 and 2.0 g/kg/day, Study GT-01-TX-10). Similar observations on vitamin levels were made in 4 weeks (rat and dog) and 13 week (dog) studies of sevelamer hydrochloride at similar or higher doses.

In the dog bridging study, no significant effect was found on vitamin A, D and E levels following 4 weeks administration of sevelamer carbonate or sevelamer hydrochloride at 0.2 and 1 g/kg/day (Study GT-153-TX-2). In rats, reduced vitamin E levels were observed following 4 weeks administration of 1.0 and 4.5 g/kg/day sevelamer carbonate and sevelamer hydrochloride (Study GT-153-TX-1). In contrast, vitamin D levels increased in female rats administered 4.5 g/kg/day sevelamer carbonate and sevelamer hydrochloride. No changes in vitamin A were observed in rats. The observations between the bridging studies and pivotal studies for sevelamer hydrochloride were generally consistent for comparable doses.

Treatment related effects were observed in serum and urine chemistry of dogs and rats in the bridging studies. However, these effects were generally similar between sevelamer carbonate and sevelamer hydrochloride. It is possible that the duration of these studies was inadequate to see all potential toxicological outcomes. On balance, the evidence from the bridging studies does not indicate exaggerated toxicity of sevelamer carbonate in comparison to sevelamer hydrochloride. Therefore, the conclusions from the pivotal studies of sevelamer hydrochloride can be used to inform the toxicological profile of sevelamer carbonate.

Other toxicity studies

A 13 week study was conducted to investigate the potential formation of urothelial tumours in rats treated with 0.25, 1.0 and 4.5 g/kg/day sevelamer carbonate, followed by a 6 week recovery period for the highest dose group. No tumour development or abnormal cell proliferation in urinary bladder or kidneys were observed. Development of calcium oxalate crystals in urine was time and dose dependent but resolved during recovery. The data indicated low risk of urothelial carcinogenesis with sevelamer carbonate administration.

An additional study was conducted to assess toxicological potential of allylamine impurity which may be present in sevelamer products at up to 10 parts per million (ppm) (maximum residual allylamine specified at end of shelf life). This study assessed the effect of 4.5 g/kg/day sevelamer hydrochloride with either low allylamine impurity (<1 ppm) or spiked to 10 ppm. There was no discernible effect of 10 ppm allylamine on toxicological outcomes, supporting the safety of the specified maximum level.

Nonclinical summary and conclusions

- The nonclinical submission contained pharmacokinetic data, toxicity studies including bridging data and other toxicity studies for both sevelamer carbonate and sevelamer hydrochloride.
- Similar to sevelamer hydrochloride, sevelamer carbonate is minimally absorbed from the GI tract and is predominantly excreted in the faeces.
- No adverse effects were observed in the single-dose toxicity study. The NOAEL was set at 20 g/kg/day.

- Four week repeat-dose toxicity studies compared the toxicity of sevelamer carbonate to sevelamer hydrochloride in rats and dogs. Similar effects on weight gain, fat soluble vitamins, serum biochemistry and urine chemistry were observed for the different salts of sevelamer. These effects were also similar to those observed in the pivotal repeat-dose toxicity studies of sevelamer hydrochloride (6 month in rats and 12 months in dogs). An additional 13 week study demonstrated that the majority of effects were reversed following 6 weeks recovery.
- A safety pharmacology study on sevelamer hydrochloride observed that the calcium deposition in the glandular stomach following cessation of drug administration was transient and therefore not of toxicological concern.
- There are no nonclinical objections to the registration of sevelamer carbonate.
- The nonclinical evaluator recommended amendments to the draft Product Information but the details of these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Chronic kidney disease (CKD) is associated with serum phosphorous levels resulting in significant pathophysiology including secondary hyperparathyroidism, renal osteodystrophy, arterial calcification and increased mortality.[3,4,5] The goal of therapy with sevelamer carbonate is to bind with phosphate in the intestinal tract in order to limit its absorption and prevent hyperphosphataemia in patients with Stage 4 and 5 CKD.

Sevelamer is an anion exchange resin with a polymeric structure of multiple amines separated by one carbon from the polymer backbone. Sevelamer salts become protonated in the stomach releasing the anions. The protonated amines of sevelamer bind negatively charged dietary phosphate ions in the intestine and the bound complex is passed out through the gut. The first salt of sevelamer developed for clinical purposes was sevelamer hydrochloride and the choice of salt was based on production considerations. However, data from clinical studies in CKD patients with hyperphosphataemia indicates that treatment with sevelamer hydrochloride may be associated with an increase in serum chloride and/or reduction in serum bicarbonate and the potential for worsening of pre-existing metabolic acidosis. The chloride anion liberated from the sevelamer backbone may contribute to these effects. Consequently, sevelamer carbonate was developed in order to mitigate the potential adverse effects on acid-base balance associated with release of the chloride iron from sevelamer hydrochloride, while maintaining the same phosphate binding properties of the original product.

[3] Delmez JA, Slatopolsky E. Hyperphosphatemia: its consequences and treatment in patients with chronic renal disease. Am J Kidney Dis. 1992;19(4):303-17.
[4] Young EW, Albert JM, Satayathum S, Goodkin DA, Pisoni RL, Akiba T, et al. Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. Kidney Int. 2005;67(3):1179-87.
[5] Slinin Y, Foley RN, Collins AJ. Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: the USRDS waves 1, 3, and 4 study. J Am Soc Nephrol. 2005;16(6):1788-93.

Sevelamer carbonate has been formulated as a tablet and as a powder for oral suspension. The sponsor states that the powder formulation will provide an alternative dosage form that could benefit those patients who dislike or have difficulties in swallowing tablets or who have a high pill burden. The sponsor states that the powder formulation '*fulfils an unmet need for those hyperphosphataemic CKD patients unable to take tablets for any reasons'.*

The clinical rationale for development of sevelamer carbonate is considered to be acceptable.

Guidance

See *Product background* above.

Contents of the clinical dossier

Scope of the clinical dossier

The sponsor states that the

> '*clinical development program for sevelamer carbonate is a continuation of the development program for sevelamer hydrochloride. The two sevelamer salts have been shown to be therapeutically equivalent, in terms of control of serum phosphorus, and have a similar safety profile with the important distinction that the carbonate salt has reduced propensity for association with potentially adverse acid base changes. The demonstration of equivalence between the two salts allows the use of the sevelamer hydrochloride data to support the MAA for Renvela (sevelamer carbonate)*'.

The sponsor provided an abridged submission supporting the registration of sevelamer carbonate that included in vivo and in vitro data aimed at establishing the equivalence of sevelamer carbonate and sevelamer hydrochloride. Demonstration of therapeutic equivalence of the two sevelamer salts would allow the known efficacy and safety data for sevelamer hydrochloride to be extrapolated to sevelamer carbonate. The submission did not repeat all the studies which had been submitted for registration of sevelamer hydrochloride with sevelamer carbonate. However, the submission included clinical efficacy and safety study reports previously provided and evaluated to support registration of sevelamer hydrochloride.

The submission contained the following clinical information:

- 1 new in vitro bioequivalence study.
- 2 new drug-drug pharmacokinetic (PK) interaction studies (1 of which included pharmacodynamic (PD) data).
- 7 previously submitted PK studies.
- 4 new, clinical efficacy and safety studies considered to be key to the current submission to register sevelamer carbonate, including
  - a 4 week, cross-over therapeutic equivalence study in patients on haemodialysis;
  - an 8 week, cross-over therapeutic study in patients on haemodialysis;
  - a 24 week, parallel group, non-inferiority study in patients on haemodialysis;
  - an open label, single arm, 12 week study in patients not on dialysis.

- 3 clinical efficacy and studies involving sevelamer carbonate not directly relevant to the current submission.
- 3 postmarketing reports relating to sevelamer carbonate.
- 17 previously submitted studies relating to sevelamer hydrochloride.
- 1 pooled safety analysis relating to sevelamer hydrochloride.
- Literature references.

Paediatric data

The proposed indication specifies that sevelamer carbonate is for the management hyperphosphataemia in adult patients with Stage 4 and 5 CKD. The sponsor drew attention to an ongoing Phase II study in the US to evaluate the safety and tolerability of sevelamer carbonate in hyperphosphataemic paediatric patients aged <18 years with CKD. The sponsor anticipates that a study report will be available by the middle of 2016.

Good clinical practice

The sponsor stated that the clinical studies were conducted in accordance with the principles of Good Clinical Practice (GCP), International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Pharmacokinetics

Studies providing pharmacokinetic data

The submission included 3 new studies providing PK data supporting the application to register sevelamer carbonate and 7 previously submitted studies providing PK data supporting the application to register sevelamer hydrochloride. The approach adopted in this clinical evaluation report (CER) to the evaluation of the PK data has been to fully evaluate the 3 new studies and to briefly summarise the 7 previously submitted and evaluated studies.

The 3 new studies were:

- Study TR-2527-07-SC: an in vitro bioequivalence study of sevelamer hydrochloride (Renagel, 800 mg tablets) and sevelamer carbonate (800 mg tablets, 0.8, 1.6 and 2.4 g sachets).
- Study SVCARB01107: an open label study to assess the potential pharmacokinetic interaction of a single dose of sevelamer carbonate with a single dose of warfarin sodium in healthy volunteers.
- Study SVCARB03107: an open label study to assess the potential pharmacokinetic interaction of a single dose of sevelamer carbonate with a single dose of oral digoxin and to investigate the pharmacodynamic effects of sevelamer carbonate on phosphorous absorption and excretion in healthy volunteers.

The 7 previously submitted and evaluated studies were:

- GTC-10-801: an open label, parallel-dose study aimed to assess the non-absorbability of sevelamer hydrochloride.
- ICR013769: DDI study to assess the effect of sevelamer hydrochloride on the PKs of digoxin.

- ICR013281: DDI study to assess the effect of sevelamer hydrochloride on the PKs of warfarin.
- GTC-45-803: DDI study to assess the effect of sevelamer hydrochloride on the PKs of metoprolol.
- GTC-45-804: DDI study to assess the effect of sevelamer hydrochloride on the PKs of enalapril.
- GTC-45-807: DDI study to assess the effect of sevelamer hydrochloride on the PKs of ciprofloxacin.
- GTC-45-808: DDI study to assess the effect of sevelamer hydrochloride on the PKs of iron.

Evaluator's conclusions on pharmacokinetics

The submission included no clinical bioequivalence studies comparing sevelamer carbonate with sevelamer hydrochloride. The sponsor states that it is not possible to conduct conventional PK studies as sevelamer is not absorbed. The sponsor's justification is considered to be acceptable. The non-absorbability of sevelamer hydrochloride was confirmed in the previously evaluated Study GTC-10-801 in healthy young and elderly (> 65 years of age) male and female subjects (n=20). On average, greater than 99% of the administered dose was recovered in the faeces of each subject (n=16). There was no detectable amount of sevelamer found in the blood of any subject at any time point (n=16). The Renagel CER states that, based on the results of this study '*conventional ADME studies were not conducted*'.

In order to investigate the bioequivalence of the two sevelamer salts, the sponsor undertook an in vitro equilibrium and kinetic binding study [TR-2527-07-SC]. This study demonstrated that sevelamer hydrochloride tablets (800 mg), sevelamer carbonate tablets (800 mg) and sevelamer carbonate powder (0.8 g, 1.6 g, and 2.4 g sachets) were equivalent based on phosphate binding with and without acid pre-treatment. In particular, the Langmuir plots for the equilibrium binding samples (with and without acid pre-treatment) for the unbound phosphate concentration (mM) versus the ratio of unbound/bound phosphate were comparable for the sevelamer hydrochloride and carbonate formulations tested. In addition, kinetic binding experiments demonstrated that sevelamer hydrochloride and sevelamer carbonate bind phosphate in a similar rapid manner, independent of the initial phosphate concentration. The equilibrium level of binding was reached at both initial phosphate (KH_2PO_4) concentrations (2.5 mM and 38.7 mM) in approximately 15 minutes for the formulations tested. The results of the in vitro equilibrium and kinetic binding study suggest that sevelamer hydrochloride tablets (800 mg), sevelamer carbonate tablets (800 mg) and sevelamer carbonate powder (0.8 g, 1.6 g, and 2.4 g sachets) formulations should bind phosphate in vivo in a similar manner.

The submission included two new drug-drug interaction (DDI) PK studies [SVCARB01107; SVCARB01307]. In SVCARB01107, single dose sevelamer carbonate powder (9.6 g) administered in combination with single dose warfarin (20 mg) had no significant effect on warfarin exposure in healthy male subjects. The 90% CIs for the peak plasma concentration (Cmax) and the area under the concentration versus time curve from time 0 to infinity ($AUC_{(0-\infty)}$) ratios of the geometric means ([sevelamer+ warfarin]/[warfarin]) were all within the standard bioequivalence interval of 80% to 125% for both R and S warfarin. The results of this study were consistent with the previously submitted and evaluated DDI interaction PK study involving sevelamer hydrochloride and warfarin [ICR01382]. In SVCARB01307, single dose sevelamer carbonate powder (9.6 g) administered in combination with single dose digoxin (1 mg) had no clinically significant effects on digoxin exposure in healthy subjects. The 90% CIs for the Cmax, $AUC_{(0-72h)}$, and

$AUC_{(0-\infty)}$ ratios of the geometric means ([sevelamer+ digoxin / [digoxin]) were all within the standard bioequivalence interval of 80% to 125% for plasma digoxin in the all Analyzable Group (excluding 1 subject who was a Cmax outlier). When the Cmax outlier was included in the analysis, the lower bound 90% CI for the Cmax ratio of 79.33% was marginally outside the lower bioequivalence interval of 80%, while the 90% CIs for the $AUC_{(0-72h)}$ and $AUC_{(0-\infty)}$ ratios were within the standard bioequivalence interval of 80% to 125%. The results in this study were consistent with the previously submitted and evaluated DDI PK interaction study involving sevelamer hydrochloride and digoxin [ICR013769].

Previously submitted data included six DDI PK studies. These previously evaluated studies (Renagel CER) showed that sevelamer hydrochloride had no effect on the absorption of digoxin [ICR013769], warfarin [ICR013821], metoprolol [GTC-45-803], enalapril [GTC-45-804] and iron [GTC-45-808]. However, Study GTC-45-807 showed that the bioavailability of ciprofloxacin (750 mg) was statistically significantly ($p < 0.05$) decreased when co-administered with sevelamer hydrochloride (7x403 mg), based on reductions in Cmax and $AUC_{(0-24h)}$. Based on the new in vitro equilibrium and kinetic binding study [TR-2527-07-SC], and the two new in vivo drug-drug interaction PK studies [SVCARB01107; SVCARB01307], it can be reasonably inferred that the results of the previously submitted and evaluated DDI PK studies relating to sevelamer hydrochloride can be extrapolated to sevelamer carbonate.

Pharmacodynamics

Studies providing pharmacodynamic data

The submission included one study [SVCARB01307] providing new PD data. The PD data from this study has been reviewed above in *Pharmacokinetics, SVCARB01307*. The previously submitted and evaluated data included two studies with PD data in 44 healthy subjects [GTC-02-101; GTC-10-801]. In study GTC-02-101 (randomised, placebo-controlled, parallel-group design), the evaluators comment that the prothrombin time was significantly decreased in all patients in the sevelamer hydrochloride group (n=15) but there were no out of range values and no clinically significant changes in prothrombin time. The sponsor's Clinical Overview included in the current submission states that Study GTC-02-101 'showed sevelamer hydrochloride decreased the urinary excretion of phosphorous in a dose related fashion'. In GTC-02-801, the evaluators comment that there were no clinically significant changes in laboratory values with the exception of 2 subjects who at the end of the study had increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and potassium levels and decreased carbon dioxide levels that returned to normal within 1 to 2 months. No plausible explanation was provided for the abnormal values observed in these two subjects.

Dosage selection for the pivotal studies

In general, the sevelamer carbonate doses used in the new clinical efficacy and safety studies were based on the approved doses for sevelamer hydrochloride.

Efficacy

Studies providing efficacy data

The submission included 4 new, previously unevaluated efficacy and safety studies in 294 patients treated with sevelamer carbonate. Each of these 4 studies has been fully evaluated and the results provided in the body of the text of this CER. The 4 studies are:

- ***GD3-163-201:*** Phase II, multicentre (USA), randomised, double-blind, cross-over, therapeutic equivalence study designed to compare the effects of sevelamer hydrochloride tablets TDS (n=78) and sevelamer carbonate tablets TDS (n=73) administered for 8 weeks on serum phosphorous levels in hyperphosphataemic patients with CKD on haemodialysis.
- ***SVCARB0005:*** Phase III, multicentre (UK), randomised, open label, cross-over, therapeutic equivalence study designed to compare the effects of sevelamer carbonate powder TDS (n=31) and sevelamer hydrochloride tablets TDS (n=28) administered for 4 weeks on serum phosphorous levels in hyperphosphataemic patients with CKD on haemodialysis.
- ***SVCARB00105***: Phase III, multinational, multicentre, open label, single arm, dose-titration study designed to assess the effects of sevelamer carbonate TDS (n=49) administered for 8 weeks on serum phosphorous levels in hyperphosphataemic CKD (Stage 4 and 5) patients not on dialysis.
- ***GD3-199-301:*** Phase III, multicentre (USA), randomised (2:1), parallel-group, open label study designed to compare the effects of a once per day (QD) sevelamer carbonate powder regimen (n=141) with the standard TDS sevelamer hydrochloride tablet regimen (n=72) administered for 24 weeks on serum phosphorous levels in patients with CKD on haemodialysis.

In addition to the 4 key studies referred to above, the clinical submission included information on 3 additional efficacy and safety studies involving sevelamer carbonate identified as EU post-approval commitment studies [SVCARB00606; SVCARB0308; APB00108]. Only the data from Study SVCARB0308 in Chinese patients with CKD who were hyperphosphataemic and on haemodialysis are considered to be relevant to the current submission. The data from this study have been reviewed and presented in *Additional studies with sevelamer carbonate* in Attachment 2 to this AusPAR. Studies SVCARB00606 and APB00108 considered to be irrelevant as regards the evaluation of the efficacy of sevelamer carbonate for the purposes of this submission for the reasons presented in the same section of Attachment 2.

In addition to the new studies relating to sevelamer carbonate, the submission included 17 studies that had been previously submitted to support the application to register sevelamer hydrochloride. These studies have been previously evaluated by the TGA, and have been reviewed in *Sevelamer hydrochloride studies* in Attachment 2.

Evaluator's conclusions on efficacy

Overview

The submission included four key, previously unevaluated clinical efficacy and safety studies supporting the application to register sevelamer carbonate (tablets and powder) for the treatment of hyperphosphataemia in adult patients with CKD Stage 4 and 5. The data from these 4 studies are summarised below.

In two, short-term equivalence studies of 4 and 8 weeks duration in a total of 77 hyperphosphataemic patients with CKD on haemodialysis, sevelamer carbonate TDS was demonstrated to be equivalent to sevelamer hydrochloride TDS, based on reductions in

time weighted serum phosphorous levels in the PP Sets [GD3-163-201; SVCARB00205]. In both equivalence studies, the 90% CIs for the geometric least square (LS) mean ratios (carbonate/hydrochloride) were within the pre-specified equivalence interval of 0.80 to 1.25. Support for the efficacy of sevelamer carbonate for the treatment of hyperphosphataemic patients with CKD on haemodialysis is provided by the previously unevaluated study undertaken exclusively in Chinese patients (Full Analysis Set (FAS) [Day 57/ET]: n=134, sevelamer carbonate; n=70, placebo) [SVCARB03808].

In an open label, single arm key study, sevelamer carbonate TDS statistically significantly lowered serum phosphorous levels from Baseline to Day 56/ET in the FAS (n=46) in patients with CKD (Stage 4 or 5) not on dialysis [SVCARB00105]. In an open label key study, a sevelamer carbonate once a day (QD) regimen (n=97) was not non-inferior to the standard sevelamer hydrochloride TDS regimen (n=51) in patients with CKD on haemodialysis [GD3-199-301].

Equivalence studies: hyperphosphataemic patients on haemodialysis

Study GD3-163-201

In the Phase II, multicentre (US), randomised, double-blind, cross-over study in patients with CKD on haemodialysis and taking phosphate binders [GD3-163-201], sevelamer carbonate was equivalent to sevelamer hydrochloride as regards reduction in serum phosphorous levels following 8 weeks treatment (n=56; Per Protocol Set (PPS)). In both treatment groups, the target dose was achieved using 800 mg tablets administered TDS with meals.

In both treatment groups (PPS), the mean ± standard deviation (SD) prescribed sevelamer dose was 7.2 ± 3.1 g/day and the mean ± SD actual dose in the randomised treatment periods was 6.0 ± 2.8 g/day. No patients in the PPS changed their prescribed dose during the randomised treatment periods. The mean duration of treatment was similar for both treatment regimens; 8.0 weeks in the sevelamer carbonate group and 7.8 weeks in the sevelamer hydrochloride group.

The primary efficacy endpoint of mean ± SD serum phosphorous time weighted averages (mmol/L) was identical for treatment with sevelamer carbonate and sevelamer hydrochloride in the PPS (1.5 ± 0.3 mmol/L). The geometric least square mean ratio between the two treatments (sevelamer carbonate/hydrochloride) was 0.99 (90% CI:, 0.95, 1.03), and the two treatments were declared to be equivalent as the 90% CI of the ratio was enclosed completely within the pre-specified equivalence interval of 0.80 to 1.25. The results of the confirmatory analysis in the FAS (n=73 [carbonate]; n=78 [hydrochloride]) for the primary efficacy endpoint were similar to the results for the primary analysis in the PPS. The results for the secondary efficacy endpoints relating to serum lipid parameters also demonstrated that the two sevelamer treatment regimens were therapeutically equivalent.

Study SVCARB00205

In the Phase III, multicentre (UK), randomised, open label, cross-over study in hyperphosphataemic patients with CKD on haemodialysis [SVCARB00205], sevelamer carbonate powder for oral solution was equivalent to sevelamer hydrochloride tablets as regards reduction in serum phosphorous levels following 4 weeks treatment (n=21; PPS). The target dose of sevelamer carbonate was administered TDS with meals using 800 mg sachets (powder) and the target dose of sevelamer hydrochloride was administered TDS with meals using 800 mg tablets. The study was open label, and would have required a double-dummy technique in order for it to have been blinded. The use of objective, laboratory determined endpoints mitigated the potential for bias associated with open label studies.

In the PPS, the mean ± SD prescribed dose during the randomised treatment periods was 7.4 ± 3.1 g/day of sevelamer carbonate powder and 7.5 ± 3.1 g/day of sevelamer hydrochloride tablets and the corresponding mean ± SD actual doses were 6.0 ± 3.1 g/day of sevelamer carbonate powder and 6.4 ± 3.3 g/day of sevelamer hydrochloride tablets. The mean duration of treatment was 4.3 weeks on sevelamer carbonate powder and 4.6 weeks on sevelamer hydrochloride tablets. Patients with less than three weeks of exposure were excluded from the PPS,

In the PPS, the primary efficacy endpoint of mean ± SD serum phosphorous time weighted average for treatment with sevelamer carbonate powder was 1.6 ± 0.5 mmol/L compared with 1.7 ± 0.4 mmol/L for treatment with sevelamer hydrochloride tablets. The geometric least square mean ratio between the two treatments (sevelamer carbonate/hydrochloride) was 0.95 (90% CI: 0.87, 1.03), and the two treatments were declared equivalent as the 90% CI was enclosed completely within the pre-specified equivalence interval of 0.80 to 1.25. The results for the primary efficacy endpoint confirmatory analysis in the FAS (n=30) were almost identical to the results for the primary analysis of this endpoint in the PPS. The results for the secondary efficacy endpoints relating to serum calcium (albumin adjusted) phosphorous product and serum lipids in the FAS (n=25 [carbonate]; n=28 [hydrochloride]) also demonstrated that the two sevelamer treatment regimens were therapeutically equivalent.

Hyperphosphataemic patients not on dialysis

The submission included one Phase III, multinational, multicentre, open label, sevelamer carbonate single arm study in hyperphosphataemic CKD patients not on dialysis [SVCARB00105]. The sevelamer carbonate treatment regimen used 800 mg tablets and the dose was administered TDS. The primary analysis of change from Baseline to Day 56/ET in the serum phosphorous level was in the FAS (n=46), and the mean ± SD actual daily dose of sevelamer carbonate administered to patients in the FAS was 5.52 ± 1.62 g. In the FAS, the mean ± SD Baseline serum phosphorus level was 2.0 ± 0.3 mmol/L and decreased to 1.6 ± 0.3 mmol/L at Day 56/ET (change (Δ) = -0.5 ± 0.3 mmol/L, $p < 0.001$). There was a statistically significant ($p < 0.001$) increase in mean ± SD levels (n=40) following post-treatment wash-out from Day 56 to Day 70 of 0.6 ± 0.3 mmol/L, indicating that the patient population was hyperphosphataemic. The results for the secondary efficacy endpoint analyses in the FAS for change from Baseline to Day 56/ET in serum calcium (albumin adjusted) phosphorous product and serum lipids were consistent with the results for the primary efficacy endpoint analysis. By the end of study treatment (Day 56/ET), 50% of patients in the FAS had reached the titration target serum phosphorus level of ≥ 0.86 mmol/L and ≤ 1.47 mmol/L. In the subgroup analyses (FAS) in patients with Stage 4 (n=16) or Stage 5 (n=30) CKD, the reductions from Baseline to Day 56/ET were similar for both subgroups and were statistically significant ($p<0.001$).

Sevelamer carbonate QD versus sevelamer hydrochloride TDS

The submission included one Phase III, multisite (USA), parallel group, open label study of 24 weeks duration comparing the effects of sevelamer carbonate QD and sevelamer hydrochloride TDS on serum phosphorous levels in patients with CKD on haemodialysis [GD3-199-301]. In this study, the sevelamer carbonate dose was administered QD as a powder for oral solution using 2.4 g sachets and the sevelamer hydrochloride dose was administered TDS as tablets using the 800 mg formulation. In the primary efficacy analysis in the PPS, sevelamer carbonate powder QD (n=97) was *not* non-inferior to sevelamer hydrochloride tablets TDS (n=51) as regards change from Baseline to Week 24/ET in serum phosphorous levels. In the PPS, the 2-sided 95% CI for the difference between the two treatments (change from Baseline) was 0.12 to 0.48 mmol/L. The upper bound 95% CI for the difference of 0.48 mmol/L was greater than the pre-specified non-inferiority margin of 0.32 mmol/L and, consequently, sevelamer carbonate QD was declared to be not

non-inferior to sevelamer hydrochloride. Therefore, this study does not support a QD dosing regimen for sevelamer carbonate.

Limitations of the efficacy data

There were a total of 294 CKD patients treated with sevelamer carbonate in the four previously unevaluated studies, including 245 on haemodialysis and 49 not on dialysis. There were no therapeutic equivalence studies longer than 8 weeks duration in CKD patients comparing sevelamer carbonate at the proposed dose (TDS) with sevelamer hydrochloride at the approved (TDS) dose in patients on haemodialysis. There was one 24 week study showing that sevelamer carbonate powder administered QD (non-proposed dosing interval) was not non-inferior to sevelamer hydrochloride tablets administered TDS (approved dosing interval) in patients on haemodialysis and that the hydrochloride regimen was more efficacious than the carbonate regimen. There were limited, 8 week data in patients with CKD Stage 4 and 5 not on dialysis treated with sevelamer carbonate, but no long-term data with this formulation in this patient group. There were no data in patients on peritoneal dialysis treated with sevelamer carbonate.

Extrapolation of the sevelamer hydrochloride efficacy data to sevelamer carbonate

It is considered that the limitations of the submitted efficacy data relating to sevelamer carbonate can be addressed by extrapolating the previously evaluated efficacy data relating to sevelamer hydrochloride for the treatment of CKD Stage 4 and 5. In the sevelamer hydrochloride clinical trial program, a total of 607 unique patients on dialysis (haemodialysis or peritoneal dialysis) have been treated with sevelamer hydrochloride in 8 key efficacy and safety studies (7 previously evaluated studies [GTC-10-201, GTC10-202, GTC-36-203, GTC-36-301, GTC-36-302, GTC-45-901, and GTC-49-301] and 1 [REN-003-04] study evaluated in this CER). It should be noted that the 607 unique patients do not include the patients from long-term extension Study GTC-45-901 who were required to have participated in an earlier sevelamer trial in order to gain entry in to this study. However, the long-term extension Study GTC-45-901 did include 7 patients who were naive to sevelamer treatment. In addition, the current submission includes 106 CKD patients on haemodialysis treated with sevelamer hydrochloride and with sevelamer carbonate in the two cross-over therapeutic equivalence studies [GD3-163-201, SVCARB00205]. Therefore, 713 unique patients with CKD on dialysis in total have been treated with sevelamer hydrochloride, while 106 patients have been treated with sevelamer carbonate. The 10 key studies in patients on dialysis are listed below in Table 2 and it should be noted that only one study [REN-003-04] included patients on peritoneal dialysis while all of the other 9 studies included patients on haemodialysis.

Table 2: Overview of 10 key efficacy and safety studies in patients on dialysis treated with sevelamer hydrochloride and/or sevelamer carbonate.

Protocol Number	Patients Treated with Sevelamer Hydrochloride	Patients Treated with Sevelamer Carbonate
GTC-10-201	24	
GTC-10-202	48	
GTC-36-203	75	
GTC-36-301	84	
GTC-36-302	172	
GTC-45-901	192†	
GTC-49-301	100	
REN-003-04	97	
GD3-163-201	78	78‡
SVCARB00205	28	31‡

† 7 patients were naïve to sevelamer; all other study participants took part in a previous sevelamer hydrochloride study.
‡ Studies GD3-163-201 and SVCARB00205 were both cross over studies. In both studies, not all patients proceeded to the cross-over treatment phase and thus did not receive therapy with both agents.

The demographic and renal history of the dialysis treated patients in the 8 key studies in the sevelamer hydrochloride clinical program are summarised in Table 3.

Table 3: Summary of demographics in 8 key studies in the sevelamer hydrochloride clinical program in hyperphosphataemic CKD patients on dialysis.

Variable	GTC-10-201 (n=24)	GTC-10-202 (n=48)	GTC-36-203 (n=75)	GTC-36-301 (n=82)	GTC-36-302 (n=172)	GTC-45-901 (n=192)	GTC-49-301 (n=99)	REN-003-04 (n=97)
Sex: M/F (%)	46/54	62/38	67/33	54/46	64/36	62/38	64/36	67/33
Race: B/C/O (%)	67/21/12	42/50/8	39/57/4	56/31/13	52/34/14	54/35/11	17/71/12	2/90/8
Mean age (yrs)	58.8	52.0	58.7	54.6	53.4	56.1	57.0	54.6
Primary Cause of CKD (%):								
hypertension	ND	29	29	36	30	34	16	7
diabetes		35	37	29	23	30	23	18
other		36	34	35	47	36	61	75
Previous Phosphate Binder: (%)								
calcium carbonate	42	42	43	44	36	12	38	46
calcium acetate	50	50	47	37	48	19	33	6
aluminium	NA	8	1	8	9	1	6	1
sevelamer	NA	NA	NA	NA	NA	53	3	14
combination	8	NA/	5	6	4	1	19	31
other	NA	NA	4	5	3	14	1	0
none	NA	NA	NA	NA	NA	NA	NA	NA
Parathyroidectomy: yes/no (%)	ND	2/98	1/99	13/87	8/92	7/93	11/89	4/96
Vitamin D therapy: yes/no (%)	ND	60/40	51/49	67/33	52/48	74/26	56/44	45/55
Mean Duration of Dialysis (yrs)	ND	3.9	3.0	4.3	3.6	3.8	5.1	2.3
Mean Kt/V	ND	ND	1.5	1.4	1.4	1.5	ND	ND

NA: not applicable, ND: not done. B/C/O= Black, Caucasian, Other

In these 8 studies, the average age of the patients ranged from 52 to 59 years, females represented 33% to 54% of patients, Caucasians 21% to 90%, and Black 2% to 67%. The majority of patients had been using calcium carbonate or calcium acetate as their previous phosphate binder, except for the long-term extension study [GTC-45-901] where previous sevelamer hydrochloride use was required by the protocol. The majority of patients had not undergone parathyroidectomy and was using vitamin D replacement therapy. The most common primary causes of CKD were hypertension, diabetes, glomerulonephritis and unspecified other causes. The demographic and renal history of the dialysis treated patients in 8 key studies in the sevelamer hydrochloride clinical program were consistent with those treated with sevelamer carbonate in the 2 therapeutic equivalence studies in the current submission.

It is considered that the data from 8 key studies from the sevelamer hydrochloride clinical trial program in hyperphosphataemic CKD patients on dialysis are consistent with the 2 key equivalence studies from the sevelamer carbonate clinical trial program. Consequently, it can be reasonably inferred that the efficacy data for sevelamer hydrochloride relating to hyperphosphataemic patients with Stage 4 and 5 CKD on haemodialysis can be safely extrapolated to sevelamer carbonate.

In the sevelamer hydrochloride clinical trial program there were 79 hyperphosphataemic patients with CKD not on dialysis treated with sevelamer hydrochloride [GTC-45-204]. However, the serum phosphate level of ≥ 1.61 mmol/L in this study (following 4 weeks phosphate buffer wash-out) determined whether patients were treated with sevelamer hydrochloride at a level lower than the PI recommended level of > 1.78 mmol/L for initiating sevelamer carbonate treatment in patients not taking a phosphate binder. Therefore, it is considered that the data from Study GTC-45-204 is of limited support for sevelamer carbonate for hyperphosphataemic CKD patients not on dialysis.

Safety

Studies providing safety data

The safety profile of sevelamer hydrochloride for the treatment of hyperphosphataemia in patients with CKD Stage 4 and 5 has been well characterised, based on the previously evaluated data from the Renagel submission and the 14 years of postmarketing data following first approval in the USA.

The data provided in the current submission demonstrate sevelamer hydrochloride and sevelamer carbonate are therapeutically equivalent as regards the proposed indication. Consequently, it is considered that the known safety profile of sevelamer hydrochloride can be extrapolated to sevelamer carbonate. However, there are likely to be differences between the two sevelamer salts relating to adverse gastrointestinal and metabolic effects based on the different physiological properties of the hydrochloride and carbonate moieties. In particular, the sponsor states that the carbonate salt has a reduced propensity for association with potentially adverse acid-base changes compared with the hydrochloride salt and mitigates metabolic acidosis that can occur in hyperphosphataemic CKD patients.

The evaluation of the clinical safety data in this CER centres on sevelamer carbonate and includes reference to relevant differences between the carbonate and hydrochloride formulations. The approach adapted to the evaluation of the safety of sevelamer carbonate for the proposed indications is outlined below:

1. The safety data from the four new sevelamer carbonate studies submitted to support registration have been evaluated [GD3-163-201; SVCARB00205; SVCARB0015; GD3-199-201]. In patients with CKD on haemodialysis, sevelamer was administered TDS and compared with sevelamer hydrochloride TDS in Studies GD3-163-201 and SVCARB00205, and sevelamer carbonate was administered QD and compared with sevelamer hydrochloride TDS in Study GD3-199-301. In patients with CKD not on dialysis, single arm sevelamer carbonate was administered TDS in Study SVCARB00105.
2. The data from the Phase IV Post Authorisation Safety Study (PASS/SVCARB06009) have been reviewed in the Postmarketing experience section of this CER. This observational, postmarketing study was designed to monitor the clinical use of sevelamer carbonate (Renvela) in adult hyperphosphataemic CKD patients with serum phosphorous ≥ 1.78 mmol/L who were not on dialysis. The sponsor was requested by the EU Committee for Medicinal Products for Human Use (CHMP) to undertake this study as a post approval safety commitment.
3. The new safety data relating to sevelamer carbonate from the two studies that are not directly relevant to the proposed indication have also been briefly summarised (APB00108 [LEAP]; SVCARB00606 [ASPIRE])
4. The submission included an Addendum to Clinical Overview for Renewal of Renvela 800 mg Film-Coated Tablets, 1.6 g and 3.4 g Powder for Oral Suspension in the European Union covering the period from 10 June 2009 to 06 June 2013. The objective of this report was to support the renewal of the EU marketing authorisation of sevelamer carbonate following its first EU marketing authorisation on 10 June 2009. This report has been reviewed in the Postmarketing experience section of this CER.

Patient exposure

The four new studies included a total of 294 hyperphosphataemic patients with CKD exposed to at least one dose of sevelamer carbonate (245 on haemodialysis, 49 not on

haemodialysis). Based on the data for the 294 patients included in safety set, the estimated exposure was 69.4 patient-years. The exposure relating to the sevelamer carbonate safety set are summarised below in Table 4.

Table 4: Sevelamer carbonate exposure in the 4 new studies.

Study	N	Duration	Mean ± SD treatment	Patient-years of exposure	Mean ± SD actual daily dose
GD3-163-201	73	8 weeks	8.0 ± 0.4 weeks	11.1	5.8 ± 2.8 g/day
SVCARB00105	49	8 weeks	7.4 ± 2.4 weeks	6.9	5.4 ± 1.7 g/day
SVCARB00205	31	4 weeks	3.7 ± 1.3 weeks	2.2	5.9 ± 2.7 g/day
GD3-199-301	141	24 weeks	18.4 ± 7.9 weeks	49.2	6.2 ± 2.6 g/day

Note: The mean ± SD actual daily dose relates to the randomised treatment period for the safety set for studies GD3-163-2012, SVCARB00205, and GD4-199-301.

Sevelamer carbonate exposure by maximum duration of treatment in the four new studies is summarised below in Table 5.

Table 5: Sevelamer carbonate maximum duration of exposure in the 4 new studies.

	GD3-199-301		SVCARB00105		GD3-163-201		SVCARB00205	
Cumulative	N	Person-time	N	Person-time	N	Person-time	N	Person-time
Up to 4 weeks	13	23.3 weeks	6	8.0 weeks	0	0	11	25.7 weeks
Up to 8 weeks	26	97.5 weeks	23	137.4 weeks	36	281.1 weeks	31	114.1 weeks
Up to 12 weeks	32	151.9 weeks	49	361.0 weeks	72	575.3 weeks	31	114.1 weeks
Up to 16 weeks	38	234.5 weeks	49	361.0 weeks	72	575.3 weeks	31	114.1 weeks
Up to 24 weeks	139	2557 weeks	-	-	-	-	-	-

Sevelamer carbonate exposure by average actual daily dose is summarised below: Table 6

Table 6: Sevelamer carbonate exposure by average actual daily dose in the 4 new studies.

	GD3-199-301		SVCARB00105		GD3-163-201		SVCARB00205	
Dose g/day	N	Person-time	N	Person-time	N	Person-time	N	Person-time
Unknown	-	-	1	9.1 weeks	1	5.1 weeks	5	13.4 weeks
≤ 4.8	49	757.4 weeks	20	119.1 weeks	30	240.7 weeks	12	46.4 weeks
> 4.8 to < 9.6	72	1392.7 weeks	27	225.1 weeks	34	273.6 weeks	12	46.0 weeks
≥ 9.6	18	406.9 weeks	1	7.6 weeks	7	55.9 weeks	2	8.3 weeks

None of the 294 patients in the sevelamer carbonate safety set were exposed to the formulation for more than 24 weeks. The majority of patients in the safety set were treated with sevelamer carbonate at a total daily dose of > 4.8 to < 9.6 g.

Postmarketing data

Post Authorisation Safety Study (PASS) [SVCARB006009]

Overview of the study

The submission included one postmarketing observational study designed to monitor the clinical use of sevelamer carbonate (Renvela®) in adult hyperphosphataemic CKD patients *not on dialysis* with serum phosphorous levels ≥ 1.78 mmol/L. This study was requested by the CHMP (European Medicines Agency) as a post-approval commitment by the marketing authorisation holder (Genzyme Europe BV) to assess the safety profile of sevelamer carbonate in the specified patient population in a clinical setting. The study was undertaken in 27 sites in Austria (2 sites), Germany (5 sites), Denmark (1 site), France (4 sites), the Netherlands (4 sites), Italy (8 sites) and Spain (3 sites). The first patient signed informed consent on 15 September 2010 and the last patient completed on 5 October 2012. The study report was dated 23 April 2013.

The study included patients in the EU who met the following criteria:

1. Adult CKD patients not on dialysis with serum phosphorus ≥ 1.78 mmol/L.
2. Prescribed Renvela (800 mg tablets or 2.4 g powder for oral suspension) in accordance with the Renvela SmPC.
3. Provided signed informed consent (patient or their legally authorised representative).

The patients were followed for up to 12 months or up to the time dialysis was started, whichever occurred first. The study investigators were required to assess the patients during clinical visits according to standard clinical practice. No study specific visits were defined but data points of interest occurring between the date of consent and the end of the 12 month observation period as documented in the patient charts were collected. Nephrologists who cared for CKD patients not on dialysis were invited to include all of their eligible patients in this study.

Safety was documented and assessed by collecting reports of adverse drug reactions (ADRs). An ADR was defined as a response to a medicinal product which is noxious and unintended and which occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. ADRs also included adverse clinical consequences associated with use of the product outside the terms of the Summary of product Characteristics (SmPC; EU equivalent to PI) or other conditions laid down for the marketing and use of the product (including prescribed doses higher than those recommended, overdoses or abuse).

It was estimated that no more than 5,000 patients in the EU would be hyper-phosphataemic due to CKD with serum phosphorous ≥ 1.78 mmol/L and Post-Authorisation Safety Study (PASS) planned to enrol 200 patients. In the clinical study with Renvela in adult hyperphosphataemic CKD patients not on dialysis with serum phosphorus ≥ 1.78 mmol/L [SVCARB00105], adverse events (AEs) considered by the investigator to be related to study treatment were most frequently reported for the 'Gastrointestinal disorders' System Organ Class (SOC) (32.7%). If the observed incidence rate for related gastrointestinal events is 32.7%, with a sample size of 200 patients, an incidence rate >39.2% can be ruled out with 95% confidence. With a sample size of 200 patients, the smallest ADR which can be excluded with 95% confidence if no case is observed is an ADR occurring at a rate of approximately 1.5%.

Addendum to clinical overview

The submission included a document titled '*Addendum to Clinical Overview for Renewal of Renvela 800 mg Film-Coated Tablets, 1.6 g & 2.4 g Powder for Oral Suspension in the European Union*'. The objective of the Addendum was to provide consolidated safety and efficacy data for the renewal of the centralised EU marketing authorisation for Renvela (sevelamer carbonate) since its first Marketing Authorisation on 10 June 2009. The period covered by the renewal application was 10 June 2009 to 06 June 2013. The Addendum reviewed the relevant published literature relating to sevelamer carbonate in adults and children and to the safety data from clinical studies undertaken by the Marketing Authorisation Holder [LEAP (APB00108), ASPIRE (SVCARB00606), SVCARB03808, SVCARB06009 (PASS), Registre de Dialyse Peritoneale de Langue Francais].

The Addendum noted that sevelamer carbonate 800 mg tablets are currently approved for marketing in 62 countries worldwide and sevelamer carbonate for oral suspension is currently approved for marketing in 43 countries worldwide. On the basis of information available during the period from 10 June 2009 to 06 June 2013, no actions relating to sevelamer carbonate were taken for safety reasons by regulatory authorities or the sponsor. The estimated exposure to sevelamer carbonate tablets and powder over the reporting interval was 1,495,673 patients, corresponding to 440,489 total patient-years for sevelamer carbonate.

The Addendum noted the following safety concerns: important identified risks: intestinal obstruction/ileus and intestinal perforation; important potential risks:- peritonitis in peritoneal disease patients, atrio-ventricular (AV) fistula site complications in haemodialysis patients, difficulty swallowing Renvela tablets, off-label use in children, drug interactions with ciprofloxacin, cyclosporin, mycophenolate mofetil, levothyroxine and tacrolimus, vitamin deficiency; and important missing information, data on use of in hyperphosphataemic patients on CKD patients on peritoneal dialysis, data on use in hyperphosphataemic CKD patients not on dialysis with serum phosphorous ≥ 1.78 mmol/L, use in pregnancy and lactation, use in hepatic impairment and immune-compromised patients.

The addendum concluded that no new nonclinical or clinical data were available which changed or resulted in a new risk-benefit evaluation from that provided 5 years previously.

Evaluator's conclusions on safety

In the sevelamer carbonate and sevelamer hydrochloride clinical trial programs, a total of 1093 individual patients received at least one dose of sevelamer during the investigative study treatment period (i.e., excluding any run-in period). A total of 900 patients received at least one dose of sevelamer hydrochloride and 294 patients received at least one dose of sevelamer carbonate, with some patients receiving both sevelamer hydrochloride and sevelamer carbonate in the cross-over studies and being counted once within each treatment group [GD3-163-201; SVCARB00205].

Of the 1093 patients individual CKD patients treated with sevelamer carbonate and/or sevelamer hydrochloride, 969 were on haemodialysis (724 patients received at least one dose of sevelamer hydrochloride; 245 patients received at least one dose of sevelamer carbonate), 97 were on peritoneal dialysis (all 97 patients received at least one dose of sevelamer hydrochloride; no patients received sevelamer carbonate), and 128 were not on dialysis (79 patients received at least one dose of sevelamer hydrochloride; 49 patients received at least one dose of sevelamer carbonate). The mean treatment duration in the studies ranged from approximately 4 to 50 weeks, and the mean actual dose of sevelamer varied across studies from 3.6 to 6.7 g/day.

The four new clinical studies presented in this submission included clinical safety data on a total of 249 adult hyperphosphataemic patients with CKD Stage 4 and 5 treated with at least one dose of sevelamer carbonate (245 patients on haemodialysis, 49 patients not on dialysis). The estimated exposure for the 294 patients was 69.4 patient-years. Of the 249 patients, 141 [Study GD3-199-301] had been treated for 24 weeks, but no patients had been treated for more than 24 weeks. The majority of the 249 patients were treated with sevelamer carbonate at a dose of > 4.8 to < 9.6 g/day.

CKD patients on haemodialysis and sevelamer carbonate versus sevelamer hydrochloride

In the two, cross-over equivalence studies in patients on haemodialysis involving 4 weeks treatment [SVCARB00205] and 8 weeks treatment [GD3-163-201], the safety profiles of sevelamer carbonate TDS and sevelamer hydrochloride TDS were similar. The key safety conclusions from the 8 week cross-over study [GD3-163-201] comparing sevelamer carbonate tablets TDS and sevelamer hydrochloride tablets TDS are reviewed under *Evaluator's conclusions on safety* in Attachment 2.

The safety profiles of sevelamer carbonate tablet TDS and sevelamer hydrochloride tablet TDS in the 8 week cross-over study [GD3-163-201] were not markedly different from the safety profiles of sevelamer carbonate powder TDS and sevelamer hydrochloride tablet TDS in the 4 week cross-over study [SVCARB00205]. However, AEs were reported less frequently in the 4 week compared with the 8 week study, which is likely to be a function of the shorter duration of exposure.

In the 24 week, parallel-group study in patients on haemodialysis [GD3-199-301] comparing sevelamer carbonate powder QD (n=141) with sevelamer hydrochloride tablet TDS (n=72), the total daily dose was similar in the two treatment groups (6.2 and 6.7 g, respectively), while the mean duration of treatment was approximately 4 weeks longer in the sevelamer hydrochloride tablet TDS group compared with the sevelamer carbonate powder QD group (22.1 versus 18.4 weeks; p=0.008). The findings are summarised under *Evaluator's conclusions on safety* in Attachment 2.

The majority of AEs in both treatment groups (Study GD3-199-301) were considered to be unrelated to treatment, with treatment related AEs being reported in 30.5% of patients in the sevelamer carbonate powder QD group and 18.1% of patients in the sevelamer hydrochloride tablet TDS group. The QD treatment regimen used for sevelamer carbonate powder in the 24 week, parallel-group study differs from the TDS regimen proposed by the sponsor for approval. Of note, nausea and vomiting occurred more commonly in the sevelamer carbonate powder QD group than in the sevelamer hydrochloride tablet TDS group. This might be a function of the QD dosing regimen in the sevelamer carbonate powder group compared with the TDS dosing regimen in the sevelamer hydrochloride group.

The major difference between the two treatment groups (Study GD3-199-301) was the two fold greater frequency of treatment related 'Gastrointestinal disorders' (SOC) in the sevelamer carbonate powder QD group (22.7%) than in the sevelamer hydrochloride tablet TDS group (11.1%). This difference was primarily due the greater incidence of both treatment related nausea and vomiting in the sevelamer carbonate powder QD group compared with the sevelamer hydrochloride tablet TDS group.

All 6 treatment-emergent deaths in Study GD3-199-301 were assessed by the study investigators as not related to the study treatment. SAEs occurred notably less frequently in patients in the sevelamer carbonate powder QD group than in patients in the sevelamer hydrochloride tablets TDS group (23.4% versus 38.9%, respectively). The majority of SAEs were considered by the study investigator to be not treatment related. Discontinuations due to AEs occurred notably more frequently in the sevelamer carbonate powder QD group than in the sevelamer hydrochloride tablet TDS group (12.0% versus 4.2%, respectively). In the sevelamer carbonate powder QD group, 5 patients discontinued due to oral administration complications (bad taste of study drug, gagging when taking study drug), 8 patients discontinued due to gastrointestinal disorders (nausea, vomiting, bloatedness, diarrhoea and rectal bleeding), and 4 patients discontinued due to other events (worsening hyperphosphataemia, renal transplant, cerebrovascular accident, and central line infection). All of the oral administration complications and 7 of the 8 gastrointestinal disorders leading to discontinuation in the sevelamer carbonate group were classified by the study investigators as treatment related. All 4 patients in the sevelamer hydrochloride tablet TDS group who discontinued did so due to a SAE (cardiac arrest, myocardial infarction, septic shock, intracranial bleed), none of which were classified as treatment related by the Investigators.

CKD patients not on dialysis and sevelamer carbonate

The submission included one single arm Phase III study assessing the safety of sevelamer carbonate tablet TDS in hyperphosphataemic patients (n=49) not on dialysis following 8 weeks treatment [SVCARB00105]. The safety profile of sevelamer carbonate in patients not on haemodialysis was similar to the safety profile of the drug in patients on dialysis. All causality AEs occurred in 89.8% (n=44) of patients (see *Evaluator's conclusions on safety* in Attachment 2 for more details).

One patient died due to bronchopneumonia considered by the study investigator to be unrelated to treatment with sevelamer carbonate. SAEs were reported in 22.4% of patients, and events occurring in > 1 patient (> 2.0%) were AV fistula operation (8.2%, n=4), lower respiratory tract infection (4.1%, n=2) and fluid overload (4.1%, n=2). Treatment discontinuations due to AEs were reported in 10.2% of patients (n=5). AEs leading to discontinuation in 4 of the 5 patients were treatment related gastrointestinal events, including nausea (2 patients), diarrhoea (2 patients), constipation (2 patients), stomach discomfort (1 patient), and vomiting (1 patient). The remaining patient discontinued due to serious pleural effusion (followed by death due to bronchopneumonia), which was assessed as not treatment related.

In addition to the pre-authorisation Phase III study in 49 CKD patients not on haemodialysis treated with sevelamer carbonate tablets TDS for 8 weeks [SCVCARB00105], the submission also included a PASS in adult CKD patients not on dialysis with serum phosphorous levels ≥ 1.78 mmol/L. In PASS, 210 patients took Renvela for a median duration of 312 days (range: 5, 373 days), at a mean ± SD prescribed dose of 3.7 ± 1.9 g/day (range: 0.8, 12 g/day), and 148 (70.5%) took the drug TDS. Overall, in PASS 15.7% of patients experienced ADRs and the most commonly reported events occurred in the SOC of 'Gastrointestinal disorders' (14.3%). ADRs (PTs) reported in ≥ 1% of patients were nausea (4.3%), constipation (3.8%). diarrhoea (1.9%), dyspepsia (1.9%), vomiting (1.4%), abdominal distension (1.0%), abdominal pain (1.0%), and upper abdominal pain (1.0%). Overall, the postmarketing ADR profile observed in PASS in patients with CKD not on dialysis was similar to the premarketing safety profile observed in patients in the Phase III Study SVCARB00105.

Other safety aspects of sevelamer carbonate

The three new studies in the submission comparing sevelamer carbonate with sevelamer hydrochloride in patients on haemodialysis showed not marked differences in mean changes in clinical laboratory parameters (haematology and clinical biochemistry) in patients treated with the two formulations [GD3-163-201, SVCARB00205, GD3-199-301]. Similarly, there were no notable differences in changes in vital signs between sevelamer carbonate and sevelamer hydrochloride in the three new comparative studies in patients on haemodialysis.

In the three new studies in the submission comparing sevelamer carbonate with sevelamer hydrochloride in patients on dialysis showed no marked difference between the two formulations based on patient age (< 65 versus ≥ 65 years), gender (male versus female), and race (non-Black/African American versus Black/African American).

Long-term safety of sevelamer carbonate

There were no pre authorisation clinical study safety data in patients on haemodialysis treated with sevelamer carbonate for more than 6 months. However, data from the Renagel CER indicates that long term safety was demonstrated in > 200 patients on haemodialysis [Study GTC-45-901; Study GTC-49-301]. In addition, the current submission included 54-week data from Study GTC-68-402 on 71 hyperphosphataemic CKD patients on haemodialysis (sevelamer hydrochloride [n=39], calcium carbonate [n=32]) showing that the long-term safety profile of sevelamer hydrochloride was consistent with the known safety profile of the formulation. In addition, the study found no detrimental effects of Renagel compared with calcium carbonate on bone turnover and mineralization.

Postmarketing of sevelamer carbonate

Reassurance concerning the long-term safety of sevelamer carbonate is provided by the data in the *Addendum to the Clinical Overview* noting that sevelamer carbonate 800 mg tablets are currently approved for marketing in 62 countries worldwide and sevelamer carbonate for oral suspension is currently approved for marketing in 43 countries worldwide. On the basis of information available during the period from 10 June 2009 to 06 June 2013, no actions for safety reasons relating to sevelamer carbonate were taken in the reporting interval by regulatory authorities or the sponsor. The estimated exposure to sevelamer carbonate tablets and powder over the reporting interval was 1,495,673 patients, corresponding to 440,489 total patient-years for sevelamer carbonate.

First Round Benefit-Risk Assessment

First round assessment of benefits

The submitted data have satisfactorily demonstrated the benefits of sevelamer carbonate administered TDS for the treatment of hyperphosphataemia in adult patients with Stage 4 and 5 CKD. The data showed that the benefits of sevelamer carbonate for the proposed indication are consistent with those of sevelamer hydrochloride, the approved product. Furthermore, it is considered that the submission has satisfactorily established that the known benefits of sevelamer hydrochloride for the treatment of hyperphosphataemic patients with Stage 4 and 5 CKD can be satisfactorily extrapolated to sevelamer carbonate for the same indication.

In the two, small, short-term, cross-over studies of 4 and 8 weeks duration in hyperphosphataemic patients with CKD on haemodialysis, sevelamer carbonate was shown to be therapeutically equivalent to sevelamer carbonate based on reductions in time weighted serum phosphorous levels in the PPS [GD3-163-201; SVCARB00205]. In Study GD3-163-201, sevelamer carbonate tablet TDS was compared with sevelamer hydrochloride tablet TDS. The mean ± SD actual sevelamer dose over the 8 week randomised treatment periods in the PPS (n=56) was 7.2 ± 3.1 g/day for both sevelamer carbonate and sevelamer hydrochloride. In Study SVCARB00205, sevelamer carbonate powder TDS was compared with sevelamer hydrochloride tablet TDS. The mean ± SD actual doses over the 4 week randomised treatment periods in the PPS (n=21) was 7.4 ± 3.1 g/day for the sevelamer carbonate regimen and 7.5 ± 3.1 g/day for the sevelamer hydrochloride regimen. In addition, the benefits of sevelamer carbonate and sevelamer hydrochloride in the FAS were equivalent as assessed by change in lipid parameters in both studies and change in serum calcium phosphorous product in Study SVCARB00205. However, while the two, cross-over equivalence studies support the benefits of sevelamer carbonate TDS compared with sevelamer hydrochloride TDS, the 24 week parallel group study [GD3-199-301] did not establish the non-inferiority of sevelamer carbonate powder QD compared with sevelamer hydrochloride tablet TDS. Therefore, the benefits of sevelamer carbonate tablet and powder for the proposed indication relate only to TDS regimens.

In an open label, single arm study in hyperphosphataemic patients with CKD not on dialysis, sevelamer carbonate tablets TDS showed a benefit in reducing serum phosphate levels from baseline over the 8 week treatment period in 46 patients in the FAS [SVCARB00105]. In this study, benefits relating to change in serum lipid levels and change in serum calcium phosphorous product were also observed. There were no data in the submission comparing the treatment benefits of sevelamer carbonate and sevelamer hydrochloride on serum phosphorous reduction in hyperphosphataemic patients with CKD not on dialysis.

There were no data exploring the benefits of sevelamer carbonate in hyperphosphataemic patients with CKD on peritoneal dialysis. However, it is considered reasonable to extrapolate the data from Study REN-003-04 demonstrating the non-inferiority of sevelamer hydrochloride tablets TDS (n=95) to calcium carbonate (n=44), as regards reduction in serum phosphorous levels from baseline over 12 weeks treatment.

First-round assessment of risks

The submission has satisfactorily characterised the risks of sevelamer carbonate for the treatment of hyperphosphataemia in adult patients with CKD Stage 4 and 5. Furthermore it is considered that the submission has demonstrated that the known risks of sevelamer hydrochloride for the proposed indication can be extrapolated to sevelamer carbonate. In the sponsor's Clinical Overview, the sponsor comments that the risks of sevelamer

carbonate are similar to the risks of sevelamer hydrochloride, with the exception of the inherent risk hyperchloraemic acidosis with sevelamer hydrochloride.

The main risks of treatment with sevelamer carbonate relate to 'Gastrointestinal disorders'. In the two, cross-over studies of 4 weeks and 8 weeks duration [SVCARB00205 and GD3-163-201, respectively], the risks of 'Gastrointestinal disorders' were similar for the sevelamer carbonate TDS and sevelamer hydrochloride TDS treatment regimens. However, in the 24 week non-inferiority study [GD3-199-301], the risks of 'Gastrointestinal disorders' were notably greater in the sevelamer carbonate powder QD regimen than in the sevelamer tablet TDS regimen. The increased risk is likely to be a function of the QD dosing regimen for sevelamer carbonate powder compared with the TDS dosing regimen for sevelamer hydrochloride tablets. Both sevelamer carbonate and sevelamer hydrochloride should be used with caution in patients with severe GI motility disorders including severe constipation, active inflammatory bowel disease, or major gastrointestinal tract surgery. In addition, the hygroscopic characteristics of sevelamer carbonate (and sevelamer hydrochloride) present a risk of oesophageal and intestinal obstruction due to swelling of the drug when it comes into contact fluid in the bowel.

In the two, small, short-term, cross-over studies of 4 and 8 weeks duration in hyperphosphataemic patients with CKD on haemodialysis, the safety profiles of sevelamer carbonate and sevelamer hydrochloride were shown to be similar [SVCARB00205 and GD3-163-201, respectively]. Furthermore, the qualitative features of the safety profiles of the two formulations were similar in the two cross-over studies but the frequency of AEs was lower in the 4 week, cross-over study than the 8 week, cross-over study.

In the 8 week, cross-over study comparing sevelamer carbonate tablets TDS (n=73) and sevelamer hydrochloride tablets TDS (n=78) [GD3-163-201], most patients (82.2% and 83.3%, respectively) experienced at least one AE (all causality). However, most of the AEs in both treatment groups were considered unrelated to sevelamer by the study investigators, with treatment related events being reported in 16.4% of patients treated with the sevelamer carbonate tablet TDS and 19.2% of patients treated with sevelamer hydrochloride tablet TDS. The most commonly reported drug related AEs reported in ≥ 2 patients with either of the two treatments and in decreasing order of frequency with sevelamer carbonate tablet TDS versus sevelamer hydrochloride tablet TDS treatment were carbon dioxide decreased (4, 5.5% versus 4, 5.1%), nausea (2, 2.7% versus 2, 2.6%), vomiting (2, 2.7% versus 1, 1.3%), blood triglycerides increased (2, 2,7% versus 1, 1.3%), GORD (1, 1.4% versus 3, 3.8%), blood bicarbonate decreased (1, 1.4% versus 2, 2.6% and blood iPTH increased (1, 1.4% versus 2, 2.6%). Overall, there were no marked differences in the treatment related AE profiles between the two sevelamer formulations.

In the 24 week, parallel-group, non-inferiority study in patients on haemodialysis comparing sevelamer carbonate powder QD (n=141) with sevelamer hydrochloride tablet TDS (n=72), AEs (all causality) occurred in 87.9% and 91.1% of patients in the two treatment groups, respectively [GD3-199-301]. However, although a similar proportion of patients in both treatment groups experienced AEs (all causality), treatment related AEs were reported notably more frequently in the sevelamer carbonate powder QD group than in the sevelamer hydrochloride tablet TDS group (30.5% versus 18.1%). The major difference between the two treatment groups was the two fold greater frequency of 'Gastrointestinal disorders' (SOC) in the sevelamer carbonate powder QD group (22.7%) than in the sevelamer hydrochloride tablet TDS group (11.1%).

In the two, cross-over equivalence studies of 4 weeks [SVCARB00205] and 8 weeks duration [GD3-199-201, and the one, 24 week non-inferiority study [GD3-199-301], sevelamer carbonate was not associated with an increased risk of death compared with sevelamer hydrochloride. In the 8 week, cross-over equivalence study [GD3-199-201], the risks of experiencing SAEs were similar in patients in the sevelamer carbonate tablet TDS group and the sevelamer hydrochloride tablet TDS group (11.0% [n=8] versus 14.1%

[n=11], respectively). The only SAEs reported in ≥ 2% of patients in either of the two treatment groups (sevelamer carbonate versus sevelamer hydrochloride) were coronary artery disease (2.7% versus 2.6%) and renal transplant (0% versus 2.6%). All SAEs in the randomised treatment periods were assessed by the study investigator as being un-related to treatment with sevelamer.

In the 24 week, parallel-group, non-inferiority study [GD3-199-301], the risk of experiencing an SAE was notably lower in patients in the sevelamer carbonate powder QD group than in patients in the sevelamer hydrochloride tablets TDS group (23.4% [n=33] versus 38.9% [n=28], respectively). SAEs reported in ≥ 2% of patients in either of the two treatment groups and by decreasing order of frequency in the sevelamer carbonate powder QD group versus the sevelamer hydrochloride tablet TDS group were pneumonia (4.3% versus 4.2%), cardiac failure congestive (3.5% versus 5.6%), hyperkalaemia (2.8% versus 2.8%), atrial fibrillation (2.1% versus 1.4%), pulmonary oedema (2.1% versus 1.4%), AV fistula thrombosis (1.4% versus 5.6%), hypoglycaemia (0.7% versus 2.8%), coronary artery disease (0.7% versus 4.2%), hypertension (0.7% versus 2.8%) and AV fistula operation (0% versus 2.8%). The majority of SAEs were considered by the Investigator to be un-related to treatment with sevelamer.

In the 8 week, cross-over, equivalence study [GD3-163-201], 6 (7.7%) patients discontinued treatment due to AEs in the sevelamer hydrochloride tablet TDS group compared with no patients in the sevelamer carbonate tablet TDS group. In the sevelamer hydrochloride tablet TDS group, 2 patients discontinued due to renal transplant, 1 patient discontinued due to AV fistula thrombosis and hepatic ischaemia, and 1 patient each discontinued due to allergic dermatitis, asthenia and muscular weakness. In the 24 week, parallel-group study [GD3-199-201], the risk of discontinuation from the study due to AEs was notably greater in the sevelamer carbonate tablet TDS group (12.0% [n=17]) than in the sevelamer hydrochloride table TDS group (5.6% [n=4]). In the sevelamer carbonate powder QD group, 5 patients discontinued due to oral administration complications (bad taste of study drug, gagging when taking study drug), 8 patients discontinued due to gastrointestinal disorders (nausea, vomiting, bloatedness, diarrhoea and rectal bleeding), and 4 patients discontinued due to other events (worsening hyperphosphataemia, renal transplant, cerebrovascular accident, and central line infection). All of the oral administration complications and 7 of the 8 gastrointestinal disorders leading to discontinuation in the sevelamer carbonate group were classified as related to the study drug by the Investigators. All 4 patients in the sevelamer hydrochloride tablet TDS group who discontinued did so due to a SAE (cardiac arrest, myocardial infarction, septic shock, intracranial bleed), none of which were classified as related to the study drug by the Investigators.

There were no studies comparing the risks of sevelamer carbonate with sevelamer hydrochloride for the treatment of hyperphosphataemia in adult patients with CKD Stage 4 and 5 not on dialysis. However, in the 8 week, open label, single arm study [SVCARB00105] in patients with these characteristics (n=49), the safety profile of sevelamer carbonate tablets TDS was consistent with the safety profiles of this formulation observed in the controlled studies in patients with hyperphosphataemia on haemodialysis [GD3-163-201, SVCARB00205, GD3-199-301]. In addition, the safety profile in the postmarketing study [PASS] in 210 adult patients with CKD not on dialysis with serum phosphate concentrations ≥ 1.78 mmol/L treated for up to 12 months was consistent with the Phase III study [SVCARB00105].

There were no studies assessing the risks of sevelamer carbonate for the treatment hyperphosphataemia in adult patients with CKD Stage 4 and 5 on peritoneal dialysis. However, it is considered reasonable to extrapolate the safety data from the 12 week study [REN-003-04] in patients treated with sevelamer hydrochloride. The safety data from Study REN-003-04 relating to sevelamer hydrochloride were generally consistent

with the known safety data for this formulation. However, in contrast to the studies in patients on haemodialysis or not on dialysis the most frequently occurring SAE in study REN-003-04 was peritonitis (8 events in 8 patients [8.2%] in the sevelamer hydrochloride group and 2 events in 2 [4.3%] patients in the calcium acetate group). Peritonitis is a common complication in patients on peritoneal dialysis and it is likely that the difference in incidence of this AE between the sevelamer hydrochloride and calcium acetate groups is due to chance.

There were no long-term (> 24 weeks), safety data from preauthorisation studies in adult patients with hyperphosphataemia and CKD Stage 4 and 5 treated with sevelamer carbonate. However, reassurance concerning the long term safety of sevelamer carbonate for the proposed indication is provided by: (1) the long-term (> 52 weeks), clinical studies with sevelamer hydrochloride in approximately 250 hyperphosphataemic CKD patients on haemodialysis; (2) the 12 month post authorisation study [PASS] referred to above in hyperphosphataemic CKD patients not on dialysis; (3) the 5 year postmarketing (EU) data for sevelamer carbonate (10 June 2009 to 6 June 2013) indicating that the estimated exposure to sevelamer carbonate tablets and powder over this interval was 1,495,673 patients, corresponding to 440,489 total patient-years, and that no significant regulatory and/or sponsor initiated actions relating to the safety of sevelamer carbonate have been required over this interval; and (4) satisfactory long-term safety of sevelamer hydrochloride demonstrated since its initial approval in the USA on 30 October 1998.

First round assessment of benefit-risk balance

The benefit-risk balance of sevelamer carbonate, given the proposed usage, is favourable. The benefits of sevelamer carbonate powder and tablets administered TDS in adult hyperphosphataemic patients with CKD Stage 4 and 5 have been satisfactorily established. The two cross-over studies demonstrated that sevelamer carbonate and sevelamer hydrochloride were equivalent in adult hyperphosphataemic CKD patients on haemodialysis as regards reduction of time weighted serum phosphorous concentration over 4 weeks (sevelamer carbonate powder TDS versus sevelamer hydrochloride tablets TDS) and over 8 weeks (sevelamer carbonate tablets TDS versus sevelamer hydrochloride tablets TDS). In addition, the benefits of sevelamer carbonate in the open label, single arm study in adult hyperphosphataemic patients with CKD not on dialysis were consistent with the benefits observed with sevelamer carbonate in the cross-over, equivalence studies in hyperphosphataemic adult CKD patients on haemodialysis. Overall, based on the in vivo therapeutic equivalence studies [GD3-163-201, SVCARB00205] and the in vitro bioequivalence study [TR-2527-07-SC] it is considered that the known benefits of sevelamer hydrochloride for the treatment of hyperphosphataemia in adult patients with Stage 4 and 5 CKD can be extrapolated to sevelamer carbonate. The risks of sevelamer carbonate have been well characterised in the 4 new clinical efficacy and safety studies, and in the post marketing safety sevelamer carbonate data over the 5 year interval from 10 June 2009 to 06 June 2013. It is considered that the extensive and well known safety data for sevelamer hydrochloride can be extrapolated to sevelamer carbonate.

First Round Recommendation Regarding Authorisation

It is recommended that sevelamer carbonate 800 mg tablets and 1.6 g and 2.4 g powder for oral solution, with trade names Renvela, Sevelamer Carbonate Winthrop, and Sevelamer Carbonate Sanofi, be approved for the management of hyperphosphataemia in adult patients with Stage 4 and 5 chronic kidney disease.

Clinical Questions

Efficacy

1. The submission included a final report for Study SVCARB002005 dated 19 July 2007 and an amendment to this report dated 11 January 2008. The sponsor states that the additional information had been identified by the sponsor during preparatory activities for a site inspection by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA). Examination of the CHMP Assessment Report for Renvela[6], accessed from the EMA website, indicates that routine inspection EMA GCP inspection at the sponsor site and one investigator site revealed '*critical and major issues, with regard to eligibility criteria, drug compliance, and adverse event reporting*'. It appears that, in response to a list of outstanding issues raised by the inspection, the sponsor '*presented a sensitivity analysis [to the CHMP] and addressed the issue at the oral explanation'*. Based on the presented data the '*majority of the CHMP members accepted that the proposed data could be accepted to support the claimed indications, provided that additional data are gathered in a post marketing study to reinforce the safety data set*'. It is noted the addendum to the clinical overview includes an observational, post marketing safety study. Please provide the following information:
    a. The list of outstanding issues raised by the MHRA following routine GCP inspection of the sponsor site and one investigator site.
    b. The sponsor's response to each of the outstanding issues raised by the MHRA, including the sensitivity analysis referred to in the CHMP Assessment Report for Renvela.
    c. Clarification of the status of the post marketing study report provided in the addendum to the clinical overview. Was this, or any other study, undertaken to meet the requirement of the CHMP for additional post marketing data to reinforce the safety set?
    d. Has the CHMP raised concerns about any other studies submitted to the EU in support of the marketing approval of sevelamer carbonate? If so, please provide all details.
    e. Have any other regulatory agencies raised concerns about any of the studies submitted to support the marketing approval of sevelamer carbonate in their country? If so, please provide all details.
    f. The term 'sponsor site' referred to in the CHMP assessment report was Genzyme Europe BV, The Netherlands, and is assumed to be the central co-ordination point for the study. Does the term 'sponsor site' refer to the central co-ordination point for the study?
    g. How many patients at the 'sponsor site' and the 'investigator site' gave rise to concern and what was the nature of these concerns? What was the proportion of the total patient population that gave rise to concern?
2. Please justify why Patient [information redacted] (4 major protocol deviations) from Study SVCARB002005 was not excluded from the PPS, given that one of the major protocol deviations resulted in the patient being crossed-over to sevelamer hydrochloride in Treatment Period 1 three weeks earlier than scheduled (that is, at Visit 10 rather than Visit 13). This appears to be significant, given that the treatment period was only 4 weeks in duration.

[6] London. 19 March 2009; Doc.Ref.: EMEA/214544/2009

3. Was the formula used to calculate the time-weighted average serum phosphorous level in studies GD3-163-201 and SVCARB00205 the same as that used to calculate this parameter in Study GD3-199-301? Have the formulas used in the studies been validated? Were the formulas used to calculate the time-weighted serum phosphorous level in the sevelamer carbonate studies the same as the formulas used to calculate this parameter in the sevelamer hydrochloride studies?
4. Please provide a justification for the non-inferiority margin of 1 mg/dL for serum phosphorous used in Study GD3-199-301.
5. In Study GD3-199-301, please account for the greater proportion of patients in the sevelamer carbonate powder QD group compared with the sevelamer hydrochloride tablet TDS group discontinuing prematurely because of withdrawn consent (12.5% [18/144] versus 5.5% [4/73], respectively).
6. In Study GTC-45-204, patients who developed hyperphosphataemia (serum phosphorous > 1.61 mmol/L) were treated with sevelamer hydrochloride for 12 weeks. What proportion of the 79 treated patients had serum phosphorous levels > 1.78 mmol/L prior to treatment and what were the efficacy outcomes for these patients?

Second Round Evaluation of clinical data submitted in response to questions

For details of the sponsor's responses to the Clinical questions and the evaluator's comments on these responses please see Attachment 2.

Second Round Benefit-Risk Assessment

Second round assessment of benefits

After consideration of the sponsor's responses to the clinical questions, the benefits of sevelamer carbonate administered TDS for the treatment of hyperphosphataemia in adult patients with Stage 4 and 5 CKD are unchanged from those identified in the First round evaluation.

Second round assessment of risks

After consideration of the sponsor's responses to the clinical questions, the risks of sevelamer carbonate administered TDS for the treatment of hyperphosphataemia in adult patients with Stage 4 and 5 CKD are unchanged from those identified in the First round evaluation.

Second round assessment of benefit-risk balance

The benefit-risk balance of sevelamer carbonate, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

It is recommended that sevelamer carbonate 800 mg tablets and 1.6 g and 2.4 g powder for oral solution, with trade names Renvela, Sevelamer Carbonate Winthrop and Sevelamer Carbonate Sanofi, be approved for the management of hyperphosphataemia in adult patients with Stage 4 and 5 chronic kidney disease.

V. Pharmacovigilance findings

Risk management plan (RMP)

The sponsor submitted a Risk Management Plan (EU-RMP, version 6.0, dated 28 August 2013, data lock point 6 June 2013 and an Australian Specific Annex (ASA) version 1.0, dated 5 March 2014) which was reviewed by the TGA. An updated ASA, version 1.1, dated 23 October 2014, was later submitted.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 7.

Table 7: Summary of Ongoing safety concerns

Important identified risks	Intestinal obstruction/ileus – intestinal perforation
Important potential risks	Peritonitis in peritoneal disease patients
	Arteriovenous fistula site complications in hemodialysis patients
	Difficulty swallowing Renvela tablets
	Off-label use in children
	Drug interactions with ciprofloxacin, ciclosporin, mycophenolate mofetil, levothyroxine and tacrolimus
	Vitamin deficiency
Important missing information	Data on use in hyperphosphataemic chronic kidney disease patients on peritoneal dialysis
	Data on use in hyperphosphataemic chronic kidney disease patients not on dialysis with serum phosphorus ≥ 1.78 mmol/l
	Use in pregnancy and lactation
	Use in hepatic impairment and immunocompromised patients

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to address all Ongoing safety concerns. In addition, a registry is ongoing at the time of this RMP evaluation to address the potential risk of 'Peritonitis'. No Australian patients will be included in this additional pharmacovigilance activity.

Risk minimisation activities

The sponsor proposes routine risk-minimisation activities for all Ongoing safety concerns except for the important potential risk of 'Arteriovenous fistula site complications in haemodialysis patients' and the missing information of 'Data on use in hyperphosphataemic chronic kidney disease patients on peritoneal dialysis', 'Data on use in hyperphosphataemic chronic kidney Disease patients not on dialysis with serum phosphorus ≥ 1.78 mmol/l' and 'Use in hepatic impairment and immunocompromised patients'. Additional risk-minimisation activities are also proposed in the EU-RMP for the potential risk of 'Decreased Vitamin Levels in CKD patients', 'Arteriovenous fistula (AVF) Complications' and 'Peritonitis in CKD Patients on Peritoneal Dialysis'. In contrast, no additional risk-minimisation activities are proposed in Australia.

Reconciliation of issues outlined in the RMP report

Table 8 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the RMP evaluator and the evaluation of the sponsor's responses.

Table 8: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	The sponsor confirms that the nonclinical and clinical evaluation reports have been reviewed to ensure that any responses provided to issues raised have been considered for relevance to the Risk Management Plan.	The sponsor's response has been noted.
2. It is recommended that the sponsor elaborates on the following issue in their response: The DUS and the PASS have been completed in June 2011 and July 2013, respectively. The RMP evaluator questions whether sufficient data has been collected in these studies which would allow some of these 'missing information' to be removed or reclassified.	The conclusions from the most recent Periodic Safety Update Report (PSUR) dated 4 July 2014 covering the period 1 May 2013 to 30 April 2014 confirm that no new safety concerns have been identified in the reporting period and sufficient data has been collected to warrant removal of missing information relating to data on use in hyperphosphataemic CKD patients on PD as well as those not on dialysis with serum phosphorus ≥1.78 mmol/L. A copy of the PSUR is attached and the information described is summarised below. A revised ASA was provided and an updated EU-RMP is scheduled to be available in the first quarter of 2015 and will incorporate the updates from PSUR. *Data on use in hyperphosphatemic CKD patients on peritoneal dialysis:* Data on the use of hyperphosphatemic CKD patients and sevelamer was obtained through the observational study	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	conducted through the dialysis registry for five years by the RDPLF (French Peritoneal Dialysis Registry). The data confirmed there was no association between peritonitis and the use of sevelamer in patients undergoing peritoneal dialysis when compared to patients taking other phosphate binders. *Data on use of hyperphosphatemic CKD patients not on dialysis with serum phosphorus > 1.78 mmol/L:* The use of sevelamer in this patient group was assessed in the Post Authorization Safety Study titled 'Renvela® Post marketing Observational Study to Monitor the Clinical Use in Adult Hyperphosphatemic Chronic Kidney Disease Patients Not on Dialysis with Serum Phosphorus ≥1.78 mmol/L' (SVCARB06009). The results of this study confirm the efficacy and safety profile of sevelamer carbonate in adult hyperphosphatemic patients not on dialysis. Final results from this study confirm that the Adverse Drug Reactions (ADRs) experienced by the patients are consistent with the patients' underlying renal disease and the known safety profile of sevelamer carbonate.	
3. As two of the studies listed in the pharmacovigilance plan were completed in June 2011 and July 2013, it is recommended that the sponsor amends the EU-RMP/ASA to delete these studies from the pharmacovigilance plan as they are not part of the planned pharmacovigilance activities in the RMP.	As per ASA version 1.0, these studies are not included in the Australian RMP for Renvela. An updated EU-RMP is scheduled to be available in the first quarter of 2015. These studies will be deleted at this time.	This is considered acceptable.
4. The sponsor describes that a request was submitted to the EMA in August 2013 to request	The EMA assessment has been completed and agreement has been reached	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
the French registry to be discontinued. It is recommended that the sponsor provides an update on the outcome of the assessment about this request by the EMA. If the status of this registry has changed since submission of the dossier, then the RMP should be updated accordingly.	that the risk of peritonitis in peritoneal dialysis patients will now be removed from the RMP. This will be reflected in the updated EU-RMP scheduled to be available in the first quarter of 2015. The sponsor will continue to monitor peritonitis in the PSUR. A revised ASA was provided reflecting the changes described above.	
5. The sponsor should provide information in the Australian PI/CMI to address the missing information of 'Data on use in hyperphosphataemic CKD patients on PD' and 'Data on use in hyperphosphataemic CKD patients not on dialysis with serum phosphorus ≥1.78 mmol/L'. Of note information to address the missing information is provided in the European Summary of Product Characteristics (SmPC). The risk minimisation plan in the ASA should be updated accordingly.	As per response to Point 2, these risks are no longer considered missing information and the ASA has been updated accordingly. No further information relating to these patient groups has therefore been added to the Australian PI.	Pending the Delegate's approval this is considered acceptable.
6. It is recommended that the potential risk of 'Arteriovenous fistula (AVF) Complications' be addressed by routine-risk minimisation in the Australian PI. The ASA should be updated accordingly.	AVF site complications are a well-recognised comorbidity in haemodialysis patients secondary to the patient's underlying disease and/or the complexity of the surgical procedure. A direct causal association with administration of sevelamer is not evident from the clinical trial safety data or from post marketing safety surveillance. Therefore information relating to AVF is not included in the Australian Renvela PI. Based on the latest PSUR, the sponsor has proposed to remove the potential risk of arteriovenous fistula (AVF) site complications in haemodialysis patients from the RMP, and this will be reflected in the updated EU-RMP scheduled to be available in the first quarter	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	of 2015. The ASA has been updated accordingly.	
7. The sponsor should provide a summary table in the ASA providing wording by which risk minimization is carried out in the Australian-PI and the EU SmPC. Differences in wording between the Australian-PI and the EU-SmPC should be identified and justification should be provided regarding the appropriateness for such differences.	The sponsor has conducted a comparison between the Australian PI and the EU SmPC. The majority of information presented in the PI to address safety concerns is considered to be equivalent to that of the EU-SmPC and in some instances additional text beyond the SmPC is provided. Some differences in approach between information included within the 'Precautions' section of the Australian PI and the SmPC relating to the potential risk of difficulty swallowing and vitamin deficiency have been identified and outlined. In both cases the information in the Australian PI is aligned with the Company Core Data Sheet and reflects the standard global approach to address these potential risks. Amending the text to align with the EU is therefore not considered necessary and the sponsor does not propose any further changes to the Australian PI.	It is noted that the sponsor's states: *The majority of information presented in the PI to address safety concerns is considered to be equivalent to that of the EU SmPC and in some instances additional text beyond the SmPC is provided.* Nevertheless, it is recommended the sponsor provide a summary table in the ASA providing wording by which risk minimization is carried out in the Australian-PI and the EU SmPC for all ongoing safety concerns. This recommendation remains.
8. The sponsor states that no additional risk minimisation is considered necessary in Australia because '*The information provided in the additional tools in Europe is considered to be part of routine clinical practice in the Australian healthcare environment and would be addressed as part of the standard product educational materials made available at the time of product launch*'. It is recommended that the sponsor clarifies what these 'educational materials' are, as it appears that provision of educational materials constitutes an additional risk minimisation activity. If this represents an additional risk	As part of quality use of medicines, general educational materials are produced at the time of launch for all products. These materials reflect the information included in the PI and are considered standard educational materials. These are not specifically risk mitigation tools, and therefore are not included in the RMP. The additional risk minimization activities presented in the EU-RMP address the following risks: • Peritonitis in peritoneal disease patients • Arteriovenous fistula site (AVF) complications in haemodialysis patients	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
minimisation activity, the sponsor should update the ASA accordingly and provide these materials for review.	• Vitamin deficiency In the latest PSUR, it has been proposed that the risks relating to peritonitis and AVF are both removed from the Renvela RMP. Information relating to the third risk, vitamin deficiency, is provided in the Product Information. No additional risk minimization activities beyond routine are proposed for this specific risk as this information is considered to be part of the routine clinical practice in the Australian healthcare environment.	
9. Amendments to the PI/CMI as recommended.	The PI and CMI have been updated as per the TGA's recommendation in the RMP evaluation report.	Pending the Delegate's approval this is considered acceptable.

Summary of recommendations

It is considered that the sponsor's response to the TGA request has not adequately addressed all of the issues identified in the RMP evaluation report (see *Outstanding issues* below)

Outstanding issues

Issues in relation to the RMP

It is recommended the sponsor provide a summary table in the ASA outlining wording by which risk minimization is carried out in the Australian PI and the EU SmPC for all Ongoing safety concerns. This table should identify any differences between the EU-RMP and the local implementation of risk management activities, for example: any differences between the risk minimisation activities undertaken as reflected in the content of the EU SmPC and the proposed Australian PI and the reasons for the difference (see Point 7 in Table 8 above).

The changes suggested by the clinical evaluator should be incorporated in the RMP when the next update of the document occurs.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Key changes to the updated RMP

In their response to the TGA requests the sponsor provided an updated ASA, version 1.1, dated 23 October 2014. An updated EU-RMP has not been provided but the sponsor refers to an update to the EU-RMP which is expected to occur in the first quarter of 2015.

The following changes to the table of ongoing safety concerns are proposed for an updated EU-RMP expected to be available in the first quarter of 2015:

1. Removal of missing information of 'Data on use in hyperphosphatemic CKD patients on peritoneal dialysis' based on data obtained through the observational study conducted through the dialysis registry for five years by the RDPLF (French Peritoneal Dialysis Registry). For further details please refer to Point 2 in Table 8.
2. Removal of missing information of 'Data on use of hyperphosphatemic CKD patients not on dialysis with serum phosphorus > 1.78 mmol/L' based on data collected in the Post Authorization Safety Study titled 'Renvela® Post marketing Observational Study to Monitor the Clinical Use in Adult Hyperphosphatemic Chronic Kidney Disease Patients Not on Dialysis with Serum Phosphorus ≥1.78 mmol/L' (see Point 2 in Table 8).
3. Removal of the potential risk of 'Peritonitis in peritoneal dialysis patients'. This amendment has been negotiated and approved by the EMA, based on data collected through the French Peritoneal Dialysis Registry (see Point 4 in Table 8).

Pending the removal of the missing information of 'Data on use in hyperphosphataemic CKD patients on PD as well as those not on dialysis with serum phosphorus ≥1.78 mmol/L' by the EMA, there are no objections to the proposed changes to the Ongoing safety concerns.

Suggested wording for conditions of registration

RMP

Implement EU-RMP, version 6.0, dated 28 August-2013, data lock point 06 June 2013 with Australian Specific Annex version 1.1, dated 23 October 2014 and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator has no objections to the registration of sevelamer carbonate.

Sevelamer carbonate is manufactured into immediate release film coated tablets or flavoured, sweetened powder for oral suspension using conventional manufacturing techniques. It has a shelf life of 3 years when stored below 25 °C, when protected from moisture and when not refrigerated. No absolute bioavailability study was provided because sevelamer carbonate is locally acting and not systemically absorbed.

Equilibrium and kinetic binding studies comparing sevelamer carbonate and sevelamer hydrochloride were conducted in a manner generally consistent with the FDA Bioequivalence Recommendations for Specific Products, Draft guidance on sevelamer carbonate tablet, sevelamer carbonate suspension and sevelamer hydrochloride tablet, although the phosphate concentration at which maximum binding occurs was not clearly established for the equilibrium or kinetic binding studies and only 6 replicates were performed of the equilibrium binding study. The quality evaluator concluded that there were no significant differences in the equilibrium binding capacity for acid pre-treated or acid non treated tablets and powder between sevelamer carbonate and the reference product, Renagel.

The sponsor has proposed assay limits of 11.3 to 14.1 mmol/g for the titrable amines on a dried basis;, equating to assay limits of 89 to 111%. This is outside the requirements of

Section 11(b) of TGO 78 which requires assay limits of 92.5 to 107.5%. The quality evaluator has accepted the sponsor's justification that these limits are within the current specification agreed in the US and EU.

Nonclinical

The nonclinical evaluator has no objections to the registration of sevelamer carbonate.

An absorption study demonstrated radiolabelled [^{14}C] sevelamer carbonate conducted in dogs showed 94% of the administered dose was recovered in the faeces in the first 24 hours and 0.04 to 0.07% was recovered in the urine. No adverse effects were demonstrated in rats exposed to single doses of up to 20 g/kg of sevelamer carbonate. Dose dependent reductions in serum vitamins, lipids and folic acid were seen in repeat-dose studies of rats (doses 0.6, 3.0 and 6.0 g/kg/day for 6 months) and dogs (0.2, 0.6 and 2.0 g/kg/day for 12 months) with sevelamer hydrochloride. No effect on fat soluble vitamin levels was found in dogs given sevelamer hydrochloride or sevelamer carbonate dosed at 0.2 and 1.0 g/kg/day for 4 weeks. In a repeat-dose rat study of sevelamer carbonate and sevelamer hydrochloride dosed at 1.0 and 4.5 g/kg/day reduction in vitamin E levels were found. In the same study female rats had an increase in vitamin D levels when given 4.5 g/kg/day sevelamer carbonate or sevelamer hydrochloride. A 13 week study to investigate the potential formation of urothelial tumours in rats treated with 0.25, 1.0 and 4.5g/kg/day indicated a low risk of urothelial carcinogenesis with sevelamer carbonate administration. A study to assess the toxicological potential of allylamine of up to 10 ppm supported the safety of this specified maximum level.

The sponsor has proposed a Pregnancy Category of B3[7], based on information about sevelamer hydrochloride. The nonclinical evaluator has not specifically commented on the pregnancy category but has not recommended changes.

Clinical

The clinical evaluator has recommended approval for the proposed indication 'Renvela is indicated for the management of hyperphosphataemia in adult patients with Stage 4 and 5 chronic kidney disease'.

Pharmacology

A review of the pharmacology studies revealed the following findings:

- The conventional pharmacokinetic information is not available for sevelamer carbonate because it is not systemically absorbed.
- Consistent with previous studies with sevelamer hydrochloride, there are no apparent interactions between warfarin or digoxin and sevelamer carbonate.
- The clinical evaluator concluded the information about the PK interaction studies involving sevelamer hydrochloride and ciprofloxacin, warfarin, digoxin, enalapril, metoprolol and iron can be extrapolated to sevelamer carbonate. The sponsor has proposed to include in the Renvela PI the same warnings about possible reductions in the levels of cyclosporin, tacrolimus, mycophenolate mofetil and levothyroxine with concomitant sevelamer use as appear in the Renagel PI. A possible interaction

[7] Pregnancy Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

between sevelamer carbonate and anti-arrhythmic or anti-epileptic medications has not been investigated and patients taking these medications were specifically excluded from clinical trials with sevelamer carbonate.

- A reduction in urinary phosphorus excretion was used as a pharmacodynamic (PD) measure of the intestinal phosphate binding by sevelamer carbonate, and was demonstrated in one study in healthy volunteers.

Efficacy

Study GD3-163-201

This was a Phase II, randomised, double-blind, two sequence, cross-over study to compare the effects of serum phosphate and serum lipids of sevelamer carbonate tablets TDS and sevelamer hydrochloride tablets TDS in 79 adult hyperphosphataemic patients with CKD on haemodialysis three times weekly for three months or longer, who required phosphate binder therapy but not more than 13.6g/day for ≥ 60 days, and had a serum phosphate ≥ 1.0 mmol/L but ≤ 2.1 mmol/L, iPTH ≤ 66 pmol/L and normal serum calcium. 92% had used sevelamer hydrochloride as their pre-study phosphate binder. Patients continued on stable vitamin D, lipid lowering agents and cinacalcet therapy. Patients were excluded if they had active dysphagia, swallowing disorder, bowel obstruction, severe gastrointestinal motility disorder; had clinically significant unstable medical conditions; and were taking anti-arrhythmic and/or anti-epileptic medication. The treatment period for either sevelamer carbonate (SC) tablets or sevelamer hydrochloride (SH) tablets began after a 5 week SH run-in period and continued for 8 weeks before the cross-over of treatments. Time weighted mean of the measurements from the last three visits in each treatment period were used for the analysis. Of the 79 patients randomised, 74 completed Treatment Period 1 (4 discontinued because of an AE, and 1 because of non-compliance) and 1 discontinued between Treatment Periods 1 and 2. Of the 73 patients that started Treatment Period 2, 69 completed (AE, death, loss to follow-up and 'other' were responsible for the discontinuation of one patient each). Fifty one percent were male and the mean ± standard deviation (SD) age was 58 ± 12 years (29 to 88 years). Most patients were Black/African-American (67%), or White (27%). CKD was mostly caused by diabetes mellitus (42%) and hypertension (23%), and the mean time on dialysis was 4.4 ± 4.9 years (0.34 to 23.4 years). Vitamin D was taken by 86% and 5% had a previous parathyroidectomy. Other medications were taken by 100% of the patients. There were no significant differences between the concomitant medications taken during the two treatment intervals.

The primary endpoint was the time-weighted mean serum phosphorus levels. The equivalence of the two treatments was assessed using natural-log transformed time-weighted mean serum phosphorus data. Sevelamer carbonate and sevelamer hydrochloride were deemed to be equivalent if the 90% CI for test (Sevelamer Carbonate) to reference (Sevelamer Hydrochloride) ratio was 0.8 to 1.25. The study had 90% power to detect equivalence based on a 5% Two, One-Sided Test equivalence test.

Table 9: Study GD3-163-201 Primary efficacy outcome – serum phosphorus equivalence test; overall mean time weighted serum phosphorus (per protocol set)

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

At the end of the study a 2 week washout period was conducted. Patients in sequence 1 (SC followed by SH) had mean ± SD serum phosphorus of 1.48 ± 0.39 mmol/L at Week 16 (end of the treatment periods) and 2.03 ± 0.58 mmol/L at the end of the washout. Patients in sequence 2 (SH followed by SC) had mean ± SD serum phosphorus of 1.71 ± 0.39 mmol/L at Week 16 and 2.13 ± 0.65 mmol/L at the end of the washout.

The secondary endpoint was serum lipids (total cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol and triglycerides) analysed by a 2x2 analysis of variance (ANOVA) model using the mean of the measurements from Weeks 4 and 8 in Treatment period 1 and Weeks 12 and 16 in Treatment period 2. Comparisons between the treatment regimens were tested at the 5% level.

Table 10: Study GD3-163-201 Serum lipids (full analysis set)

Laboratory parameter mmol/L	Sevelamer carbonate (n=73) Mean ± SD	Sevelamer hydrochloride (n=78) Mean ± SD	p-value	Geometric LS mean ratio	90% CI of ratio
Total cholesterol	3.72 ± 0.88	3.59 ± 0.87	0.009	1.04	1.01-1.06
LDL - Cholesterol	1.54 ±0.64	1.45 ± 0.60	0.035	1.07	1.01-1.12
HDL cholesterol	1.29 ± 0.46	1.27 ± 0.39	0.707	1.01	0.98-1.03
Triglycerides	1.99 ± 1.24	1.91 ± 1.18	0.243	1.03	0.99-1.07

Study SVCARB00205

This was a Phase III, multicentre, randomised, open label, cross-over study, of sevelamer carbonate powder dosed three times daily with meals versus sevelamer hydrochloride dosed three times daily with meals in 31 adult hyperphosphataemic patients with CKD on haemodialysis requiring not more than 14.4 g/day of phosphate binder. A 2 week screening and washout period was followed by a 4 week sevelamer hydrochloride run-in period and two 4 week treatment periods (sevelamer carbonate followed by sevelamer hydrochloride or sevelamer hydrochloride followed by sevelamer carbonate) with no washout period between the two treatments. Eligible patients had a serum phosphorus ≥ 1.76 mmol/l at the end of the washout period; , and ≥ 0.96 and ≤2.08mmol/L and an intact parathyroid hormone (iPTH) of ≤ 88 pmol/L after the run-in period. Patients taking Vitamin D, calcimimetics and lipid-lowering medications continued these but doses were not adjusted and new medications were not permitted. The dose of sevelamer salt during the run-in period was titrated to keep the serum phosphorus between 1.12 and 1.76 mmol/L and this dose was used throughout the randomised cross-over treatment periods. The study had a 90% power to detect equivalence based on a 5% Two One-Sided Test equivalence test, assuming the ratio of means was 1 and the SD on the log scale was 0.22. Premature discontinuations occurred for 3 patients during the first treatment period (1 due to an AE and 2 withdrew) and for 4 patients during the second treatment period (1 due to AE and 3 withdrew). The mean age was 52.9 ± 13.2 years, 68% were female, 71% were Caucasian and 84% were non-smokers. The most common cause of the CKD was 'other' (42%), followed by glomerulonephritis (26%) and diabetes (13%). The mean time on dialysis was 7.2 ± 8.0 years, 26% had a previous renal transplant and 13% had undergone a parathyroidectomy. All the patients took a concomitant medication and medication changes were permitted during the run-in and treatment periods. Vitamin D analogues were changed by 13% of patients in the run-in period. Compliance was similar during the run-in and treatment periods (87% and 86% for the Per-Protocol Set (PPS)).

The primary endpoint was serum phosphorus time-weighted averages using serum phosphorus assessment during the last two weeks of each treatment period.

Table 11: Study SVCARB00205 – Serum phosphorus time weighted averages (per protocol set)

Analysis set	Sevelamer carbonate powder Serum phosphorus (mmol/L) (mean ± SD)	Sevelamer hydrochloride tablets Serum phosphorus (mmol/L) (mean ± SD)	Geometric LSM Ratio (Carb/HCl)	90% CI
Per protocol (n=21)	1.6 ± 0.5 (n=21)	1.7 ± 0.4 (n=21)	0.95	0.87, 1.03

The mean ± SD serum phosphorus at screening was 1.6 ± 0.3 mmol/L and at the end of the washout period was 2.5 ± 0.6 mmol/L.

Secondary endpoints were the elevated calcium x phosphorus (Ca x P) product and serum lipid profile. The least squares (LS) mean ratio of the Ca x P product for sevelamer carbonate versus sevelamer hydrochloride was 0.98 (90% CI: 0.88, 1.09). The serum lipids results were as shown in Table 12.

Table 12: Study SVCARB00205 – serum lipids (full analysis set)

Laboratory Parameter	Sevelamer Carbonate Powder (N=30) mean ± SD	Sevelamer Hydrochloride Tablets (N=28) mean ± SD	P-value	Geometric LS Mean Ratio	90% CI of Ratio
mmol/L	(n=22)	(n=27)			
Total Cholesterol	3.5 ± 0.7	3.3 ± 0.8	0.218	1.02	0.99-1.06
LDL Cholesterol	1.8 ± 0.5	1.8 ± 0.7	0.109	1.05	1.00-1.10
HDL Cholesterol	1.2 ± 0.5	1.1 ± 0.4	0.537	0.98	0.93-1.04
Triglycerides	2.2 ± 1.6	2.1 ± 1.5	0.992	1.0	0.89-1.12

Study GD3-199-301

This was a Phase III, multicentre, randomised, two-arm, parallel, open label study in CKD patients on haemodialysis conducted in 217 patients over a 24 week treatment period comparing once a day sevelamer carbonate powder dosing (n=144) with three times daily sevelamer hydrochloride tablet dosing (n=73) in CKD patients on haemodialysis. The study consisted of a 2 week screening period, a 2 week phosphate binder washout period and a 24 week randomised treatment period.

Eligible patients had a serum iPTH of < 88 pmol/L, serum phosphorus of ≥ 1.78 mmol/L at the end of the washout and were randomised 2:1 to receive sevelamer carbonate once daily powder or sevelamer hydrochloride three times daily tablets. The randomised patients were stratified for screening iPTH (≤ 42 or > 42 pmol/L) and use of cinacalcet. The starting dose was 4.8 g daily and was titrated to a target serum phosphorus range of ≥ 1.13 mmol/L and ≤ 1.78 mmol/L). The target serum iPTH was ≤ 16 and ≤ 32 pmol/L and was managed with vitamin D and cinacalcet. The treatments were either sevelamer hydrochloride 800 mg tablets or sevelamer carbonate powder in 2.4 g packets. Those in the sevelamer hydrochloride tablet group had a starting dose of 1.6 g TDS and those in the sevelamer carbonate powder group 4.8 g once daily. The sevelamer dose was titrated in 2.4 g/day increments to a target serum phosphorous of ≥ 1.13 mmol/L to ≤ 1.78 mmol/L.

Ninety three patients in the sevelamer carbonate group and 62 patients in the sevelamer hydrochloride tablet completed the study. Overall 22 (10.1%) discontinued because of AEs, 20 (9.2%) withdrew consent and there were 3 deaths, resulting in 84.9 % of the sevelamer hydrochloride completing the study compared with 64.6% of the sevelamer carbonate group.

Baseline demographics were similar between the two groups. The four most common causes of chronic renal failure reported with an incidence of ≥ 10% in at least one of the treatment groups (sevelamer carbonate versus sevelamer hydrochloride, respectively) were diabetes (40.4% versus 34.7%), hypertension (29.1% versus 33.3%), other causes (16.3% versus 20.8%) and glomerulonephritis (10.6% versus 5.6%). Mean ± SD time on dialysis was 44.4 ± 45.0 versus 52.6 ± 43.9 months, vitamin D use at screening 85.1% versus 84.7% and previous parathyroidectomy (total or partial) 3.5% versus 1.4% in the sevelamer carbonate versus the sevelamer hydrochloride groups, respectively. All patients took concomitant medications and 91.5% of the sevelamer carbonate and 93% of the sevelamer hydrochloride patients added new medications or changed their prior medications during the treatment period.

The mean dialysate bicarbonate concentration was similar between the two treatment groups. There was no statistically significant difference reported in the diet of each treatment group and treatment compliance was similar and 85% or above. The study had 90% power based on a two-group student's t-test with a one-sided 2.5% type I error rate for a non-inferiority margin of 0.32 mmol/L. Non-inferiority was concluded if the one-sided 97.5% upper confidence bound for the difference in serum phosphorus change from baseline between the treatment groups was < 0.32 mmol/L.

The primary efficacy endpoint was the change from baseline to Week 24 in serum phosphorus. The results for the per protocol set were as follows:

- Sevelamer hydrochloride change from baseline -0.96 ± 0.42 mmol/L ($p<0.001$)
- Sevelamer carbonate change from baseline -0.66 ± 0.57 mmol/L ($p<0.001$)
- Difference = 0.30 mmol/L (95% CI 0.12, 0.48)

In the full analysis set the sevelamer change from baseline was -0.61 ± 0.54 mmol/L $p<0.001$ and for sevelamer hydrochloride was -0.82 ± 0.50 mmol/L.

The difference in change from baseline between sevelamer carbonate and sevelamer carbonate 0.21 mmol/L (95% CI 0.06, 0.36).

The non-inferiority of once daily sevelamer carbonate powder with sevelamer hydrochloride TDS was *not* demonstrated. The upper bound 2-sided, 95% CI of 0.48 mmol/L (per protocol set) or 0.36 mmol/L (full analysis set) were greater than the pre-specified non-inferiority margin of 0.32 mmol/L. Dose-responsiveness was seen in the sevelamer hydrochloride (TDS) group but not the sevelamer carbonate (once daily) group.

The secondary efficacy endpoints were a time-weighted average of serum phosphorous, percent responders for serum phosphorus, Ca (albumin-adjusted) x P product and serum lipids change from baseline to Week 24. Time weighted average values for serum phosphorus were higher in the sevelamer carbonate group compared with the sevelamer hydrochloride group (1.70 ± 0.3 mmol/l versus 1.59 ± 0.24mmol/L, $p=0.021$). Serum phosphorus response was more common in the sevelamer hydrochloride TDS group (73%) than the sevelamer carbonate powder once daily group (56%), $p=0.052$. Both sevelamer carbonate and sevelamer hydrochloride groups showed a statistically significant decrease in Ca (albumin-adjusted) x P compared with baseline for the respective group. Total cholesterol, LDL-cholesterol and non-HDL cholesterol were all significantly reduced from baseline irrespective of group. The differences between baseline were greater in the sevelamer hydrochloride group both compared with baseline and in the between group comparison. There were no within-group or between group statistically significant differences in HDL-cholesterol and triglycerides. The baseline reductions in serum phosphorus were statistically significant within both treatment group in the subgroup analyses for baseline iPTH (≤ 400 pg/mL versus > 400 pg/mL) and baseline cinacalcet use (used versus not used).

Study SVCARB00105

A Phase III, multinational, multi-centred, open label, single arm, dose titration study of sevelamer carbonate tablets dosed three times daily in 49 adult hyperphosphataemic CKD patients not on dialysis in which patients acted as their own controls. After a two week washout period, 49 patients with 25-hydroxyvitamin D ≥ 10 ng/mL and iPTH ≤ 88 pmol/L and a serum phosphorus of ≥ 1.76 mmol/L after the washout period (prior treatment with phosphate binders) or at the beginning of the treatment period (no prior phosphate binder treatment) were all given sevelamer carbonate tablets for approximately 8 weeks followed by a further 2 week washout period. Sevelamer carbonate started at a dose of 1.6 g TDS and was titrated in 2.4 g daily increments to achieve a serum phosphorus of ≥ 0.86 mmol/L to 1.47 mmol/L. Calcium supplementation, vitamin D, cinacalcet and lipid-lowering medication were all permitted during the study if the patient was taking these at study entry but the doses were to be maintained and no new medications were permitted. All patients received 400 IU vitamin D to minimise any effect of sevelamer carbonate on vitamin D levels, this was in addition to any ongoing vitamin D therapy. The study was powered to detect a 0.32 mmol/L average change from baseline on a two-sided paired t-test with a 5% type I error SD for the change from baseline of 0.45 mmol/L. Patients had a mean age of 62.0 ± 12.1 years, 65% were male, 92% were Caucasian, 65% had stage 5 CKD and 35% had Stage 4. The primary cause of the CKD was 'other' (22%) and diabetes (18%). No patients had undergone a renal transplant or parathyroidectomy. All patients took concomitant medications, with 77.6% on vitamin D supplements. Changes in concomitant medications during the treatment phase were most common for vitamin D preparations. Compliance was more than 87%.

The primary efficacy outcome (Full Analysis Set (FAS)) was change in serum phosphorus levels from baseline to the end of the treatment period. The mean ± SD at baseline was 2.0 ± 0.3 mmol/L. The mean ± SD difference from baseline was -0.5 mmol/L ($p<0.001$). Patients with CKD Stage 4 and stage 5 both had a significant decrease from baseline. From the conclusion of the treatment period to the end of the final 2 week washout period there was a mean ± SD increase of 0.6 ± 0.3 mmol/L.

The secondary efficacy endpoints were the Ca (albumin-adjusted) x P product, serum lipids and percent serum phosphorus responders. The Ca x P product decreased by 0.8 ± 0.73 $mmol^2/L^2$ ($p<0.001$) from baseline to the end of the treatment period, with an increase of 1.1 ± 0.77 $mmol^2/L^2$ at the end of the final 2 week washout period. Total cholesterol and LDL-cholesterol showed a significant decrease from baseline, but not HDL-cholesterol or triglycerides. Fifty percent of the patients reached the target serum phosphorus at the end of the 8 week treatment period.

Study APB00108

This is a multicentre, randomised, double-blind, placebo-controlled Phase II study comparing sevelamer carbonate, in doses of 2.4 g/day, 4.8 g/day and 7.2 g/day and the Genz-644470 (an experimental phosphate binder not for evaluation in this submission). The clinical evaluator has not considered this study relevant for efficacy data.

Study SVCARB00606

A multinational, multicentre, randomised, double-blind, placebo-controlled Phase III study designed to investigate the efficacy and safety of sevelamer carbonate tablets TDS in patients not on dialysis. Only 5 patients were randomised to this study and consequently it was terminated early. The sample size was too small to draw meaningful conclusions.

Sevelamer hydrochloride studies.

The sponsor also provided studies previously evaluated in support of the registration of sevelamer hydrochloride (see clinical evaluation report for details). In addition, ***Study REN-003-04,*** not previously evaluated, provided data on the use of sevelamer

hydrochloride in patients undergoing peritoneal dialysis. This was a multinational multicentre study to compare sevelamer hydrochloride 800 mg tablets TDS with calcium acetate 538 mg tablets TDS in 143 adult patients receiving peritoneal dialysis and with a serum phosphorus level of >1.77 mmol/L and a serum calcium (albumin adjusted) of 2.10 to 2.60 mmol/L after a 2 weeks phosphate binder-free washout period. The mean patient age was 54 ±16 years, 65% were male and 90% were Caucasian.

The most common cause of CKD was reported to be 'other' (32%) followed by glomerulonephritis (18%), diabetes (18%) and polycystic kidney (13%). The mean duration ± SD of dialysis was 26 ± 34 months and 80% of patients had a urine output > 200 mL/day. Most had not undergone renal transplantation (83%) or parathyroidectomy (95%). All patients were taking a pre-study phosphate binder. The primary efficacy endpoint was the change in serum phosphorus level from baseline to the end of Week 12. Non-inferiority was determined if a one-sided 97.5% upper confidence interval was less than 0.3 mmol/L for the difference of the serum phosphorus between the two groups (sevelamer minus calcium). Superiority could be concluded if non-inferiority was established and the 97.5% upper CI was <0.0 mmol/L. The one-sided 97.5% upper confidence bound serum phosphorus level for the difference between sevelamer carbonate and calcium acetate was 0.012 mmol/L with the one-sided 95% CI 0.163 mmol/L. Both sevelamer hydrochloride and calcium acetate met the secondary endpoint of a reduction in the Ca x P product at Week 8 compared with baseline but there was no significant difference between the two groups. A statistically significant difference from baseline in total, LDL and non-HDL cholesterol was seen in the sevelamer group but not the calcium acetate group. No difference from baseline was seen for HDL-cholesterol and triglycerides increased over the study period in the calcium acetate but not the sevelamer hydrochloride group. Uric acid concentration decreased in the sevelamer group. A similar decrease in iPTH was seen in each of the treatment groups compared with baseline.

Safety

In the clinical trial programs for both sevelamer salts 1093 patients were exposed to at least one dose. The exposure to sevelamer carbonate was 294 patients (245 on haemodialysis and 49 not on haemodialysis), with an estimated total exposure of 69.4 patient years but for any individual the maximum exposure was 24 weeks. The majority of patients received > 4.8 g/day but <9.6 g/day. In the 8 week, cross-over study comparing sevelamer carbonate tablets TDS (n=73) and sevelamer hydrochloride tablets TDS (n=78) [GD3-163-201], 82.2% and 83.3%, respectively experienced at least one AE.

The AEs reported in ≥ 5% of patients in the sevelamer carbonate versus the sevelamer hydrochloride were nausea (9.6% versus 12.8%), vomiting (8.2% versus 10.3%), hypercalcaemia (8.2% versus 2.6%), AV fistula site complications (6.8% versus 1.3%), cough (5.5% versus 3.8%), AV fistula site haemorrhage (5.5% versus 2.6%), carbon dioxide decreased (5.5% versus 5.1%), muscle spasms (5.5% versus 3.8%), AV-fistula thrombosis (4.1% versus 11.5%), pain in extremity (4.1% versus 7.7%), diarrhoea (2.7% versus 6.4%), GORD (1.4% versus 5.1%), and fatigue (1.4% versus 5.1%).

For AE and SAE safety findings from Studies GD3-199-301, SVCARB00205, APB00108, GD3-163-201 see Attachment 2.

Treatment related AEs (TRAEs) are discussed in the evaluations of Studies GD3-163-201, GD3-199-301, SVCARB00105, APB00108 and Study SVCARB00205 (see Attachment 2). Overall, there were no marked differences in the treatment related AE profiles between the two sevelamer salts when given according to the proposed dosage regimens but when sevelamer carbonate was given as a once daily dose gastrointestinal events were approximately doubled.

Two patients died during Study GD3-163-201 2; one in the sevelamer carbonate tablet TDS group (worsening of coronary artery disease) and one in the sevelamer hydrochloride tablet TDS group (diabetic complications following renal transplant). In Study GD3-199-301 there were two deaths (1.4%) in the sevelamer carbonate group (1 from a cardiac arrest of unknown cause, 1 after withdrawal of renal replacement therapy) and four deaths (5.6%) in the sevelamer hydrochloride group (1 patient each with a cardiac arrest of unknown cause; septic shock, staphylococcal pneumonia and hypertensive cardiovascular disease; septicaemia; and intracranial haemorrhage). In Study SVCARB00105, there was one death from bronchopneumonia in the sevelamer carbonate group. In Study APB00108 one patient died from abdominal pain and septic shock (possible perforated viscus). All deaths were considered unrelated to the study treatment. There were no deaths in Study SVCARB00205.

The only six (7.7%) treatment discontinuations due to AEs in Study GD3-163-201 were in the sevelamer hydrochloride tablet TDS group, two due to renal transplantation, one due to AV fistula thrombosis and hepatic ischaemia, and one patient each due to allergic dermatitis, asthenia and muscular weakness. In Study GD3-199-301, discontinuations due to AEs occurred more frequently in the sevelamer carbonate powder once daily group than in the sevelamer hydrochloride tablet TDS group (12.0% versus 4.2%, respectively).

In the sevelamer carbonate group, five patients discontinued due to oral administration complications (bad taste of study drug, gagging when taking study drug), eight discontinued due to gastrointestinal disorders (nausea, vomiting, bloatedness, diarrhoea and rectal bleeding), and four discontinued due to other events (worsening hyperphosphataemia, renal transplant, cerebrovascular accident and central line infection). Seven of the gastrointestinal disorders were considered treatment related. The four discontinuations due to a SAE in the sevelamer hydrochloride group were because of a cardiac arrest, a myocardial infarction, septic shock, and an intracranial bleed; and none was classified as treatment related. In Study SVCARB00105, treatment discontinuations due to AEs were reported in 10.2% of patients (n=5) and in 4 of the 5 patients these were treatment related gastrointestinal events. The remaining patient had a pleural effusion (followed by death due to bronchopneumonia), which was assessed as not treatment related. In Study SVCARB00205 3 patients from the sevelamer carbonate powder TDS group discontinued because of nausea (2 patients) and vomiting (1 patient) and chest pain (1 patient).

In a PASS in adult CKD patients not on dialysis with serum phosphorous levels ≥ 1.78 mmol/L, 210 patients took Renvela for a median duration of 312 days (range: 5, 373 days), at a mean ± SD prescribed dose of 3.7 ± 1.9 g/day (range: 0.8, 12 g/day) and 148 (70.5%) took the Renvela TDS. Overall, 15.7% of patients experienced ADRs. Gastrointestinal disorders were reported by 14.3% of patients and included nausea (4.3%), constipation (3.8%), diarrhoea (1.9%), dyspepsia (1.9%), vomiting (1.4%), abdominal distension (1.0%), abdominal pain (1.0%) and upper abdominal pain (1.0%). Overall, the post marketing ADR profile observed in PASS in patients with CKD not on dialysis was similar to the pre-marketing safety profile observed in patients in the Phase III Study SVCARB00105.

There was a statistically significant decrease from baseline in the mean ± SD serum chloride in the sevelamer carbonate group but not in the sevelamer hydrochloride group in Study GD3-163-201 (-2.6 ± 3.6 mEq/L versus 0.00 ± 4.1 mEq/L, respectively) and Study SVCARB00205 (-2.7 ± 2.7 mEq/L versus -0.4 ± 2.7 mEq/L, respectively). In the 24 week study no increase serum chloride was seen in the sevelamer carbonate group but there was in the sevelamer hydrochloride group (0.5 ± mEq/L versus 2.4 ± 3.85 mEq/L, respectively). In the single arm sevelamer chloride study there were no changes from baseline in serum chloride. In the single arm study there was a significant increase in serum bicarbonate (+1.3± 2.9 mEq/L). Serum carbon dioxide was significantly increased

in the sevelamer carbonate group but not in the sevelamer hydrochloride group in Study GD30163-201 (1.3 ± 4.1 mEq/L v -0.3 ± 3.6 mEq/L). Serum bicarbonate was significantly increased in the sevelamer carbonate group but not in the sevelamer hydrochloride group in Study SVCARB00205 (2.7 ± 3.7 mEq/L v 0.1 ± 3.3 mEq/L). In Study GD3-199-301 there was no change in serum carbon dioxide in the sevelamer carbonate group (0.1 ± 3.42 mEq/L) but there was a significant decrease in the sevelamer hydrochloride group (-1.0 ± 3.62 mmol/L). Serum uric acid decreased with the sevelamer hydrochloride TDS but not sevelamer carbonate once daily in this 24 week study. There were no clinically meaningful differences in laboratory parameters between the sevelamer carbonate and placebo treatment groups in Study APB00108.

Postmarketing Sevelamer carbonate

The estimated exposure to sevelamer carbonate tablets and powder over the reporting interval was 1,495,673 patients, corresponding to 440,489 total patient-years for sevelamer carbonate. An analysis of postmarket data summarised the safety concerns for sevelamer carbonate similarly to the Summary of Safety Concerns in the RMP. The important identified risks with Renvela included intestinal obstruction/ileus and intestinal perforation. Difficulty swallowing the sevelamer carbonate tablets was also mentioned as a potential risk.

Clinical evaluator's recommendation

The clinical evaluator recommended that sevelamer carbonate 800 mg tablets and 1.6 g and 2.4 g powder for oral solution, with trade names Renvela, Sevelamer Carbonate Winthrop and Sevelamer Carbonate Sanofi, be approved for the management of hyperphosphataemia in adult patients with Stage 4 and 5 chronic kidney disease.

Risk management plan

The RMP evaluator has accepted the EU-RMP, version 6.0, dated 28 August 2013, data lock point 6 June 2013 with Australian Specific Annex version 1.1, dated 23 October 2014 and any future updates as a condition of registration.

The following were outstanding matters and should be followed up with the RMP evaluator and in the Pre-ACPM response:

- Provide a summary table in the ASA outlining wording by which risk minimization is carried out in the Australian PI and the EU SmPC for all Ongoing safety concerns.

Risk-benefit analysis

Delegate's considerations

Efficacy

Hyperphosphataemia in CKD is a condition associated with significant morbidity and increased mortality if untreated. The management of hyperphosphataemia is multifaceted. The aspect of most relevance to this discussion is phosphate binding. Sevelamer is an orally administered polymeric anion exchange resin that is not systemically absorbed and the usual bioequivalence studies are not relevant. Sevelamer carbonate is an alternative salt of the registered sevelamer hydrochloride (Renagel). The efficacy of sevelamer carbonate is supported by in vitro and clinical studies to demonstrate the phosphate binding and reduction in serum phosphorus in the proposed population of patients with

CKD Stage 4 or 5 and hyperphosphataemia, including patients on haemodialysis and those not on any form of dialysis.

The in vitro phosphate binding studies were not conducted in accordance with the current FDA draft guidance for in vitro bioequivalence studies for sevelamer carbonate compared with sevelamer hydrochloride in that only 6 replicates of the binding studies were performed and the kinetic phosphate binding study was conducted to a maximum concentration of 38.7 mM phosphate. These studies, performed in isolation would be insufficient to support the equivalence of sevelamer carbonate. Although the FDA guidance documents are not adopted by the TGA it is expected that the most recent version of the guidance should be followed. To address this deficiency however, there is additional support for the therapeutic equivalence of sevelamer carbonate with sevelamer hydrochloride based on the clinical studies.

Three times daily dosing with both the sevelamer carbonate tablets and the powder for oral suspension is supported by the clinical studies conducted in patients with CKD Stage 4 or 5 and hyperphosphataemia, including patients on haemodialysis and those not on any form of dialysis. When sevelamer carbonate powder was given once daily it was not non-inferior to sevelamer hydrochloride dosed TDS. By extrapolation with sevelamer hydrochloride, sevelamer carbonate is likely to be efficacious in patients on peritoneal dialysis. Both sevelamer salts reduce total cholesterol and LDL cholesterol and decrease the Ca x P product, which further supports the therapeutic equivalence of two sevelamer salts. Drug interactions have been explored with warfarin and digoxin and by extrapolation drug interactions known for sevelamer hydrochloride are assumed to be similar. Anti-arrhythmic drugs and anti-epileptic drugs were not permitted in patients during the clinical development program. Some of these are anions and may be bound to the sevelamer polymer (for example, sodium valproate).

Long term clinical trial efficacy data has not been submitted in support of the sevelamer carbonate salt however, by demonstrating therapeutic equivalence between sevelamer hydrochloride and sevelamer carbonate, the efficacy over years based on sevelamer hydrochloride has been extrapolated. This is acceptable because the studies were conducted in sufficiently similar patient populations in terms of baseline demographics and underlying disease processes, with similar efficacy endpoints. A weakness is the clinical trial supporting the use in the non-haemodialysis population for sevelamer hydrochloride versus sevelamer carbonate where the eligibility criterion of baseline serum phosphorus of > 1.6 mmol/L in the sevelamer hydrochloride study is lower than that for the sevelamer carbonate study.

Safety and RMP

The safety profile of sevelamer hydrochloride has been extrapolated to sevelamer carbonate. In the short term exposure in the clinical trial setting and in the postmarketing experience summarised by the sponsor, the safety profiles of the two sevelamer salts appear similar.

No long term safety data has been obtained from pre-authorisation studies, with the longest duration of exposure only 24 weeks, however a post authorisation safety study included data from hyperphosphataemic CKD patients who were not on dialysis and there is approximately 7 years post authorisation experience internationally.

The deaths and most of the SAEs were attributable to underlying renal disease or the complications of renal replacement therapy. Gastrointestinal disorders were similar for both preparations of sevelamer carbonate and sevelamer hydrochloride with the proposed dosage regimen. All formulations pose a risk of oesophageal and intestinal obstruction in predisposed patients although neither was reported in the clinical trials.

The analysis of the post marketing data suggests a risk of intestinal obstruction and perforation that has been noted with sevelamer hydrochloride. The clinical trials for sevelamer carbonate specifically excluded patients at risk of these events. Swallowing difficulties has been listed as a potential problem in the analysis of the postmarketing data. The sponsor has proposed inclusion of a precautionary statement about difficulty swallowing the Renvela tablet. The physical dimensions of the proposed Renvela tablet have not been provided and have been requested from the sponsor. The powder for oral suspension is an alternative dose form for the patients with swallowing difficulties. Differences between sevelamer carbonate and sevelamer hydrochloride for the effect on serum carbon dioxide/bicarbonate and serum chloride were observed. No changes consistent with a worsening hyperchloraemic metabolic acidaemia were seen in the patients taking sevelamer carbonate. This was expected because of the substitution of carbonate for hydrochloride in the formulation of the new salt. The effect was seen even with once daily dosing with sevelamer carbonate powder.

Dose

Three times daily dosing is supported by data from the clinical trials. Dose adjustment is a part of the clinical management of hyperphosphataemia. The proposed starting dose of 2.4 to 4.8 g/day is consistent with the clinical trials and internationally. In providing information on switching from other medications the sponsor has included a dosing instruction of 0.8 g for the sevelamer carbonate powder for oral suspension. Approval for a 0.8 g strength has not been sought by the sponsor and the 1.6 g and 2.4 g powder preparations are not presented in a manner that the patient could easily reduce the dose given by one half or one third, respectively. The sponsor has been requested to provide a justification for the inclusion of instructions for this dosage strength in this section of the PI.

Indication

The proposed indication '*Renvela is indicated for the management of hyperphosphataemia in adult patients with Stage 4 and 5 chronic kidney disease*' is the same as the currently approved Renagel. It is noted that in the EU SmPC the indication restricts the use of sevelamer carbonate to patients with a serum phosphorus of >1.7 mmol/L when not on dialysis. ACPM is requested to provide advice on this matter.

Data deficiencies

The clinical studies of both sevelamer carbonate and sevelamer hydrochloride excluded patients taking anti-arrhythmic drugs and anti-epileptic medications. Children were excluded from the clinical trials. The safety and efficacy of sevelamer carbonate has not been established in patients less than 18 years of age. The availability of an oral suspension may see more (off-label) use in children, although a drug utilisation study mentioned in the RMP showed that <1% of the use was in children. No direct comparison of the therapeutic equivalence of sevelamer carbonate powder given TDS with the sevelamer carbonate tablets also given TDS. There is no clinical trial data to support the use of sevelamer carbonate in patients with CKD and hyperphosphataemia undergoing peritoneal dialysis. There is an absence of long term exposure data in the clinical trial program although there is now several years of postmarket experience and there is longer term data from the sevelamer hydrochloride development program.

Conditions of Registration

The following are proposed as conditions of registration:

1. Implement EU-RMP, version 6.0 dated 28 August 2013, data lock point 06 June 2013 with Australian Specific Annex version 1.1, dated 23 October 2014 and any subsequent revisions, as agreed with the TGA.

2. The following studies/reports must be submitted to the TGA, as soon as possible after completion for evaluation as a Category 1 submission:

    a. Provide the final clinical study report for the Phase II study in the US to evaluate the safety and tolerability of sevelamer carbonate in hyperphosphataemic paediatric patients aged < 18 years with CKD.

Summary of Issues

The primary issues with this submission are as follows:

1. Whether there is sufficient evidence to support the interchangeability of sevelamer carbonate powder and sevelamer carbonate tablets.
2. Whether there is sufficient evidence to support this use of sevelamer carbonate in patients with hyperphosphataemia not on dialysis, with an elevated serum phosphorus that is <1.78 mmol/L.

Questions for the sponsor

The sponsor is requested to address the following issues in the Pre-ACPM Response:

1. Difficulty swallowing the tablets is mentioned in the Precautions section of the draft PI. Please provide the physical dimensions of the finished tablet. Please compare these dimensions to the physical dimensions of Renagel.
2. In Study GD3-163-201 hypercalcaemia was reported in 8.2% and 2.6% of the sevelamer carbonate and sevelamer hydrochloride patients respectively. Please provide an analysis of these patients.
3. Table 9 of the proposed PI includes a starting dose of 0.8 g for the Renvela powder, but the preparation instructions only mention the 1.6 g and 2.4 g powder sachets and the sponsor has not made an application for a 0.8 g powder sachet. Please provide a justification for the inclusion of this dose without accompanying instructions about how it is to be prepared.
4. In the PI, in the Presentation and Storage Conditions section, below the description of the powder, in the footnotes for the section, an asterisk denoting presentations currently not marketed is present. There are no presentations marked with an asterisk in this version of the PI. Please clarify the intention of the footnote.

Proposed action

The Delegate had no reason to say, at this time, that the application for sevelamer carbonate (Renvela) should not be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. The proposed PI includes a precaution under the heading Hyperparathyroidism to use sevelamer in the context of a multi-therapeutic approach that could include calcium supplement, 1,25-dihydroxy Vitamin D3 or one of its analogues to lower iPTH. Is this advice to prescribers only relevant to patients with elevated iPTH levels, or does it apply more generally to patients with CKD Stages 4 or 5?
2. Has sufficient efficacy data been submitted to support the use of sevelamer carbonate in hyperphosphataemic CKD patients not requiring haemodialysis?

3. The majority of the clinical trials supporting the use of sevelamer carbonate in hyperphosphataemic patients with CKD included patients with an untreated serum phosphorus of ≥ 1.78 mmol/L. Should the indication be restricted to these patients only, or is the broader indication proposed by the sponsor acceptable?
4. Table 7 of the Renagel PI is a dose titration guideline for sevelamer hydrochloride based on the patient's serum phosphorus. Should this type of guidance for dose titration also be included in the Renvela PI?
5. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from Sponsor

The sponsor's comments on the issues for which the advice of the ACPM is sought and additional information requested, as outlined in the Delegates Overview of 6 January 2015, are presented below.

The sponsor is seeking registration of Renvela (sevelamer carbonate), which is an alternative salt to the currently registered product Renagel (sevelamer hydrochloride), which has been available in Australia as a tablet formulation since 2007. Renvela has been formulated as a tablet (800 mg) and as a powder for oral suspension in fill volumes of 1.6 g and 2.4 g. The availability of a phosphate binder in powder form fulfils an unmet need for those hyperphosphataemic CKD patients unable to take tablets who have difficulty swallowing tablets or those who have a high pill burden.

The intended patient population for Renvela is identical to that of Renagel with the following proposed indication as currently approved by the TGA for Renagel:

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

Treatment of hyperphosphataemia consists of dietary phosphorus restriction and/or dialysis and use of phosphate binders. Sevelamer is a non-absorbed phosphate binder free of calcium and aluminium. The use of calcium based phosphate binders can result in chronic calcium overload, hypercalcaemia and soft tissue calcification. Aluminium based phosphate binders are associated with significant toxicity due to small amount of absorbed aluminium.

Renvela tablets and powder for oral suspension are approved for marketing in more than 70 countries worldwide. The patient exposure is estimated to be 1.9 million patient-years cumulatively for both the hydrochloride and carbonate salts (reporting period 1 May 2014 to 30 October 2014). Collated safety data from the sevelamer clinical development program in hyperphosphataemic CKD patients, together with extensive world-wide post marketing experience for over 10 years, provide a robust and comprehensive safety database and confirms the therapeutic value of the compound in clinical practice.

1. *The proposed PI includes a precaution under the heading Hyperparathyroidism to use sevelamer in the context of a multi-therapeutic approach that could include calcium supplement, 1,25-dihydroxy Vitamin D3 or one of its analogues to lower iPTH. Is this advice to prescribers only relevant to patients with elevated iPTH levels, or does it apply more generally to patients with CKD stages 4 or 5?* In regard to the proposed PI precaution under the heading Hyperparathyroidism, patients with elevated iPTH attributed to CKD will generally have relatively advanced stages, that is CKD Stages 4 or 5. It would be unusual to have patients with milder CKD Stages 1 to 3 have secondary hyperparathyroidism. The advice therefore applies more generally to patients with CKD 4 or 5.
2. *Conditions of registration*

Implement EU-RMP, version 6.0 dated 28-Aug-2013, data lock point of 06-Jun-2013 with the Australian Specific Annex version 1.1, dated 23-Oct-2014 and any subsequent revisions, as agreed with the TGA.

On the basis of availability of a new version of the EU-RMP and updates to the ASA, the registration conditions will need to reference EU-RMP version 7.0 dated 17 December 2014 and data lock point of 30 October 2014 with and an ASA version 1.2 dated 19 January 2015. The updated documents are provided as part of this Pre-ACPM response.

3. *The following studies/reports must be submitted to the TGA as soon as possible after completion for evaluation as a Category 1 submission:*

    a. *Provide the final clinical study report for the Phase II study in the US to evaluate the safety and tolerability of sevelamer carbonate in hyperphosphataemic paediatric patients aged <18 years with CKD.*

The study described above is ongoing and upon availability of the clinical study report, appropriate submission of data will be made in alignment with the submission approach in the EU and US.

Questions for the Sponsor

1. *Difficulty swallowing the tablets is mentioned in the Precautions section of the draft PI. Please provide the physical dimensions of the finished tablet. Please compare these dimensions to the physical dimensions of Renagel.*

The physical dimensions of Renagel and Renvela were measured using calibrated measuring equipment as per in-process control procedures. The mean results are displayed in Table 13. The information shows that the dimensions between the two products are comparable.

Table 13: Dimensions of the Renvela 800 mg and Renegal 80 mg tablet

Mean value	Length (mm)	Width (mm)	Thickness (mm)
Renvela 800 mg	19.79	10.08	7.82
Renagel 800 mg	19.54	9.87	7.49

2. *In Study GD3-l63-201 hypercalcaemia was reported in 8.2% and 2.6% of the sevelamer carbonate and sevelamer hydrochloride patients respectively. Please provide an analysis of these patients.*

Hypercalcaemia adverse events were of limited duration in most cases. They were resolved at the next time serum corrected calcium was measured in 3 of the sevelamer carbonate cases (patients [information redacted]) and 1 of the sevelamer hydrochloride cases (patient [information redacted]). In one sevelamer carbonate case (patient [information redacted]), calcium carbonate was being taken by the patient prior to and at the time of start of the event. In one sevelamer carbonate case (patient [information redacted]), hypercalcaemia was present at baseline and was resolved the next time serum corrected calcium was measured. A detailed analysis for the requested patients in Study GD3-163-201 is provided below.

- Patient [information redacted] was randomised to sevelamer carbonate followed by sevelamer hydrochloride. One hypercalcaemia adverse event was reported during both sevelamer carbonate treatment (moderate, unrelated, recovered) and sevelamer hydrochloride treatment (mild, unrelated, ongoing). The serum corrected calcium level was 2.30 mmol/L (9.2 mg/dL) at baseline and ranged from 2.53 to 2.63 mmol/L (10.1 to 10.5 mg/dL) during sevelamer carbonate treatment and 2.43 to 2.60 mmol/L (9.7 to 10.4 mg/dL) during sevelamer hydrochloride treatment. The first event started

6 weeks into sevelamer carbonate treatment and was resolved by the next time serum corrected calcium was measured 15 days later. The second event 6 weeks into sevelamer hydrochloride treatment and was continuing at the end of the study.

- Patient [information redacted] was randomised to sevelamer hydrochloride followed by sevelamer carbonate. One hypercalcaemia adverse event (mild, unrelated, recovered) was reported during sevelamer carbonate treatment. The serum corrected calcium level was 2.40 mmol/L (9.6 mg/dL) at baseline and ranged from 2.20 to 2.40 mmol/L (8.8 to 9.6 mg/dL) during sevelamer hydrochloride treatment and 2.30 to 2.63 mmol/L (9.2 to 10.5 mg/dL) during sevelamer carbonate treatment. The hypercalcaemia event started two weeks into sevelamer carbonate treatment and was resolved at the time serum corrected calcium results were measured 6 days later.
- Patient [information redacted] was randomised to sevelamer carbonate followed by sevelamer hydrochloride. One hypercalcaemia adverse event (mild, unrelated, recovered) was reported during sevelamer carbonate treatment. The serum corrected calcium level was 2.73 mmol/L (10.9 mg/dL) at baseline and ranged from 2.43 to 2.50 mmol/L (9.7 to 10.0 mg/dL) during sevelamer carbonate treatment and 2.40 to 2.48 mmol/L (9.6 to 9.9 mg/dL) during sevelamer hydrochloride treatment. The hypercalcaemia event started at baseline (pre-treatment) and was resolved at the time serum corrected calcium results were measured 8 days later.
- Patient [information redacted] was randomised to sevelamer hydrochloride followed by sevelamer carbonate. One hypercalcaemia adverse event (mild, remote, recovered) was reported during sevelamer hydrochloride treatment. The serum corrected calcium level was 2.35 mmol/L (9.4 mg/dL) at baseline and ranged from 2.30 to 2.63 mmol/L (9.2 to 10.5 mg/dL) during sevelamer hydrochloride treatment and 2.38 to 2.50 mmol/L (9.5 to 10.0 mg/dL) during sevelamer carbonate treatment. The hypercalcaemia event started 4 weeks into sevelamer hydrochloride treatment and were resolved at the time serum corrected calcium was measured 15 days later.
- Patient [information redacted] was randomised to sevelamer carbonate followed by sevelamer hydrochloride. One hypercalcaemia adverse event (mild, unrelated, recovered) was reported during sevelamer carbonate treatment. The serum corrected calcium level was 2.23 mmol/L (8.9 mg/dL) at baseline and ranged from 2.43 to 2.58 mmol/L (9.7 to 10.3 mg/dL) during sevelamer carbonate treatment and 2.33 to 2.58 mmol/L (9.3 to 11.4 mg/dL) during sevelamer hydrochloride treatment. The hypercalcaemia event started at 4 weeks into sevelamer carbonate treatment and continued through to the time serum corrected calcium was measured 71 days later (through the sixth week of sevelamer hydrochloride treatment). Of note, the patient was taking calcium carbonate 2500 mg QD starting 54 days prior to the adverse event start date and continuing until 27 days prior to the adverse event end date.
- Patient [information redacted] was randomised to sevelamer carbonate followed by sevelamer hydrochloride. One hypercalcaemia adverse event (mild, unrelated, recovered) was reported during sevelamer carbonate treatment. The serum corrected calcium level was 2.35 mmol/L (9.4 mg/dL) at baseline and ranged from 2.30 to 2.68 mmol/L (9.2 to 10.7 mg/dL) during sevelamer carbonate treatment and 2.20 to 2.40 mmol/L (8.8 to 9.6 mg/dL) during sevelamer hydrochloride treatment. The hypercalcaemia event started at 4 weeks into sevelamer carbonate treatment and was resolved by the next serum corrected calcium was measured 15 days later.
- Patient [information redacted] was randomised to sevelamer carbonate followed by sevelamer hydrochloride. Two hypercalcaemia adverse events (mild, unrelated, recovered) were reported during sevelamer carbonate treatment. The serum corrected calcium level was 2.48 mmol/L (9.9 mg/dL) at baseline and ranged from 2.58 to 2.78 mmol/L (10.3 to 11.1 mg/dL) during sevelamer carbonate treatment and

2.33 to 2.48 mmol/L (9.3 to 9.9 mg/dL) during sevelamer hydrochloride treatment. Both hypercalcaemia events started at about 5 weeks into sevelamer carbonate treatment. The first was listed as ongoing and the second was listed through the time serum corrected calcium as measured 38 days later.

Summary

In summary, the positive benefit risk profile for sevelamer carbonate as an alternative to sevelamer hydrochloride supports approval of Renvela for the management of hyperphosphataemia in adult patients with Stage 4 and 5 chronic kidney disease based on:

- demonstrated therapeutic equivalence of the two salts supported by extensive world-wide postmarketing experience for over 10 years.
- long established use of sevelamer in adult patients with Stage 4 and 5 chronic kidney disease in clinical practice in Australia.
- well characterised safety profile based on an estimated cumulative exposure of 1.9 million patient-years for both the hydrochloride and carbonate salts.

The availability of a powder for oral suspension formulation of Renvela also addresses an unmet need for those patients unable to take tablets, who have difficulty swallowing tablets or who have a high pill burden, thus providing a useful addition to existing therapeutic options.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following (Resolution 2926):

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Renvela film coated tablets and powder for solution, containing sevelamer carbonate 800 mg film coated tablets; 1.6 g and 2.4 g powder of to have an overall positive benefit–risk profile for the proposed indication**;**

> *Sevelamer carbonate is indicated for the management of hyperphosphataemia in adult patients with stage 4 and 5 chronic kidney disease (CKD).*

In making this recommendation the ACPM

- Noted that the level of evidence provided in support of efficacy and safety was limited.
- Noted the sponsor presumed that other potential drug interactions have been covered by sevelamer hydrochloride results.
- Noted there were no paediatric or pharmacodynamic data presented.
- Noted the results of the one study which included non-dialysis patients were supportive of efficacy, with a similar safety profile to that in the dialysis patient population.
- Expressed some concern that no long term clinical trial efficacy data were submitted.
- Noted no study has examined whether there is sufficient evidence to support the interchangeability of sevelamer carbonate powder and sevelamer carbonate tablets. Both forms have efficacy. If changed over, monitoring and adjustment of dosing in accordance with measured phosphate is required.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- The ACPM agreed with the Delegate and advised the PI and CMI required considerable editing, including Pharmacology and Dosing and Administration sections.
- The ACPM noted several references to calcium acetate in the PI all of which should be removed as this product is not used in Australia.
- A statement in the *Dosage and Administration* sections of the PI and relevant section of the CMI that Renvela must be used in conjunction with dietary phosphate restriction.
- Removal from the CMI of the statements;
  - "*Your doctor, however, may have prescribed Renvela for another purpose*".
  - On the possible need for calcium or Vitamin D supplementation
  - The potential for peritonitis and need for sterile technique.

Specific Advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *The proposed PI includes a PRECAUTION under the heading Hyperparathyroidism to use sevelamer in the context of a multi-therapeutic approach that could include calcium supplement, 1,25-dihydroxy Vitamin D3 or one of its analogues to lower iPTH. Is this advice to prescribers only relevant to patients with elevated iPTH levels, or does it apply more generally to patients with CKD stages 4 or 5?*

The ACPM acknowledged the further advice on this point from the sponsor in its pre-ACPM response but the Precaution applies to patients diagnosed with hyperparathyroidism. The committee was unable to see how this is relevant to CKD 4 and 5 without hyperparathyroidism.

2. *Has sufficient efficacy data been submitted to support the use of sevelamer carbonate in hyperphosphataemic CKD patients not requiring haemodialysis?*

The data is sufficient considering the Precaution to allow nephrologists discretion in use.

3. *The majority of the clinical trials supporting the use of sevelamer carbonate in hyperphosphataemic patients with CKD included patients with an untreated serum phosphorus of ≥ 1.78 mmol/L. Should the indication be restricted to these patients only, or is the broader indication proposed by the sponsor acceptable?*

Given the indication for Renegal, restriction of the indication proposed for Renvela would not be reasonable. The data are sufficient to allow nephrologists discretion in use.

4. *Table 7 of the RENAGEL PI is a dose titration guideline for sevelamer hydrochloride based on the patient's serum phosphorus. Should this type of guidance for dose titration also be included in the Renvela PI?*

The ACPM noted the sponsor concurs with the Delegate's suggestion for inclusion of the dose titration guidance in the Renvela PI as is currently included in the Renagel PI.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Sevelamer Carbonate Sanofi sevelamer carbonate 1.6 g powder for oral suspension sachet, Sevelamer Carbonate Winthrop sevelamer carbonate 2.4 g powder for oral suspension sachet, Sevelamer Carbonate Sanofi sevelamer carbonate 800 mg tablet bottle, Renvela sevelamer carbonate 1.6 g powder for oral suspension sachet, Renvela sevelamer carbonate 2.4 g powder for oral suspension sachet, Sevelamer Carbonate Winthrop sevelamer carbonate 800 mg tablet bottle, Renvela sevelamer carbonate 800 mg tablet bottle, Sevelamer Carbonate Sanofi sevelamer carbonate 2.4 g powder for oral suspension sachet, Sevelamer Carbonate Winthrop sevelamer carbonate 1.6 g powder for oral suspension sachet, for oral administration indicated for:

> *Renvela/Sevelamer Carbonate Winthrop/ Sevelamer Carbonate Sanofi is indicated for the management of hyperphosphataemia in adult patients with Stage 4 and 5 chronic kidney disease.*

Specific conditions of registration applying to these goods

1. The sevelamer carbonate Risk Management Plan (RMP), version 7.0, dated 17 December 2014, data lock point 30 October 2014, and Australian Specific Annex (ASA) Version 1.2 dated 19 January 2015, included with submission PM-2013-04961-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. The following studies/reports must be submitted to the TGA, as soon as possible after completion for evaluation as a Category 1 submission:
    a. Provide the final clinical study report for the Phase 2 study in the US to evaluate the safety and tolerability of sevelamer carbonate in hyperphosphataemic paediatric patients aged < 18 years with CKD.

Attachment 1. Product Information

The Product Information approved for Renvela/Sevelamer carbonate Winthrop/Sanofi Sevelamer carbonate at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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