Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 1

Extract from the Clinical Evaluation Report for Sevelamer hydrochloride

Proprietary Product Name: Sevelamer GPPL, Sevelamer GxP, Sevelam, Sevlar, Apo-sevelamer, Apotex-sevelamer, Chemmart sevelamer, Genrx sevelamer, Terry White sevelamer

Sponsor: Generic partners Pty Ltd

First Round Evaluation: 24 January 2014

Second Round Evaluation: 29 April 2014

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 the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse Events
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
^{o}C	degrees Celsius CI
CI	Confidence Interval
CKD	chronic kidney disease
CMI	Consumer Medicine Information
CV	coefficient of variation
EPAR	European Public Assessment Record
EU	European Union
FDA	Food and Drug Administration
GFR	glomerular filtration rate
g	gram
HC	Health Canada
HCl	hydrochloric acid
HD	haemodialysis
HAS	Health Sciences Authority (Singapore)
iPTH	intact parathyroid hormone
kD	kilodalton
KDOQI	Kidney Disease Outcomes Quality Initiative
kg	kilogram
m^2	square metre
mEq	milliequivalents
mg	milligrams

Abbreviation	Meaning
MHRA	Medicines and Health Regulatory Agency
min	minute
mm	millimetres
mM	millimolar
mmol	millimols
mL	millilitre
L	litre
PD	peritoneal dialysis
PI	Product Information
pg	picogram
rpm	revolutions per minute
SD	standard deviation
tds	ter die sumendum (three times daily)
TGA	Therapeutic Goods Administration
TGO	Therapeutic Goods Order
T/R	test to reference ratio
US(A)	United States of America
µm	micrometre

1. Introduction

This is a Category 1 type D submission to register a new generic formulation of the previously approved sevelamer hydrochloride (Renagel, Sanofi-Aventis).

Sevelamer hydrochloride is polymeric anion exchange resin that acts in the gastrointestinal tract to bind dietary phosphate ions.

The proposed indication is as follows:

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

2. Clinical rationale

Chronic kidney disease is defined as either kidney damage or glomerular filtration rate (GFR) <60 mL/min/m^2 for ≥ 3 months. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) definitions of the stages of chronic kidney disease are presented in Table 1 below.

Table 1: Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with mildly decreased GFR	60-89
3	Moderately decreased GFR	30 - 59
4	Severely decreased GFR	15 - 29
5	Kidney failure	<15 (or dialysis)

Apart from GFR, other renal functions that may be affected by chronic kidney disease include action as a filtration barrier to proteins, reabsorption or secretion of water or specific solutes and various endocrine functions. For example renal failure may cause parathyroid hormone excess and/or Vitamin D deficiency with resultant bone disease.

Sixty to 70% of intestinal phosphate is absorbed in the gut by two processes: passive diffusion across an electrochemical gradient between cells and via a transcellular Na^+ dependent pathway via a co-transporter. Sixty to 70% of ingested phosphate is absorbed in the duodenum and jejunum and 30 – 40% in the ileum. Serum phosphorus levels are higher in individuals with decreased renal function and there is evidence to suggest that serum phosphorus levels become abnormal in some patients at a GFR below approximately 60 mL/min/1.73 m^2.

Hyperphosphataemia is largely asymptomatic even at high levels. In patients with chronic kidney disease it tends to be chronic. Haemodialysis can remove phosphorus from the serum. Approximately 1000 mg of phosphorus can be removed per 4 hour treatment with blood and dialysate flows of 300 mL/min and 500 mL/min respectively (Daugirdas et al 2011). Most removal occurs early in dialysis.

Phosphate is a major mineral component of bone and excess phosphate alters bone pathology by several mechanisms. Phosphate complexes with serum calcium, leading to subnormal serum ionised calcium levels. The lowered calcium stimulates parathyroid hormone release (secondary hyperparathyroidism), as do high phosphate levels alone. Elevated parathyroid hormone levels result in high bone turnover, releasing calcium to normalise the calcium-phosphate imbalance.

High phosphate levels also inhibit renal alpha-1 hydroxylase which produces activated Vitamin D. Decreased activated Vitamin D reduces calcium absorption from the gut, decreased renal reabsorption of calcium and impaired bone mineralisation. This is manifest by bone pain and fractures.

Patients with kidney failure and uncontrolled hyperphosphataemia also develop extensive soft tissue calcifications including in the skin, joints and the eye.

Vascular calcification is a cause of significant morbidity and mortality as a consequence of chronic uncontrolled hyperphosphataemia. All types of blood vessels as well as the valves and conducting system of the heart can be involved.

Although dietary restrictions can be useful, additional measures may be required in patients with advanced kidney disease. Phosphate binders have been used to reduce serum phosphate. Phosphate binders containing calcium salts largely replaced aluminium containing products because of the toxicity from absorbed aluminium. However the calcium containing salts have the disadvantage of providing additional calcium and unwanted calcification from absorbed calcium.

Sevelamer hydrochloride is a phosphate binder that does not contain calcium.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- No clinical trials using generic products for which this application pertains
- In vitro and kinetic studies
- Published papers referenced in Clinical Overview in Module 2

3.2. Paediatric data

The submission did not include paediatric data.

3.3. Good clinical practice

Not applicable - no clinical trials were conducted by the sponsor in support of this generic formulation.

3.4. Guidance

3.4.1.1. Australian regulatory guidance

The reference product for this formulation is a polymer which acts locally in the gut to reduce serum phosphate in patients with Grade 4 or 5 kidney disease and hyperphosphataemia. The TGA has its own guidelines and has adopted European Union (EU) guidelines that are of relevance to generic formulations of these types of medicines.

3.4.1.1.1. TGA guidelines:

- Schedule 9 of the Therapeutic Goods Regulations 1990 Part1 1 Interpretation of table Section 1(1) - definition of a generic product
- Australian Regulatory Guidelines for Prescription Medicines Appendix 15
  - Section 2: Products for which biopharmaceutic data are not normally required
  - Section 4: Justification for not submitting biopharmaceutic data
  - Section 7: Choice of the reference product for bioequivalence of generic medicines
- Therapeutic Goods Order No. 78 – Standard for Tablets and Capsules (29/10/2008) Subsection 11(b)

3.4.1.1.2. TGA adopted EU Guidance:

- 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

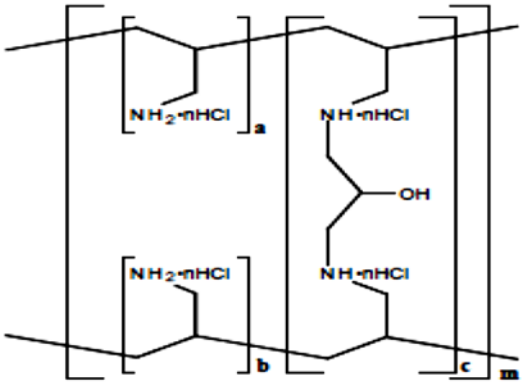
4. Pharmacokinetics

4.1. Summary of pharmacokinetics of the reference formulation

The sponsor has not included pharmacokinetic studies of the generic product, but has included references which provide information regarding the pharmacokinetics of the reference product. The following is a summary of that information.

Sevelamer hydrochloride is a polymer of allyl amine with the amines spaced by one carbon from the polymer backbone (Figure 1). It is a white to off-white water insoluble powder (Renagel PI). It is a partial hydrochloride salt, approximately 40% amine hydrochloride and 60% free base. It is hydrophilic but is insoluble in water. It has a pKa of 9 (Goldberg et al 1998).

Figure 1: Structure of sevelamer hydrochloride



a, b = number of primary amine groups	a + b = 9
c = number of crosslinking groups	c = 1
n = fraction of protonated amines	n = 0.4

m = large number to indicate extended polymer network

Sevelamer hydrochloride is a large molecule, of the order of magnitude of 10^{13} kD (Plone et al 2002). Each molecule forms a particle. The mean particle size for the reference product is 25 – 65 µm (Plone et al 2002). The particle size affects outcome in terms of phosphate binding, with

smaller particles more efficacious than larger ones (23µm versus 182µm (Rosenbaum et al 1997).

Evaluator comment: Particle size is important for phosphate binding and therefore efficacy. The generic product only controls for the largest particle size. In Module 2.3 the sponsor states the specification limit for the particle size by sieve is less than 500 µm, and that no more than 1.00% will be greater than 500 µm. There is no lower limit set for the particle size and the mean particle size has not been described. The quality evaluator has raised this issue with the sponsor.

It does not degrade in conditions simulating gastric fluid i.e. pH 1.2 with added pepsin (Renagel EPAR).

There are cross-linkages within the molecule, which is important for phosphate binding. The sponsor states that the reference product is 10.6 – 13.9% cross-linked. Cross-linkage in the molecule is also related to the amount it swells. The reference formulation of sevelamer hydrochloride has been show to swell approximately 6 to 8 times its weight when placed in aqueous solutions (Rosenbaum et al 1997). Plone et al (2002) state that from unpublished data from GelTex Pharmaceuticals it swells to 8 times its volume.

The sponsor has presented the average physical dimensions from four batches of Renagel 800 mg tablets; two batches from Australia and two European batches. The two Australian batches had average tablet lengths of 19.07mm and 19.08mm, average widths of 9.79 and 9.78 mm and average heights of 7.62 and 7.60 mm, respectively.

In studies of the reference formulation, ^{14}C radiolabelled sevelamer hydrochloride was not systemically absorbed. Plone et al (2002) conducted a study to examine the absorption, distribution and excretion of sevelamer hydrochloride in twelve Sprague-Dawley rats and twenty human volunteers.

In the rat study [^{3}H] sevelamer hydrochloride was given to rats either as a single dose in treatment naïve rats (6 rats) and in rats pre-treated (approximately 6 g/kg/day)for 28 days with unlabelled sevelamer hydrochloride and given labelled sevelamer on day 29 (6 rats). Urine and faeces were collected for 72 hours. The average recovery of radioactivity in the faeces was 97.6 ± 6.22% in the single dose group and greater than 104.65± 2.97% in the pre-treated group. In non-gastrointestinal tissue 0.06 – 0.07% of the dose was found.

In the human study all participants were pre-treated with unlabelled sevelamer (6.975 g/day in 3 divided doses for 28 days) and received a single 2.5 g dose of [^{14}C] sevelamer on day 29, followed by a further 11 x 2.365g doses of the unlabelled sevelamer. Blood urine and faeces samples were collected for up to 96 hours. Most subjects had no detectable ^{14}C in the urine. In some subjects less than 0.02% radioactivity was detected in the urine, a level equivalent to the free ^{14}C in the sample. On average 99% of the administered dose was recovered in the faeces, and 0.009 ± 0.01% was found in the urine. No detectable amounts of radioactivity were found in blood samples.

The reference formulation is not systemically absorbed and is therefore not systemically bioavailable. It is not known to undergo metabolism in the gut. There are no metabolites that are known to be systemically absorbed. Over 99% of the reference product is excreted in the faeces.

The target population has either Stage 4 or 5 chronic kidney disease. Absorption studies were not conducted in patients with renal failure. The pharmacokinetics of sevelamer has not been evaluated in patients with hepatic disease, patients with gastrointestinal disorders, and paediatric patients.

4.2. Studies providing pharmacokinetic data

The sponsor has provided an in vitro equilibrium phosphate binding study and a kinetic phosphate binding study, and a justification for not conducting a bioequivalence study. The sponsor has only conducted the in vitro studies using the 800 mg dosage strength, but has provided justification for studying only one dosage strength. The sponsor has not used an Australian brand product in in vitro equivalence studies and has provided a justification for so doing.

4.2.1. In vitro bioequivalence studies

A detailed account of in vitro and kinetic studies was provided. This has been evaluated by the quality evaluator. The following are descriptions of the studies.

4.2.2. The equilibrium binding study:

In the 'Draft FDA guidance' equilibrium binding study is considered the pivotal bioequivalence study. The Guidance states that:

- *The analyte for the study is unbound phosphate in the filtrate (to calculate phosphate bound to resin)*
- *The Langmuir binding constants k_1 and k_2 should be determined and the test/reference ratio should be calculated for k_1*
- *The 90% confidence interval should be calculated for k_2 with the acceptance criteria of 80% to 120%.*
- *Bioequivalence is based on the 90% CI of the Langmuir binding constant k_2 from the equilibrium binding study.*

The study was conducted by incubating sevelamer hydrochloride at eight different phosphate concentrations (1 mM, 2 mM, 5 mM, 10 mM, 15 mM, 20 mM, 30 mM, 40 mM), with and without acid pre-treatment (at pH 4.0 and pH 7.0). The generic product was compared with the overseas reference product.

All tests were carried out in a 500 mL volumetric flask that was incubated at 37^{o}C, and shaken at 90 rpm for 2 hours. Samples were then filtered, diluted and analysed to estimate bound phosphate using ion chromatography.

The study was carried out to obtain six replicate sets of data.

The Langmuir binding constants – affinity constant (k_1) and capacity constant (k_2) were the outcomes reported for the study.

Table 2 shows the log-transformed data for the generic and reference products. The test/reference (T/R) ratio of the geometric least squares means of the affinity constant was 76.4 (%CV4.4) without acid pre-treatment. The capacity constant T/R ratio was 97.25% (90% CI 95.17 – 99.38) which was within the pre-specified 80 – 125% set down in the guidance document.

Table 2: Geometric Least Squares Mean (GSLM) and 90% CI for Generic Sevelamer hydrochloride

Parameters	Condition	GLSM		90% CI for log-transformed data				
		Generic	Ref.	TR ratio (%)	Lower limit	Upper limit	Power (%)	Intra-set CV (%)
k1	With acid pre-treatment	0.6387	0.8520	74.96	NA	NA	NA	5.5
	Without acid pre treatment	0.5875	0.7690	76.40	NA	NA	NA	4.4
k2	With acid pre-treatment	6.5603	6.6251	99.02	96.81	101.28	100.0	2.2
	Without acid pre-treatment	6.3609	6.5406	97.25	95.17	99.38	100.0	2.1

k1=affinity constant; k2=capacity constant.

This study has been reviewed in detail by the quality evaluator.

Evaluator comment: The Langmuir binding constants are components of the Langmuir adsorption equation. The constant k_1 is the affinity constant and is a measure of the forces involved in the binding. The constant k_2 is binding constant and is the apparent maximum amount of adsorbate that can be adsorbed per unit weigh of adsorbent.

The sponsor has relied of FDA 'Draft Guidance on Sevelamer Hydrochloride'. It is noted that the guidance states that each binding study and should be repeated 12 times. The sponsor has reported the results of six repeats. The quality evaluator will comment on the conduct of this study. The acceptance criteria for the k_2 variable (90% CI 80 – 125%) are also being considered by the quality evaluator.

The clinical significance of the difference in affinity between the generic and the reference products is unknown, however it would appear to indicate there is a difference in the behaviour between the generic and the reference product. The sponsor has not specifically addressed this issue.

4.2.3. The kinetic binding study

The kinetic binding study measured the binding of phosphate ions of the generic product and the (overseas) reference product over time. The binding was measured at phosphate concentrations of 1 mM and 40 mM and at pH of 4.0 and 7.0. The observation times were 15, 30, 60 90, 120, 150, 180 and 240 minutes.

All tests were carried out in a 500 mL volumetric flask, shaken at 90 rpm and incubated at 37°C.

Samples were then filtered, diluted and analysed to estimate bound phosphate using ion chromatography.

The study was carried out to obtain six replicate sets of data.

The test (generic product)/reference (T/R) ratios were the outcomes reported for the time intervals. As shown in Table 3, the phosphate binding of the generic and reference products appear similar at conditions of 1 mM, and 40 mM and pH 7.0. In conditions of 40 mM phosphate and pH 4.0 the ratio of affinity constants of the generic to the reference product was approximately 94%.

Table 3: Kinetic Binding Study - Test/Reference ratio for Generic Sevelamer hydrochloride.

Parameters	Condition	% Ratio (T/R)		
		Minimum	Maximum	Overall Mean
Affinity constant (k1)	1 mM, pH 4.0	98.37	99.17	98.72
	1 mM, pH 7.0	97.22	98.06	97.66
	40 mM, pH 4.0	93.95	94.61	94.23
	40 mM, pH 7.0	97.10	97.86	97.55

This study has been reviewed in detail by the quality evaluator.

> Evaluator comment: All phosphate binding occurred between 0 and 15 minutes. The choice of time intervals for sampling is consistent with the FDA guidance but may not have been sufficiently frequent to detect small differences between the reference and generic products.
>
> The guidance document states that at each binding study should be repeated at least 12 times. The quality evaluator will comment on the conduct of this study.
>
> The clinical significance of the ratio of the affinity constants at 40 mM phosphate and pH 4.0 of approximately 94% is unknown. The sponsor has not specifically addressed this issue.

4.2.4. Cross-linking study

A cross-linking study has been provided by the sponsor in support of its Justification for not submitting biopharmaceutical data (Section *Justification for not submitting biopharmaceutical data* below). This study has been evaluated by the quality evaluator. The sponsor states that the reference product is [information redacted] cross-linked whereas the generic product is [information redacted] cross-linked

> Evaluator comment: Cross-linkage is important for the binding of ions. A difference in cross-linkage may contribute to a lower phosphate binding measured in the generic product compared with the reference product. It may also have safety implications if the product swells proportionately more. The quality evaluator has raised this issue with the sponsor.

4.2.5. Justification for not submitting biopharmaceutical data

The sponsor has provided a justification for the submission of in vitro data. The sponsor has made several points in this justification which are considered individually below. Each of these points is shown in italics followed by the clinical evaluator's comments.

The US Code of Federal Regulations on bioequivalence study requirements (21CFR 320.25(a) states that 'The basic principle in an in vivo bioavailability study is that no unnecessary human research

should be done'. The sponsor states that a requirement to undertake comparative efficacy studies in severely ill patients with end-stage renal disease is unethical and unnecessary when an internationally-accepted in vitro alternative is available to demonstrate equivalence.

> Evaluator comment: The sponsor cites Title 21 Chapter 1 Subchapter D Part 320 – Bioavailability and Bioequivalence Requirements Section 320.24 Guidelines of the conduct of an in vivo bioavailability study, (a) Guiding principles (1). The FDA guidance does not suggest that no human studies should be performed. Part (2) of this subsection of the requirements goes on to describe the study design for bioavailability studies and the populations in which they may be undertaken.
>
> The CHMP has stated that in the ESRD population receiving HD treatment it would be ethically problematic to perform long term double-blind placebo-controlled trails due to the risks involved with hyperphosphataemia. A placebo-controlled trial would not be required to demonstrate therapeutic equivalence between the reference and generic products in this case.
>
> The assumption by the sponsor is that there is equivalence between the generic and reference products based on the observation that the phosphate binding is similar between the generic and reference products. However, there are differences in the chemical characteristics of the generic formulation compared with the reference formulation. The clinical consequences of these differences for the safety, efficacy and tolerability of the generic formulation have not been investigated.
>
> Because of the vulnerable nature of the target population, the testing for efficacy, safety and tolerability in a sample of consenting patients would be appropriate in the pre-market rather than in the post-market setting as a smaller number would be exposed and all adverse events could be collected.
>
> It is noted that the drug development of an alternative sevelamer salt included a number of clinical studies to demonstrate the safety and efficacy of this product in the target population of patients with end-stage renal disease including those with regular renal replacement therapies (Renvela EPAR).

Sevelamer is completely insoluble in aqueous media, is not absorbed by the body and acts chemically rather than pharmacologically in the gastrointestinal tract to bind phosphate ions. A standard bioequivalence study is therefore not appropriate to sevelamer compare formulations, as blood levels of sevelamer cannot be measured and are not relevant to this clinical action even if such levels could be determined.

> Evaluator comment: The primary pharmacodynamic action of sevelamer hydrochloride is the reduction of serum phosphate. This is a pharmacological action.
>
> Plone et al conducted a study using radiolabelled sevelamer to demonstrate that it is not systemically absorbed. Data from a study of this type is mentioned in the Pharmacology section of the reference PI, and which the sponsor proposes to include in its own PIs for the generic formulation.
>
> It is accepted that a standard bioequivalence study is not appropriate to compare sevelamer formulations. It is agreed that any measurable blood levels of sevelamer would not be relevant to the understood mechanism of action of sevelamer.
>
> If sevelamer is measurable in blood or tissue it would suggest that the proposed formulation of sevelamer is different from the reference product and clinical data would be required to demonstrate that the presence of sevelamer in the systemic circulation has no clinical consequences.

Clinical or pharmacodynamic studies in healthy subjects or those with only moderate kidney dysfunction would also not be expected to provide any useful comparative data as tight phosphate

homeostasis in these populations would attenuate the effect of any study medications keeping plasma phosphate levels relatively constant, irrespective of which treatment was administered.

> Evaluator comment: Faecal and urinary phosphate excretion and the ratio of stool to urine phosphorus have been used to demonstrate the pharmacodynamic effects of sevelamer in healthy volunteers. Burke et al 1997 conducted a study in 24 healthy volunteers using a decrease in urine phosphorus and increased faecal phosphorus excretion as measure of effect, and total serum cholesterol and LDL cholesterol levels were also used as surrogate markers of the ion-binding effect.
>
> The sponsor has highlighted an important difference between the target population and healthy volunteers in their handling of phosphate. For this reason a clinical study to demonstrate the therapeutic equivalence between the generic and reference products in the target population of adult patients with Stage 4 or 5 renal disease would be relevant.

Comparison of sevelamer formulations by in vitro phosphate binding has been used for more than 10 years to determine their equivalence and is now accepted by major regulatory agencies for the approval of alternative dosage formulations of this product.

Sevelamer hydrochloride was originally developed by GelTex (subsequently acquired by Genzyme) and the in vitro method was used by this company to assess the equivalence of dose forms under development. Mazzeo and co-workers (1999) working for GelTex developed phosphate-binding in vitro method for measurement of the product's efficacy. Swearingen et al used in vitro phosphate binding to demonstrate the equivalence of three dosage forms of sevelamer over a range of phosphate concentrations, and to investigate the binding mechanisms of the drug over the physiological pH range. This work was repeated by the same laboratory (Swearingen et al 2004) giving the same conclusion to earlier work.

The registration of Renagel 400 mg and 800 mg tablets was based on in vitro phosphate binding data alone. The conclusion is that the EU and US authorities all agree that in vitro testing is an adequate alternative to clinical trials for the registration of new products containing sevelamer hydrochloride.

> Evaluator comment: Clinical trials were conducted during the development of the alternative sevelamer salt, sevelamer carbonate (EPAR Renvela). Four Phase 3 studies of clinical efficacy are noted in the EPAR of Renvela. In patients with CKD on haemodialysis two trials were designed to demonstrate the therapeutic equivalence of sevelamer carbonate and sevelamer hydrochloride. A third trial in patients with CKD on haemodialysis was designed to demonstrate the non-inferiority of sevelamer carbonate powder once daily with sevelamer hydrochloride three times daily, and the fourth was designed to demonstrate the safety and efficacy of sevelamer carbonate in CKD patients not on dialysis. There were also pharmacology and toxicology trials in dogs and rats.
>
> In vitro phosphate binding studies were used to demonstrate equivalence between two dosage forms of sevelamer hydrochloride made the same sponsor (Genzyme), which was considered acceptable by the EMA. The sponsor has included a publication reporting comparisons of the tablets and capsules using equilibrium binding and phosphate binding (Swearingen et al 2002, Swearingen et al 2004). The studies used different techniques (ion chromatography and high performance capillary electrophoresis) to demonstrate the similarity of the Langmuir constants between Renagel 403mg capsules and 800 and 400 mg tablets, particularly at pH 7.0 and 5.5. The safety and efficacy of the capsules were supported by clinical pharmacokinetic, pharmacodynamic, efficacy and safety data from trials testing the capsules.
>
> The FDA has published its analysis of in vitro studies comparing Renagel tablets and capsules. The pooled k_1 affinity constant test/reference ratio of the tablets with the 403 mg capsule was 1.15 using three different media. In another experiment comparing 403mg capsules and 400 mg tablets using 8 media the test/reference ratio was 0.97 for

both k_1 and k_2. The evaluation report has a comment that k_1 was within ± 20% which was considered acceptable. The results of the study provided by the sponsor in which the k_1 affinity constant T/R comparing the generic and reference products is 0.749 and 0.764 in with and without acid pre-treatment, respectively, are outside the range considered acceptable by the FDA when evaluating the Renagel submission. The justification that the in vitro testing was acceptable to the FDA and led to registration of a product and that such testing should be considered sufficient in Australia does not take into account the similarity between the capsules and tablets shown in the results of the tests.

FDA has published guidance for bioequivalence guidance on this matter.

A copy of the draft guidance is included in the submission and is included for reference in the Appendix of this report. The guideline describes an equilibrium binding study and a kinetic study The sponsor has included similar studies in the submission.

The guidance further indicates that a waiver may be acceptable based on: an acceptable equilibrium and kinetic in vitro bioequivalence studies on the 800 mg strength, proportional similarity in the formulations of the 400 mg and 800 mg strengths, and acceptable disintegration testing in 0.1NHCl.

Evaluator comment: The quality evaluator will provide an evaluation of the adequacy of the in vitro studies the sponsor has provided in support of the submission. The sponsor states that the in vitro comparison of Renagel versus the generic formulation is the criteria to prove that both the formulations are therapeutically equivalent, using the FDA Draft Guidance document.

There is no mention in the document that the studies described in the FDA Draft guidance demonstrate therapeutic equivalence.

This FDA draft guidance document has not been adopted by the TGA. The TGA definition of a generic product includes a requirement that it has the same efficacy and safety properties as the reference product. This evaluator has not located any evidence that FDA has approved a generic formulation of sevelamer hydrochloride applying this guidance.

The EU has not released an analogous guideline but the MHRA in correspondence with Generic partners advised that an application based on in vitro studies would 'seem acceptable'. An application has been submitted to German authorities by USV in December 2012 and was accepted without questions raised.

Evaluator comment: The sponsor has not provided the MHRA correspondence for review so its exact wording cannot be commented upon. Regardless, an agreement to accept a submission for review does not equate with an agreement to register the product. The TGA is not bound by advice provided by other international regulatory agencies to the sponsor.

There is no publically available information to suggest that this generic formulation has been approved in Europe at this time. The sponsor will be asked to provide details of the progress of the submission in Germany.

The sponsor considered that because doses of up to '14 g' had been given to subjects with no adverse effects the clinical risk from any slight bioinequivalence is therefore considered low.

Evaluator comment: Doses of up to 14.4 g of Renagel (anhydrous dose) or 5g three times daily were given to 4 male and 2 female healthy volunteers over 8 days of a repeated dose pharmacokinetic study. This was short term exposure in a healthy population.

The clinical implications of 'slight bioinequivalence' are in the target population and in the longer term are unknown, especially if the 'bioinequivalence' also changes the

number or extent of off-target molecular bindings by the generic sevelamer polymer. No clinical data has been provided for the proposed generic formulation to support an assertion that any difference or 'slight bioinequivalence' compared with the reference is of low risk to the often elderly and systemically unwell patients population for whom they will be prescribed.

The expectation of a generic product is that it is interchangeable with the reference product. The comment by the sponsor regarding 'slight bioinequivalence' would suggest it suspects this is may not be the case. A pharmacodynamic study could resolve this question and quantify any differences between the generic and reference products, if they exist, and would be best conducted in the target population.

The TGA guidelines state that bioequivalence studies are not required for non-biodegradable ion-exchange resins that are not absorbed.

Evaluator comment: It is agreed that bioequivalence studies are not relevant to products that are not absorbed into the systemic circulation. However, the TGA guidelines do not state that no clinical data are required.

The starting materials are the same, the level of cross-linking is comparable and particle size specifications are in place to provide control on molecular weight.

Evaluator comment: The cross-linking is similar to, but not the same as the reference formulation. The particle size specifications and controls do not appear to be the same as those for the generic formulation as there is no lower particle size limit for the generic product. The particle size distribution as compared to the reference product has not been provided. From the references provided by the sponsor there is evidence that particle size is important for the phosphate binding of the sevelamer hydrochloride.

The clinical implications of a formulation with a different geometry (difference in cross linking, see Section *Cross-linking study* above) and/or difference in particle size distribution are not known. Human trials have not been conducted by the sponsor to establish that these possible physicochemical differences are of no clinical relevance.

Sevelamer acts entirely in the gastrointestinal tract to bind phosphate by chemical means; it has no pharmacological action.

Evaluator comment: Sevelamer lowers serum phosphate by binding phosphate in the gut. A reduction in serum phosphate in ESRD patients with hyperphosphataemia to normal levels aims to reduce the associated morbidity and mortality. Therefore sevelamer has a pharmacological action even if it is not via a drug-receptor mediated mechanism. Action by a mechanism other that a drug-receptor mediated mechanism is not mentioned in any of the guidance documents as a justification for the absence of clinical data.

4.3. Justification for only submitting studies using the 800 mg dosage strength

The sponsor has provided a justification for not conducting in vitro equivalence studies on the lower dosage strength of 400 mg.

The justification states that both dosage forms are immediate-release tablets. They contain the same active ingredient, a hydrophilic, water insoluble cross-linked polymer. The pharmacokinetic characteristics of the reference product are such that it is not systemically absorbed, and the risk of systemic toxicity is low. The reference product has a wide therapeutic margin and the dosage range that is required ranges from 800 – 1600 mg per meal. The generic formulation in the 400 mg and the 800 mg strength are scale formulations of the active and excipient ingredients..

Evaluator comment: The sponsor has relied on the points from Section 4 of Appendix 15 of the ARGPM: Justification for not submitting biopharmaceutical data to support its decision to conduct in vitro equivalence studies in the 800 mg dose only.

The sponsor has provided the justification that there is quantitative chemical proportionality between the 400 mg and 800 mg doses.

Point 4 of the issues to be addressed concerns the clinical consequences of differences in bioavailabilities of the products under consideration. The sponsor has stated that on the basis of high doses given to healthy volunteers for 8 days with no adverse event reported, the risk of systemic toxicity is low. The sponsor has not addressed the issue of a decreased effective dose leading to lack of efficacy.

It is possible that there may be dose titration using the 400 mg dose if it is available, and that patients may elect to take two 400 mg tablets instead of one 800 mg tablet because of ease of swallowing. It is not possible to demonstrate dose proportionality in terms of AUC for a given dose as sevelamer is not absorbed. Of clinical importance is the dose-response relationship with increasing dose, that is, whether the 400 mg tablet is likely to bind half the phosphate of the 800 mg dose (or that two 400 mg tablets would bind approximately the same phosphate as the 800 mg tablet). The results from Burke et al 2007 did not demonstrate this type of dose-response relationship between the 1g tds and 2.5g tds dosages for urinary and faecal phosphate or LDL cholesterol and no analysis of the raw data was presented by the authors to suggest a linear relationship. No data has been included in this submission that addresses this question from a clinical perspective.

4.3.1. Justification for use of an overseas reference product

The sponsor has used a non-Australian reference (UK) product in its in vitro studies. The sponsor has not provided a declaration from the reference company that it markets the same reference product in the EU and Australia.

The TGA specific guidance in the use of an overseas reference product for bioequivalence studies in generic medicines is found in Section 7 of Appendix 15 of the ARGPM. In this guidance a set of requirements is laid out, which must be met or otherwise justified. These are discussed below. If the sponsor is unable to meet or justify the inability to meet these requirements, an appropriate bioequivalence study or studies is required.

The sponsor states that both the UK and Australian reference products are conventional immediate-release oral dosage forms. It also states that the UK has a regulatory system that is comparable with Australia, and that the same company (Genzyme) sponsors the products in the UK and Australia.

Evaluator comment: Sevelamer hydrochloride is a non-absorbed product that acts in the gastrointestinal tract and as such it not a conventional pharmaceutical agent. It is presented as a tablet by the sponsor and so has a conventional dosage form. It is an immediate release product. The sponsor listed on the Renagel SPC provided in the submission is Sanofi, of which Genzyme is a subsidiary.

The sponsor states that sevelamer has a well described dose-response curve. The sponsor cites a study of the safety tolerability and efficacy of sevelamer hydrochloride in 24 healthy volunteers. In this study urinary and faecal phosphate and serum cholesterol were the outcomes measured. A comment is made by the sponsor that consistent changes in the serum phosphate were not observed.

Evaluator comment: Serum phosphate is the major clinical outcome that will be monitored for patients taking sevelamer hydrochloride as a phosphate binding agent. The comment that inconsistent changes in serum phosphate were observed would suggest that the response in this population is not easily predicted from the dose.

The sponsor states that sevelamer has a wide therapeutic margin, and cites the maximum dose from the above study in healthy volunteers, that was well tolerated, as evidence of its lack of risk of serious undesired effects. The sponsor also states that there are no reported overdoses of sevelamer in patients.

> Evaluator comment: A search of the WHO Vigibase reveals a prescribed overdose where death was the outcome from 2005, and an intentional overdose that resulted in oesophageal perforation from 2003. Although these events are rare and the reports contain minimal detail and could have other factors that may have contributed the outcome, it is not correct to state that there are no reported cases of overdose. Renal failure can be associated with conditions that alter the structure and function of the oesophagus such as scleroderma. A temporal association between an overdose and an oesophageal perforation is a concern.

The sponsor states that sevelamer does not exhibit complicated or variable pharmacokinetics, as it is not systemically absorbed.

Evaluator comment: This statement is accepted for the reference product.

The sponsor states that both the Australian and the UK products contain 800 mg of active ingredient. It states that a 400 mg strength dosage form is registered but not marketed in Australia. It is also not marketed in the UK.

Sevelamer hydrochloride is insoluble so no comparative dissolution profiles were conducted by the sponsor. Instead, the sponsor has compared the disintegration between the UK and Australian. The sponsor states a comparison of disintegration between the UK and Australian products is presented at the beginning of the justification. At the end of the justification a series of analytical reports is presented. The disintegration test includes one result for batch D0037B03 of 4 minutes and 52 seconds. For the other batches tested the comment is 'Complies'.

> Evaluator comment: The evaluation of the disintegration test methodology and results has been undertaken by the quality evaluator.

4.4. Evaluator's overall conclusions on pharmacokinetics

Sevelamer hydrochloride is a polymer that binds dietary phosphate in the gut. The reference product is not systemically absorbed, and therefore bioequivalence studies are not suitable. The sponsor has chosen in vitro studies to establish equivalence between its generic product and the reference product Renagel. The studies are based on a draft FDA guidance document on in vitro studies for generic sevelamer hydrochloride compounds. The sponsor has used a non-Australian version of the reference product for its studies and has based its justification for so doing on Section 7 of Appendix 15 of the ARGPM. The sponsor has only conducted the FDA recommended studies on the 800 mg dosage strength, although there is a 400 mg dosage strength of the reference product on the ARTG.

The reference product is a large polymer and each molecule forms a particle. The reference product has an average particle size range of 25 – 65 μm. Particle size is important for phosphate binding. The generic product does mention a lower limit for particle size raising the possibility of the presence of water soluble oligomers and monomers present in the formulation that may be systemically absorbed. It is therefore unknown if any systemic absorption would occur after taking this formulation and if so, what the implications for its safety and efficacy may be. From a clinical perspective, an absorption study could address the question of whether or not the generic formulation is absorbed in any potentially meaningful way. Also, the phosphate binding of the individual tablet may vary if there is insufficiently tight control on particle size, with resultant differences in efficacy compared with the reference product. The issue of limits on the particle size has been identified by the quality evaluator.

The reference product is a cross-linked polymer. The cross-linkages are important for phosphate binding and may have importance for the binding of off-target anions such as bicarbonate and low density lipoprotein cholesterol. The sponsor has described the conditions of manufacture at which it considers the generic product is sufficiently similarly cross-linked as compared to the reference product. The generic product is more cross-linked at[information redacted]crosslinking as compared to the reference product's 10.6 – 13.9% cross-linking. The issue of the differences in cross-linking is under consideration by the quality evaluator.

Sevelamer swells in the presence of physiological fluids and the swelling is important for its phosphate binding. The reference product swells to 6 – 8 times its initial weight and 8 times its volume. The amount of swelling is related to the cross-linking within the molecule. The sponsor has not provided a measure of the swelling of the generic product but as the cross-linking of the generic formulation is different, the swell index is also likely to be different. The quality evaluator has identified this issue and additional information has been sought from the sponsor.

Sevelamer hydrochloride 800 mg tablets are physically large. The reference product is approximately 19.04 mm x 9.76 mm x 7.6 mm. The final dimensions of the generic product after film coating have not been provided by the sponsor. The tablets have a larger mass than the reference products tested, although that may reflect a difference in the amount of excipient added to the active ingredient. There is concern regarding difficulty swallowing such a large tablet and whether it poses a choking hazard. The final physical dimensions of the generic 400 mg and 400 mg tablets have not been provided.

The sponsor has provided two vitro studies in support of the generic product. The first is an equilibrium binding study, conducted at 37^{o}C. The characteristics of the phosphate binding are described using a Langmuir isotherm. The affinity constant of the reference product is 25% greater than that of the generic product and suggests a difference between the two products. The binding constants of the reference and generic products, however, are very similar.

The sponsor also conducted a kinetic in vitro study to show the phosphate binding of the generic and the reference product with time. Both products reached maximal binding within 15 minutes. The reference product has a phosphate binding capacity of 5.57 mmol/g ± 15%. The generic product had a mean phosphate binding capacity of approximately 98% of the reference product at free phosphate concentrations of 1 mM and pH 4.0 and 7.0. It had similar phosphate binding at free phosphate concentrations of 40 mM and pH 7.0 and approximately 94% at a pH of 4.0. The clinical significance of the difference at a 40 mM concentration and pH 4.0 is unknown

The equilibrium and kinetic phosphate binding studies were conducted using the 800 mg dosage strength. The sponsor has provided a justification based on Section 4 of Appendix 15 of the ARGPM. There is qualitative proportionality of the active ingredients and excipients between the 400 mg and 800 mg dose forms. The portion of the guidance relating to the dissolution of the product is not relevant to sevelamer because it is insoluble in most solvents. Disintegration data is under evaluation by the quality evaluator. The sponsor has not addressed the issue of decreased efficacy if the effective dose is decreased.

It is not possible to demonstrate dose proportionality in terms of AUC for a given dose as sevelamer is not absorbed. Because there may be dose titration using the 400 mg dose if it is available, and patients may elect to take two 400 mg tablets instead of one 800 mg tablet because of ease of swallowing, the dose-response relationship with increasing dose is of clinical importance. Because the results from the study by Burke et al 2007 did not demonstrate this type of proportional dose-response between the 1g tds and 2.5g tds dosages for urinary and faecal phosphate or LDL cholesterol it is unclear whether two 400 mg tablets would provide the same phosphate binding as one 800 mg tablet, and a comment from the sponsor has been requested.

Disintegration testing is a requirement of the FDA guidance. It is not known if there would be any clinical implications from the slower disintegration time for the generic formulation, as sevelamer hydrochloride should be taken with meals and is likely to remain in an acid environment for a minimum of 20 – 30 minutes.

The sponsor has chosen to use overseas reference products in preference to Australian reference products, and has relied on the guidance from Section 7 of Appendix 15 of the ARTG. The guidance generally refers to products with have measurable pharmacokinetics. The quality evaluator has evaluated the information provided by the sponsor in support of the use of the overseas product.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

The sponsor has not provided any pharmacodynamic data for the generic formulation of sevelamer hydrochloride. The sponsor states that on the basis of the presented in vitro studies the generic formulation and the reference product are of sufficient physicochemical similarity that the pharmacodynamic effects of the reference product can be extrapolated to the generic formulation.

5.2. Summary of pharmacodynamics of the reference formulation

The information in the following summary of the pharmacodynamics of the reference product is derived from published literature included in the dossier for this submission unless otherwise specified.

5.2.1. Mechanism of action

The amines in the sevelamer polymer become partially protonated (become cationic) in the intestine and interact with phosphate molecules through anionic and hydrogen bonding, releasing one HCl for each anion bound. Diffusion controls ion exchange at the anion binding sites.

Phosphate binding is optimal at pH 7. One gram of the reference product binds approximately 2.6 mmol of phosphate at an estimated physiological concentration of 5 mM.

Although sevelamer hydrochloride preferentially binds anions such as phosphate and citrate it will also bind negatively charged compounds such as bile acids and negatively charged amino-acid conjugates (Burke et al 1997).

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

Burke et al 1997 reported a pharmacodynamic study conducted in 24 healthy volunteers. The aim of the study was to determine the safety and tolerance of single doses of sevelamer (1, 2.5 and 5g doses) and to determine the safety efficacy and tolerability of repeated dose sevelamer (placebo, 1.2, 2.5 and 5 g) given over an 18 day period. All participants were given a phosphate-controlled diet providing 378.5 mmol of elemental phosphorus per day. The average urinary phosphorus was 27.2 ± 3.8 mmol in the placebo group versus 23.8 ± 3.4mmol, 19.5 ± 3.1 mmol and 16.6 ± 2.5 mmol in the sevelamer 1g, 2.5g and 5g per day groups respectively. The average faecal phosphate was 11.6 ± 4.1 mmol, 9.1 ± 4.1 mmol, 10.7 ± 5.3 mmol, and 19.1 ± 10.6 mmol for the placebo, and sevelamer 1g, 2.5g and 5g per day groups respectively. There were large individual variations in the data.

The receptor binding profile of the reference formulation was not tested but this was considered acceptable because sevelamer hydrochloride acts locally in the gastrointestinal tract (Renagel EPAR).

A decreased serum phosphate has been observed in haemodialysis requiring therapeutic intervention for hyperphosphataemia. Goldberg et al, 1998, reported a reduction in mean serum phosphate in patients with ESRD from a baseline of 2.65 mmol/L to 2.10 mmol/L after 7 weeks of treatment with sevelamer capsules. The dose was titrated to serum phosphate level. Slatolopolsky et al 1999 also reported a reduction in mean serum phosphate from 2.94 mmol/L to 2.13 mmol/L after 8 weeks of sevelamer hydrochloride therapy in an open-label dose-titration study in patients with ESRD. The mean sevelamer dose at the end of the treatment was 5.4g per day.

5.2.2.2. Secondary pharmacodynamic effects

The use of sevelamer hydrochloride has been associated with changes to biochemistry in addition to a reduction in serum phosphate.

A decrease in serum bicarbonate has been noted in clinical trials. The binding of one phosphate ion bound to sevelamer hydrochloride results in the formation of one molecule of hydrogen chloride. de Francisco et al (2010) observed a mean bicarbonate decrease from baseline of 0.823 ± 4.3323 mmol/L in 101 patients treated for 25 weeks. Delmez et al (2007) observed serum bicarbonate of 20.8 ± 3.7 mEq/L from a baseline of 21.1 ± 3.8 mEq/L after 8 weeks of treatment. Goldberg et al (1998) reported a statistically significant decrease in serum bicarbonate concentration from 18.8 mEq/L to 17.1 mEq/L in an eight week period. Bicarbonate can also be bound to sevelamer hydrochloride as depicted in Figure 2 below.

Consistent with the liberation of chloride ions in the binding of sevelamer, Goldberg et al (1998) reported a statistically significant increase in mean serum chloride from 98.9 mEq/L to 101.8 mEq/L in an eight week period.

Evenpoel (2009) reported a decrease in uric acid of approximately 8% in peritoneal dialysis patients.

In an in vitro study, bile acids were found to bind to sevelamer, displacing bound phosphate (Autissier et al 2007). A number of studies have shown a decrease in serum LDL-C and total cholesterol without an increase in triglycerides in healthy volunteers and patients with chronic kidney disease undergoing haemodialysis and peritoneal dialysis taking sevelamer. A decrease in these blood lipids has been used as a surrogate endpoint of efficacy. Sevelamer hydrochloride has also been associated with a decrease in inflammatory markers, such as C-reactive protein and apolipoprotein B.

A decrease in fibroblast growth factor 23, an inhibitor of renal tubular phosphate reabsorption has been observed although the resultant clinical outcomes are as yet unclear (Raggi et al 2010).

5.3. Time course of pharmacodynamic effects

A decrease in serum phosphate has been observed after two weeks of taking sevelamer hydrochloride with the reference formulation.

5.4. Pharmacodynamic interactions

Pharmacodynamic interactions have not been studied with the generic formulation.

Sevelamer is given with meals to bind with the purpose of binding ingested phosphate. The timing of administration of drugs known to interact by competitive binding with sevelamer is important, particularly when those drugs have a narrow therapeutic index. Its pharmacodynamic interactions may include cyclosporin or its major metabolite AM1,

mycophyolate mofetil, levothyroxine, and fat soluble vitamins because of the binding of bile acids. In single dose, open label, crossover design studies no interaction was found between sevelamer and digoxin, warfarin, enalapril or metoprolol for the reference product (Burke et al 2001, Burke et al 2001).

Phosphate binding of sevelamer is concentration dependent so differences in dietary intake and gut wall tissue phosphate levels could be expected to influence the amount of phosphate bound as would the presence and local concentration of competing anions. Inter and intra-individual variability is anticipated.

5.5. Evaluator's overall conclusions on pharmacodynamics

The sponsor has not conducted pharmacodynamic studies using the generic formulation.

Sevelamer hydrochloride exerts its pharmacological effects as an ion-exchange resin in the gut. It is non-selective and while the target anions are phosphate, off-target anions include some with clinical consequences such as interaction with some medications, bicarbonate, bile acids with an associated decrease in levels of fat soluble vitamins including Vitamin D, levothroxine, mycophenolate mofetil, uric acid, vitamin C and folate. Other negatively charged medications that undergo enterohepatic circulation are potential substrates for binding with sevelamer.

The quality evaluator has raised concerns that the generic and reference products may not be chemically the same, both structurally and in terms of phosphate binding. Of particular interest is whether the geometry of the molecule, its cross-linking and the particle size result in the binding of other anions to a lesser or greater extent as this may have clinical consequences. This is important clinically as the prescriber will generally not know if the patient has been dispensed the reference product or a generic product by their pharmacist.

6. Dosage selection for the pivotal studies

No clinical trials were provided in this application.

7. Clinical efficacy

The sponsor has not provided any studies investigating the clinical efficacy of the generic formulation.

7.1. Clinical efficacy of the reference formulation

The following is a brief summary of the clinical efficacy of the reference product derived from the literature references provided, unless otherwise specified.

In patients undergoing haemodialysis and peritoneal dialysis a reduction in serum phosphate has been observed, without an increase in serum calcium, resulting in a reduced calcium phosphate product in patients. This is associated with a decreased or unchanged in intact parathyroid hormone (iPTH). Adynamic bone disease and high turnover bone disorders have been shown to either not progress or to improve in patients taking sevelamer hydrochloride. There is a suggestion that sevelamer may improve trabecular bone structure and density, although the long term outcomes of bone health such as reduced fracture risk and bone pain have not been shown to improve.

In haemodialysis patients taking sevelamer, a stabilisation or decrease in arterial calcification scores, a measure of vascular calcification, which is associated with cardiovascular morbidity and mortality, have been shown.

The effects seen in haemodialysis (HD) and peritoneal dialysis (PD) patients have been extrapolated to CKD patients not yet on dialysis as the clinical problem of hyperphosphataemia and the mechanism of action of sevelamer hydrochloride are the likely to be the same in these patients.

7.2. Evaluator's conclusions on clinical efficacy

The sponsor has not provided any data on the clinical efficacy of the generic formulation.

The clinical overview and the references provided support the use of sevelamer hydrochloride as a therapeutic option to decrease serum phosphate, reduce the calcium phosphorus product, and reduce iPTH. Improvements in these parameters have implications for bone health and cardiovascular disease.

The basic premise of the sponsor's submission is that in only vitro studies are required in support of the registration of the generic formulation. This additional information describing the efficacy of the reference product, although helpful, does not of itself demonstrate the therapeutic equivalence of the reference and generic formulations. As there are outstanding concerns regarding the similarity of the physicochemical properties of the generic formulation as compared with the reference product, there is insufficient surety of the therapeutic equivalence of the generic formulation and the reference products. This uncertainty may be overcome with a clinical trial comparing the two formulations.

8. Clinical safety

The sponsor has not provided any studies evaluating the clinical safety of the generic formulation.

8.1. Adverse events

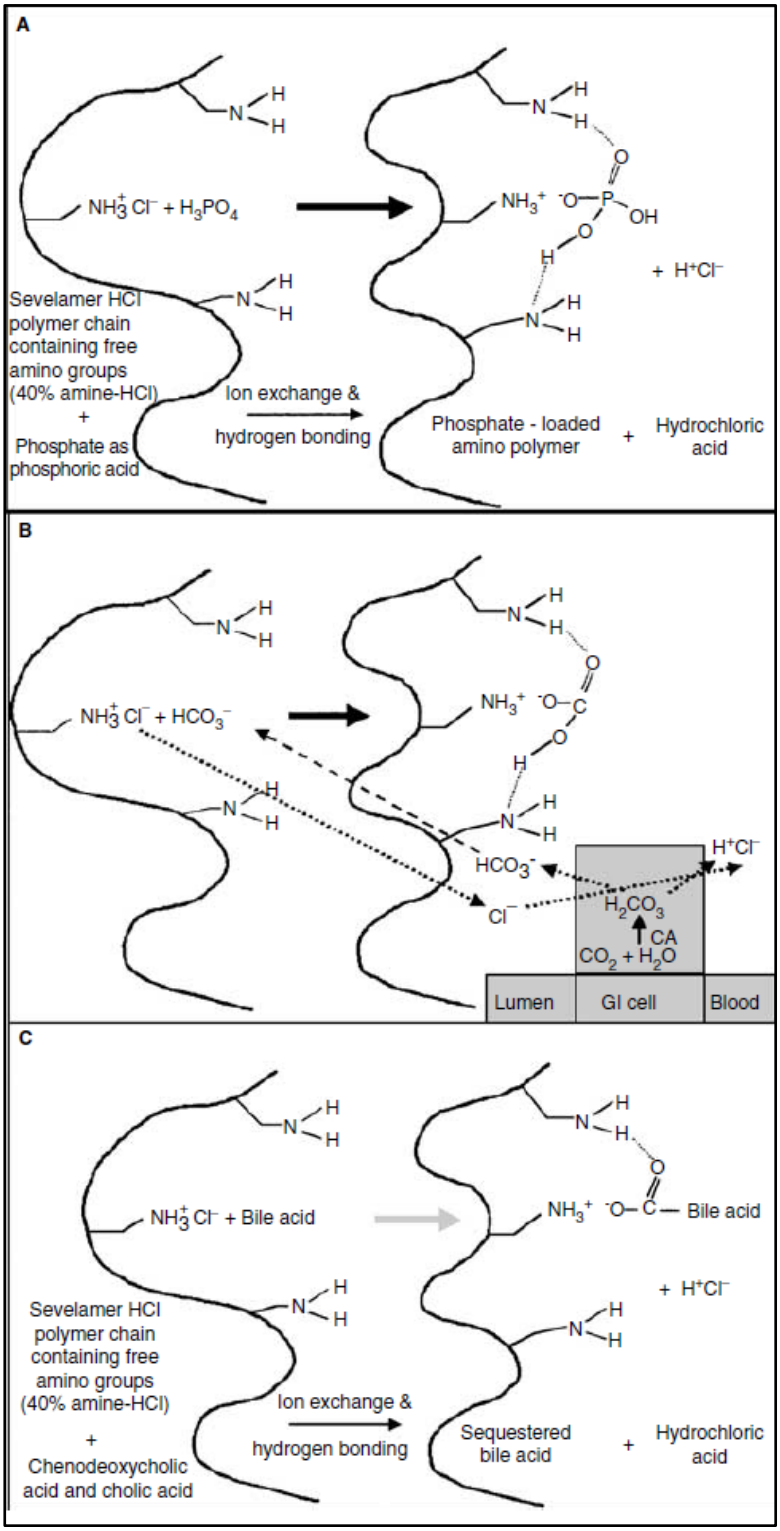
No adverse event data has been provided for patients exposed to the generic formulation.

8.2. Summary of the safety information provided for the reference formulation

The sponsor has provided published literature and a description of the known safety profile of the reference product. Section *Summary of the safety information provided for the reference formulation*, below, is a summary of the key safety concerns for the reference product.

As mentioned above, metabolic acidosis is a potential concern with the use of sevelamer. Figure 2, includes a diagrammatic representation of the chemical processes in the gut that result in this occurrence. A reduction in serum bicarbonate has been noted in patients undergoing peritoneal dialysis taking sevelamer, with an increase observed in a small number of patients after the discontinuation of sevelamer (Borras et al 2002). de Franscico et al 2010 found a significant reduction in serum bicarbonate in HD patients taking sevelamer compared with a calcium acetate/magnesium carbonate comparator. Pieper et al 2006, in a small study comparing the efficacy and safety of sevelamer with calcium acetate in children with chronic kidney disease, described metabolic acidosis in 34% (11/32) of the children taking sevelamer, compared with 3.3% (1/30) taking calcium acetate.

Figure 2: Theoretical mechanisms of acid loading during treatment with sevelamer hydrochloride



Monovalent phosphate is bound to the sevelamer polymer via ionic and hydrogen-bonding interactions in exchange for release of the leaving anion chloride. For each phosphate molecule bound, one molecule of hydrochloride is produced.

(A) Exchange of chloride for bicarbonate in the small intestine. Loss of carbonated stool leads to gastrointestinal losses of bicarbonate in excess of chloride. The net effect is production of excess HCl resulting in metabolic acidosis by a mechanism akin to development of non-anion gap metabolic acidosis in the setting of diarrhoea.

(B) Sequestration of bile acids (cholic acid and chenodeoxycholic acid) by sevelamer in exchange for release of chloride. The net effect is the production of one

Source Brezina B, Quinbi WY and Nolan N 2004

The reference product's PI makes mention that sevelamer hydrochloride does not contain alkali supplementation and that serum bicarbonate and serum chloride levels should be monitored. This could be particularly problematic for some patients with the loss of phosphate which acts as a buffer, the possible binding of bicarbonate ion in the gut and the substitution of chloride ions.

While bone buffering of hydrogen ion can help to maintain acid-base balance the long term effects on bone mineralisation are a concern (Borras et al 2002). The KDOQI recommends that serum bicarbonate be maintained at > 22 mmol/L to promote improvement in bone histology and to ameliorate excess protein catabolism associated with chronic metabolic acidosis (Brezina et al 2004). A number of papers in the submission describe the addition of bicarbonate to the regimen of patients with renal failure and particularly those taking sevelamer hydrochloride.

An increased binding of bicarbonate in the gut could have safety consequences in a subgroup of patients, particularly when coupled with gastrointestinal upset such as vomiting and diarrhoea that have been associated with sevelamer.

Evenpoel et al 2009 noted in their study comparing sevelamer hydrochloride (n = 72)and calcium acetate (n = 31) in patients undergoing peritoneal dialysis that 11% of the patients taking sevelamer experienced peritonitis versus 4% in the calcium acetate group, although the authors comment that overall the frequency did not exceed that previously reported for peritonitis in patients undergoing peritoneal dialysis.

In the study by de Fransico et al 2010 23% of patients, 6 taking sevelamer hydrochloride reported gastrointestinal symptoms compared with 13.6% taking calcium acetate/magnesium carbonate.

In a study comparing sevelamer carbonate with sevelamer hydrochloride, gastrointestinal events were reported in 35.9% of the 78 patients taking sevelamer hydrochloride, with the majority being nausea and vomiting (Pai and Shepler 2009). Gastrointestinal bleeding has been reported with sevelamer use. A possible contributor is gut wall ulceration from hard impacted faeces resulting from constipation.

The following is a table of commonly occurring adverse events derived from clinical trial data for the reference product as found in its PI.

Table 4: Treatment Emergency Adverse events (≥10%) from a parallel design trial of sevelamer tablets versus calcium acetate for 52 weeks of treatment (regardless of causality)

Adverse Event	Sevelamer (n=99) Patients (%)
Gastrointestinal Disorders	
Vomiting	22.2
Nausea	20.2
Diarrhoea	19.2
Dyspepsia	16.2
Constipation	8.1
Infections and Infestations	
Nasopharyngitis	14.1
Bronchitis	11.1
Upper Respiratory Tract Infection	5.1
Musculoskeletal Connective Tissue and Bone Disorders	13.1

Adverse Event	Sevelamer (n=99) Patients (%)
Pain in limb	12.1
Arthralgia	4.0
Back Pain	
Skin Disorders	
Pruritis	13.1
Respiratory, Thoracic and Mediastinal Disorders	
Dyspnoea	10.1
Cough	7.1
Vascular Disorders	
Hypertension	10.1
Nervous System Disorders	
Headache	9.1
Disorders and Site Administration Disorders	
Mechanical Complication of Implant	6.1
Pyrexia	5.1

Source: Table 3 Renagel PI Version renagel-ccdsv10-piv11-28may12 as presented in the Proposed PI for Sevelamer GPPL

Deficiency of vitamins D, E and K and folic acid were noted in animal models at doses 6 – 10 times the recommended average human dose by weight. A decrease in serum folic acid concentrations has been observed in in vitro studies and in on study of haemodialysis patients after 6 months of treatment (Schiff and Lang 2011).

8.3. Post-marketing experience

This is not applicable for the generic product. The sponsor has not provided any post-market data for the reference product, but in the Renagel PI ileus, intestinal obstruction and intestinal perforation are mentioned in the post marketing experience section. There is also mention that constipation may precede the development of intestinal obstruction.

> Evaluator comment: Although end stage renal disease can occur at any age, many patients with renal disease are older adults. Both increasing age and renal disease are associated with gastrointestinal dysfunction. The prevalence of gastrointestinal symptoms in patients with renal failure is approximately 70 – 79%. The prevalence of constipation may be as high as 63% in patients with haemodialysis and 29% on peritoneal dialysis compared with a prevalence of 10 – 20% in the general population (Shirazian and Radhakarishnan 2010). Reduced colonic transit time was found in approximately 46% of patients on haemodialysis in a study reported by Wu et al (2004), with increases noted in total, right sided and rectosigmoid colon transit times. The reductions were greater in patient undergoing haemodialysis than those undergoing

peritoneal dialysis and the control group. Women were more likely to be affected than men, but other factors such as diabetes and medications were not found to be statistically significant contributors.

Age related changes in the colon include muscular atrophy, changes to the mucosal glands hypertrophy of the muscularis mucosa and atrophy of the muscularis externa. Functional changes include altered coordination of contraction. In severe renal disease dietary and fluid restrictions and medications can contribute to constipation. Although constipation is generally uncomfortable with an impact on the patient's quality of life, severe constipation can be associated with intestinal pseudo-obstruction and bowel perforation.

Any chemical differences between the generic and reference products that increase the transit time of sevelamer through the gut are of concern. There is no clinical data from human use of the generic product provided in the submission. No comment can made as to whether the generic and reference products behave similarly in the target population with regards to intestinal transit time and the risk of intestinal obstruction.

8.4. Other safety issues

8.4.1. Safety in special populations

In the literature provided, no additional safety concerns were identified when the reference formulation was given to children, although metabolic acidosis was common (see Section *Summary of the safety information provided for the reference formulation*). The sponsor has not applied for approval for the use of the generic formulation in children. Renagel, the reference product, is indicated for use in adult patients. Its PI states that the safety and efficacy of Renagel in paediatric patients have not been established.

Evaluator comment: The sponsor proposes to retain the same indications as the reference product. The generic product, if approved, would only be indicated for use in adult patients. The sponsor also proposes to retain the statement regarding paediatric use.

8.5. Trade names

The sponsor has proposed the trade names Sevelamer GPPL, Sevelamer GxP, Sevelam, Sevlar, Apo-Sevelamer, Apotex – Sevelamer, Chemmart Sevelamer, Genrx Sevelamer, and Terry White Chemists Sevelamer.

The sponsor at the pre-submission stage had proposed Sevelamer – KP and Sevelamer-CSP but has changed these to Sevelam, and Sevlar respectively.

8.6. Evaluator's overall conclusions on clinical safety

The sponsor has not provided any evidence for the clinical safety of the generic formulation.

As mentioned previously, there is at this time some uncertainty regarding the therapeutic equivalence between the reference and generic formulations, including the safety profile.

As the sponsor has not indicated a lower limit for the particle size concern is raised regarding the presence of allyl amine monomers and small oligomers that may be absorbed. The clinical safety implications of a measurable systemic absorption of a portion of this formulation are unknown, but at this time there is no certainty that it is negligible.

The size of the 800 mg tablet is a concern. The final physical dimensions of the tablet have not been provided. Difficulty swallowing tablets occurs at all ages. Factors affecting swallowing include increasing age due to age related changes in salivary gland , oropharyngeal and/or oesophageal muscle function; certain co-morbidities such as with scleroderma or after stroke;

and with some medications such as those with anticholinergic effects. Although it is recognised that the issue of large tablet size and potential choking hazard is present in the reference product, and that there are warnings already in place in the PI, the generic product should not exceed the dimensions of the reference product for these reasons. A large tablet size is also a tolerability concern in that patients who have difficulty swallowing tablets and more likely to miss doses or be completely non-compliant with the therapy. Failure to comply with therapy is associated with possible increased morbidity and mortality. There is no clinical information in the submission that addresses the issue of whether swallowing difficulties and the potential choking hazard is are equal to or less than those recognised for the reference product.

The swell characteristics of the final product have not been provided. The reference swells to 6 – 8 times its original weight and 8 times its volume. This of itself raises safety concerns around the potential for gastrointestinal tract obstruction including intestinal obstruction and partial obstruction of the oesophagus, especially in patients with ulceration and strictures, and for adverse outcomes if the tablet is lodged outside the gastrointestinal tract. The sponsor has not provided evidence that the generic product does not swell more than the reference product.

Metabolic acidosis is a safety concern. It is expected that HCl would be liberated from the generic product on binding of phosphate ions as it is with the reference product. It is unknown whether binding of bicarbonate ions in the gut occurs similarly between the reference and generic products.

With the outstanding concerns regarding the physicochemical similarity between the reference and the generic formulation as yet unresolved, the safety profile characterised for the reference product cannot be extrapolated to the generic product with confidence.

8.6.1. Trade names:

Two of the proposed trade names give cause for concern with regards to look alike and sound alike medication errors. The proposed trade name Sevelam looks like Sevelon, particularly when handwritten, sounds alike when the emphasis is placed on the first syllable, and is unacceptable. The evaluation team pharmacist has provided the advice that the proposed trade name Sevlar both sounds and looks like Sevikar and is unacceptable.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of the generic formulation of sevelamer hydrochloride in the proposed usage are:

- The presence of an alternative product in the market in the event of a shortage of the reference product.
- Offers a choice to the consumer.
- As the 400 mg tablet is not marketed by the sponsor of the reference product, a 400 mg product would offer the prescriber options for dose titration. The 400 mg tablet is likely to be smaller than the 800 mg tablet and would be easier to swallow. The sponsor has indicated in the CMI that this dosage strength will not be marketed. If this is the case, the potential benefits of this dosage strength would not be realised.

The physicochemical properties of the generic formulation have not yet been established as sufficiently similar to the reference to accept bioequivalence based on the outcome of the in vitro studies as presented. It is not possible to extrapolate of the known benefits of the reference formulation of sevelamer hydrochloride to the generic formulation with any certainty at this time.

9.2. First round assessment of risks

The risks of the generic formulation in the proposed usage are:

- No human data for the generic product to establish that its pharmacodynamic, efficacy and safety characteristics are the same as the reference product
- No lower limit on particle size and no evidence there are no water soluble monomers or oligomers that could be absorbed and no studies that show there is not absorption in human. The pharmaceutical or toxic actions, if any, of absorbed monomers are unknown. Particle size is also important for efficacy. No in vivo studies have been performed. Efficacy and pharmacodynamic effects of the reference product have not been investigated in human subjects and are unknown for the generic product.
- There is a higher percentage of cross-linking in the generic formulation compared with the reference product, with the potential for increased swelling as the two properties are related. Cross-linking that differs from the reference product may result in a different capacity to bind dietary phosphate, but also may affect drug-drug interactions, and interactions with other anions, including bile salts. Swelling has safety implications, with the potential to cause bowel obstruction, oesophageal obstruction, and airway obstruction if the tablet is inadvertently inhaled.
- The proposed tablet size is large. The final dimensions are not provided but the press size for the uncoated 800 mg tablet is 19.00 mm x 9.5 mm x 8 mm. This may pose a choking hazard, particularly in the target population who are often elderly, with significant comorbidities.
- Other safety concerns of relevance to the reference product may be of relevance to the generic product, such as metabolic acidosis, and the potential for intestinal obstruction and vitamin deficiencies. Whether these occur with a similar frequency and with a similar severity compared to the reference product is unknown and cannot be assumed with certainty.

9.3. First round assessment of benefit-risk balance

The sponsor has not provided any clinical data from the use of the generic product in this submission, but has relied on two in vitro studies to demonstrate bioequivalence of the generic and reference products.

The sponsor has relied on FDA guidance to support its approach to this submission for registration of a generic product. However, the reliance is on a method for establishing bioequivalence for sevelamer hydrochloride. The justification for undertaking these studies alone is contingent upon demonstration of the chemical equivalence of the two formulations. There are concerns raised by the quality evaluator regarding the equivalence of physicochemical properties of the generic product compared with the reference products. Of specific concern are the potential differences in particle size, cross linking and phosphate binding characteristics of the generic product as compared with the reference product. Additional data and clarification will be sought from the sponsor by the quality evaluator.

The concern regarding the particle size is relevant for the efficacy of the product. There is evidence in the submission that particle size is related to phosphate binding in a non-clinical study, and controlling the particle to size to be within the same range as that of the reference product would appear to be important for its clinical efficacy of phosphate binding. There is no human data to suggest there are no differences in efficacy between the generic and reference products in the target population. There is currently no lower limit to the particle size, suggesting there may be monomers or small oligomers that may be absorbed. The clinical consequences of this are unknown.

Cross-linking is important for the geometry of the molecule, its ion binding and its swelling. There is a difference in cross-linking between the generic and reference products. No data has been provided that the generic product swells in the same proportions as the reference product. There are potential safety concerns regarding the swelling of the product particularly if it lodges outside the gastrointestinal tract, but also if it draws more fluid from the gut contents than the reference product and is associated with a greater risk of constipation and therefore bowel obstruction.

The binding of other anions has not been tested, and there is concern regarding the physicochemical properties of the generic product compared with the reference product. In the absence of clinical data to suggest otherwise, there is concern regarding potential differences in the binding of other anions.

The final dimensions of the tablets of the generic product have not been provided. The sizes of the compression moulds of the generic tablets have been provided and the assumption must be made that film coating will add to the size of the tablet. Swallowing difficulties are recognised by the sponsor of the reference product and warnings appear in the PI and CMI for Renagel. This is of great concern as the reference product is approximately 19mm in maximum dimension and further increases in size will have implications for the safety (potential choking hazard) and tolerability (poor compliance when tablets are difficult to swallow). This concern is increased as the potential for the swelling of the tablet is not quantified.

The proposed indication is for the reduction of serum phosphate in patients with Stage 4 or 5 chronic kidney disease. The target population has ESRD. This is a complex metabolic disorder, and multiple therapeutic interventions are required in patient management. It is important that any generic medication not only binds dietary phosphate in the same manner and to the same degree as the reference product, but that it has the same interaction with other medications and other ions in order that patients and clinicians can be confident of the interchangeability of the generic and reference products. The behaviour of the polymer in vivo has not been tested in any model.

The potential benefits of an alternative sevelamer hydrochloride product in the market place in terms offering a choice of a 400 mg dosage form with a smaller, potentially easier to swallow tablet and the potential benefits of choice for patients and alternatives in the event of a shortage of the reference product, are outweighed by the concerns outlined above. There are no clinical data to characterise the safety and efficacy of the generic product compared with the reference product, and that comparability cannot be assumed.

The benefit-risk balance of the generic formulation of sevelamer hydrochloride, given the proposed usage, is unfavourable.

10. First round recommendation regarding authorisation

It is recommended that the submission as it stands is rejected. The reasons for this recommendation are as follows:

- The lack of specification of particle size in the generic formulation and the lack of mention of a specific lower limit for particle size. There is non-clinical data to show that particle size is important for the therapeutic effect. It is possible that monomers and oligomers within the formulation may be systemically absorbed. The safety outcomes related to these molecules is unknown. There are no clinical data in support of the safety and efficacy of the generic product, and to indicate that the concerns regarding particle size are of no clinical consequence.
- The differencein cross-linkages in the molecules between the reference and the generic formulations. Cross linkages within the molecule are important for arrangement of binding

sites for phosphate. There is an absence of evidence to suggest a difference in molecular geometry is of no clinical consequence. The binding of other anions including bile acids, other drugs and bicarbonate is important for the interchangeability of the generic and reference products. Crosslinking is also related to the swelling of the molecule.

- There is missing information regarding the final size of the tablet. A possible increased difficulty swallowing the tablet if the final dimensions are larger than the reference product cannot be ruled out in the absence of this information.
- The sponsor has not provided clinical data to suggest that the differences in chemical properties between the generic and reference product are of no clinical consequence. The efficacy, safety and tolerability of the generic as compared with the reference product are unknown.

11. Clinical questions

11.1. Pharmacokinetics

1. The sponsor submitted a justification for the use of in vitro studies alone to determine similarity between the generic formulation of sevelamer hydrochloride and the reference product. However, there have been issues raised including possible differences of particle size and particle size distribution, cross-linkages within the molecule and tablet size between the generic and reference formulations. Given these issues, the sponsor is requested to address the following questions below:
    a. A potential difference between the reference formulation and the generic formulation is the particle size and control for monomers and small oligomers. As there is no description of a control on the lower limit of the particle size, and no absorption study in the submission to demonstrate that the generic formulation is not systemically absorbed, then please discuss the basis for the conclusion that there is no systemic absorption of the generic formulation and that it only acts locally within the gastrointestinal tract.
    b. Please indicate upon what basis the pharmacodynamic interactions (drugs and other molecules such as bile salts) described for the reference can be assumed for the generic formulation, given the potential difference in particle size distribution and cross-linkages between the reference formulation and the generic formulation.
    c. In reference to the justification for not including a bioequivalence study the sponsor states that the clinical risk from any 'slight bioinequivalence' is low based on short term data derived from healthy volunteers. Please define 'slight bioinequivalence'. Please discuss the clinical consequences of this 'bioinequivalence' for the target population, which often has significant co-morbidities, and who may take this product over the long term. In this discussion please include a discussion of the clinical efficacy, safety and tolerability of the reference and the generic products.
2. A justification is provided for not performing in vitro studies using the 400 mg strength tablet. In this justification, the dose proportionality of ingested tablets between 800 mg tablet and 400 mg tablets is assumed on the basis of their derivation from a common blend of ingredients. However, in Burke et al 1997 a dose of 2.5g of sevelamer 500 mg capsules did not bind double the phosphate of a 1.25 g dose, which suggests that there is not a direct linear relationship between phosphate binding and dose. Please discuss the clinical implications of this observation for the generic formulation as patients may choose to take two 400 mg tablets in preference to one 800 mg tablet, and to support the registration of a 400 mg strength tablet.

11.2. Safety

3. The reference product carries a warning about choking for its tablet. The sponsor states that the generic 800 mg tablet is pressed into a 19 x 9.5 mm plain mould. Please provide the final physical dimensions of the generic product compared to the Australian reference product and if there are differences in size, shape or swell volume then discuss the clinical consequences for patients, including the potential for choking, and the risks of swelling and tablet size if the tablet is lodged in the airway or in the upper gastrointestinal tract.

11.3. Other questions

4. It is mentioned that an application for approval for this generic formulation was made in the EU - Germany in December 2012. Please provide an update on the status of that application. In your response please include information about the following:
    a. whether additional data or other information has been requested of the applicant in support of the application in Europe; and/or
    b. whether there has been a requirement to undertake any further in vitro studies, animal studies or human clinical trials to support the application.

Where additional information has been requested please provide the questions asked and the responses the sponsor provided. If additional studies have been requested please provide details of the request and a synopsis of the studies the sponsor is planning to conduct.

12. Second round evaluation of clinical data submitted in response to questions

12.1. Pharmacokinetics Question 1

12.1.1. Part (a) – particle size

The sponsor has provided revised specifications for the proposed product that it states comply with the draft monograph for sevelamer hydrochloride in Pharmacopoeial Forum 38 (6) in terms of the particle size and control for monomers and small oligomers at both release and expiry. On this basis the generic formulation can be expected to not differ substantially from the reference formulation in terms of particle size and gastrointestinal absorption.

The sponsor also states that the drug substance has been demonstrated to be stable both in formal stability studies as well as in forced degradation studies under conditions which are considerably harsher than any likely to occur in vivo.

Based on this, the sponsor believes that it is reasonable to conclude that no significant systemic absorption is likely.

> Evaluator comment: The sponsor's revised specifications will be evaluated by the quality evaluator. If this evaluation concludes that the manufacture of the generic product complies with the draft monograph the sponsor's response is acceptable.

12.1.2. Part (b) – pharmacodynamic interactions

The sponsor has stated that because the generic version of sevelamer hydrochloride meets the specifications of the draft monograph for sevelamer hydrochloride in Pharmacopoeial Forum 38 (6) in terms of the particle size and control for monomers and small oligomers, and the level of cross-linking observed in the comparative study overlapped for both the proposed and reference products, the binding of all species is likely to be similar for both products. On this basis, any other interactions described for the reference can also be assumed for the generic formulation.

Evaluator comment: The cross-linking in the generic formulation was in the range of 13.9% - 15.0% and the reference product was 10.6% - 13.9%. The sponsor had assumed the binding of other anions will be the same given the similarity of the cross-linking, but it is unclear if the geometry of the polymer is sufficiently similar to bind anions including other medications to the same extent as the reference product. This is of particular concern for drug such as cyclosporin and smaller anions such as bicarbonate.

12.1.3. Part (c) – consequences of 'slight bioinequivalence' for the target population

The sponsor states that in accepting a waiver of the requirements for in vivo bioequivalence, it is mindful that there is always some risk that the assumptions underlying the justification are not entirely valid.

The sponsor has highlighted the limitation of the TGA bioequivalence guideline where one of the issues to be addressed in the biowaiver justification is the clinical consequences of any potential differences in bioavailabilities of the products under consideration that could lead to toxicity or lack of efficacy. Given that sevelamer is not absorbed from the gastrointestinal tract the sponsor has suggested that bioavailability should be considered synonymous with clinical activity.

In addressing this issue the sponsor states that the reference product is well tolerated with gastrointestinal adverse effects most commonly encountered in the 52 week open label study of sevelamer hydrochloride, and that there was no systemic toxicity in healthy volunteers exposed to up to 14 g of sevelamer hydrochloride. The sponsor states that the drug has a high therapeutic margin.

The sponsor also cites the PI for Renagel, and specifically two trials of sevelamer hydrochloride in patients with ESRD. In trial GTC-36-301 a mean dose of 4.3 g/day was used, while study GTC-49-301 used a mean of 6.5 g/day and that despite this increase in dose, mean reductions in phosphate levels were comparable, with a reduction of 0.65 mmol/L reported in study GTC-36-301 and 0.61-0.71 mmol/L in study GTC-49-301. Adverse events were similar in both studies. Clinical studies discussed in the Product Information provide evidence that sevelamer has a flat dose-response curve, indicating that slight increases in clinical activity would also not be likely to have significant clinical consequences.

Based on this, the sponsor has concluded that slight increases in clinical activity of the products would be unlikely to result in clinically significant differences.

Evaluator comment: The studies cited are of a different design, using different formulations of Renagel (capsules and tablets) but both were conducted in patients with ESRD. Neither was conducted as pharmacodynamic study to determine the relationship between sevelamer dose and serum phosphate.

It is agreed that these results would suggest there is a complicated dose-response relationship between the dose of sevelamer hydrochloride administered and serum phosphate. This information highlights the relevance of a clinical study to investigate the therapeutic equivalence between the generic and reference products.

12.2. Pharmacokinetics question 2

The sponsor has provided its own analysis of the data from the study by Burke et al. The sponsor has performed a linear regression to determine there was a linear relationship between dose and urinary phosphorus excretion ($R_2 = 0.94$) and between dose and faecal phosphorus excretion ($R_2 = 0.95$).

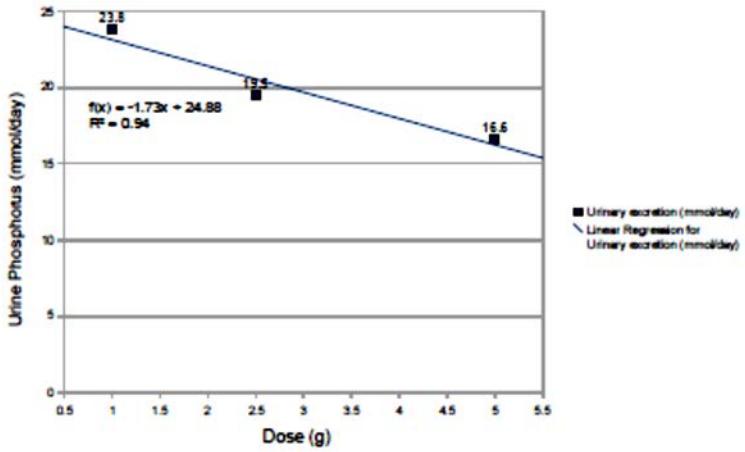
The sponsor has used summarised data from the article (Table 5).

Table 5: Phosphorus excretion data from Burke et al (as provided by the sponsor)

Dose (g)	Urinary phosphorus excretion (mmol/day)	Fecal phosphorus excretion (mmol/day)
1	23.8	9.1
2.5	19.5	10.7
5	16.6	19.1

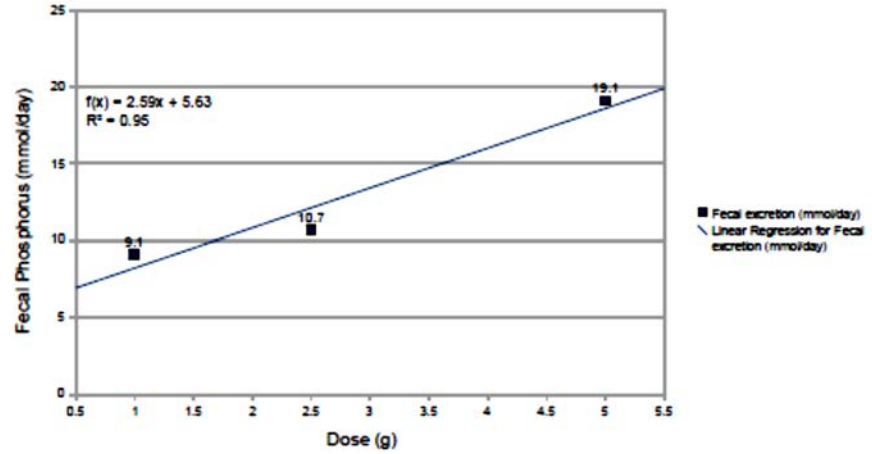
The regression line derived from the sponsor's model for urinary phosphate excretion is shown in Figure 3: Linear regression of Urine Phosphorus excretion with Dose (as provided by the sponsor).

Figure 3: Linear regression of Urine Phosphorus excretion with Dose (as provided by the sponsor)



The regression line derived from the sponsor's model for faecal phosphate excretion is shown in Figure 4.

Figure 4: Linear regression of Faecal Phosphorus excretion with Dose (as provided by the sponsor)



The sponsor has concluded that the model demonstrates linearity. It has concluded that the qualitative composition of both strengths is the same, and that the in vitro equilibrium binding study and in vitro kinetic binding study, conducted with 800 mg generic formulation showed

the effectiveness of the formulation. Based on these conclusions the sponsor has assumed that in vitro studies are not required for 400 mg formulation due to the dose proportionality.

> Evaluator comment: The sponsor has used three mean values from the study for each of faecal phosphate and urinary phosphate in order to demonstrate a linear dose-response relationship between sevelamer dose and observed response. The observations for the placebo group have not been included. In the publication of the result of this study the only measure of central tendency of the observed results was the mean +- standard deviation. It is not certain that the results were normally distributed and that the mean is the best measure of central tendency for the data such that it may be used in a linear regression model. One of the assumptions of a simple linear regression is that the error on the included sample points is normally distributed. It is not clear that this is the case and that the assumption is correct. Also the sponsor has not justified using only three data points in its linear regression model.
>
> The sponsor has stated there is a linear relationship between the dose and effect. This effect was seen in healthy volunteers with a fixed dietary phosphate load. But from the studies cited in response to question 1(c), above, it would appear that the clinical response as measured by serum phosphate reduction is not easily predictable from the dose for the reference product. The 400 mg tablet proposed by the sponsor is quantitatively proportional to the 800 mg tablet in terms of active ingredient and it should be expected to have an in vitro phosphate binding capacity of half the 800 mg tablet. It is not certain that another in vitro study using the 400 mg tablet would address this issue.

12.3. Safety

In response to this question the sponsor provided the physical dimensions of the Renagel 800 mg tablets and the generic formulation. A tabulated summary of the measurements of 10 tablets of each of the 800 mg Renagel and 800 mg generic products was provided and a copy is included below (Table 6).

Table 6: Comparison of the Physical Dimensions of the Reference and Generic Products

Parameter	Renagel 800 mg (B.No: B3255B01) Mean (SD)	Sevelamer Hydrochloride tablets 800 mg (B. No.2280214) Mean (SD)
Length (mm)	18.952 (0.02)	19.041 (0.03)
Breadth (mm)	9.768 (0.01)	9.534 (0.02)
Thickness (mm)	7.597 (0.05)	8.328 (0.05)

The sponsor states that the results of the comparison demonstrate that the sizes of the proposed and reference products are comparable.

The sponsor acknowledged the TGA comment regarding the potential for choking or lodgement of the tablet in the airway or upper gastrointestinal tract that is present for any large tablets, and acknowledged the potential for swallowing difficulties. The sponsor pointed to the statement in the Precautions section of the proposed PI cautioning health professionals regarding the potential for swallowing difficulties, and suggested a willingness to strengthen the statement if required.

> Evaluator comment: The sponsor has not indicated whether this Renagel batch is an Australian or an overseas product. From the data provided the final dimensions of the

generic product tablets are marginally larger than the reference product. The differences represent an approximately 7% increase in cross-sectional area and volume. The FDA draft Guidance for Industry Size, Shape and Other Physical Attributes of Generic Tablet and Capsules (2013) states that if the reference tablets are greater than 17 mm in their largest dimension generic versions should be no larger in any single dimension or volume. For a tablet as large as these it is possible the increased surface area could contribute to an increased difficulty swallowing. No clinical data has been provided by the sponsor to indicate the difference in tablet size does not increase the swallowing difficulty compared with the reference product in this population where such difficulties may be expected.

The sponsor has acknowledged there is a difference in tablet size and has indicated a preparedness to place additional warnings in the PI and CMI. The Risk Management Plan evaluator is requested to make a comment regarding whether this risk mitigation strategy is adequate and sufficient to manage the potential risk of swallowing difficulties with the generic formulation.

12.4. Other questions

In response to this question the sponsor stated that the application to the German authority, submitted in December 2012 was currently in progress and that to date no questions or feedback has been received.

12.5. Trade names

The sponsor has proposed the trade name Seveligand in the place of the proposed name Sevelam. This is acceptable.

The sponsor has proposed the trade name Phosomer in the place of the proposed name Sevlar. This sounds like Fosamax and is not acceptable.[1]

13. Overview of sponsor responses to (Milestone 5) second round evaluation report

The sponsor had addressed a number of issues raised in the second round evaluations by the quality evaluator and the clinical evaluator. The following is a summary of the additional information provided by the sponsor of relevance to the clinical evaluation.

13.1. Cross-linking

The sponsor has tested 5 further batches of the reference product from the EU and Australian markets. The sponsor has not identified which is the Australian product and which is the EU product. [information redacted]

13.2. Titrable amines

The sponsor has provided the chemical characterisation of three reference product batches that were included in the cross-linking information above, and two additional generic product batches.

[1] At Milestone 5 the sponsor provided the following response: 'The sponsor has proposed alternative trade names for consideration to replace Phosomer.'

[information redacted]

The sponsor states that this demonstrates the products are equivalent.

13.3. Particle size

The sponsor stated that the proposed particle size limits included a typographical error and should have read d (0.01) NLT 3 µm, d (0.5) NLT 100 µm and d (0.9) NMT 375µm.

13.4. Phosphate binding

The sponsor has retained the proposed phosphate binding specification of 4.9 – 6.1 mmol/g based on values obtained for the reference and generic products during product development allowing for reasonable manufacturing variability.

The quality evaluator noted that the equilibrium binding study did not determine the maximum binding of phosphate (as required by the FDA draft guidance provided by the sponsor in support of its approach to demonstrating equivalence between its product and the reference product without clinical data). The sponsor has performed a bridging study to include concentrations of 1 mM to 70 mM but has used two sets of testing compared with the 6 sets from the initial submission and the 12 sets required according to the version of the FDA guidance cited by the sponsor in the initial submission. Langmuir constants were also calculated in this study and compared to the values in the submission.

It is anticipated that the quality evaluator will provide comment on the adequacy of the study and an analysis of the results.

13.5. Trade names

The sponsor has proposed Phosligand as an alternative to Phosomer. This has been tested with the Clinical Evaluation Unit 3 pharmacist and has been considered acceptable.

13.6. Sponsor responses to the clinical evaluation report.

The sponsor stated that the additional testing, outlined above, together with the justifications contained in the initial submission and the responses to the questions is sufficient to demonstrate the equivalence of the products and that the product can be approved on this basis.

13.6.1. Tablet size

The sponsor provided the dimensions of 10 tablets each from batch 2280214 for the generic product and from three Renagel Australian batches, including two from the original submission and one from the Section 31 responses.

Table 8: Comparison of Mean Physical Dimensions of Generic and Reference Tablets

	Sevelamer 800 mg Batch 2280214	Renagel 800 mg B3255B01	Renagel 800 mg B2284B01	Renagel 800 mg B2151B01
Mean Length (mm) (SD)	19.04 (0.03)	18.95 (0.02)	19.07 (0.03)	19.08 (0.05)

	Sevelamer 800 mg Batch 2280214	Renagel 800 mg B3255B01	Renagel 800 mg B2284B01	Renagel 800 mg B2151B01
Mean Width (mm) (SD)	9.53 (0.02)	9.79 (0.01)	9.79 (0.01)	9.78 (0.01)
Mean Depth (mm) (SD)	8.39 (0.05)	7.60 (0.05)	7.62 (0.03)	7.60 (0.04)

The longest generic tablet was 19.08 mm, and the longest Renagel tablet was 19.10 mm. The sponsor has considered the length to be the critical dimension for swallowing. There was no overlap in the measured width and depth of the generic and reference products.

Because the sponsor considers the tablet dimensions to be similar it states that the choking hazard is similar to the reference product and can be managed similarly.

13.6.2. Swell index

The sponsor states that because the tablets disintegrate into particles rapidly in an acid environment and these particles swell to form a gel, in contrast to metformin 1000 mg tablets which swell as intact tablets in the gastrointestinal tract. The sponsor also states that because the cross-linking falls within the range of the reference product the particles are likely to swell similarly to the reference product. For this reason the sponsor states that there is unlikely to be any difference in the risk of constipation or intestinal obstruction between the generic product and the reference product. The sponsor has made no comment on swelling if the tablet should become lodged in the airway.

The sponsor has stated that it wishes to withdraw the 400 mg strength tablet from the application for commercial reasons.

13.6.3. Conclusion

The sponsor has presented additional information regarding the range of cross-linking that is observed in the reference product. The cross-linking observed in three batches of the generic product lies within the range of that observed for the innovator.

The assumption that because swelling is related to cross-linking and occurs at the particle level there is unlikely to be any greater risk of intestinal obstruction and constipation with in the generic product is untested in patients with ESRD.

The reference product has a higher proportion of titrable amines and phosphate binding capacity. [information redacted] This would suggest some difference between the reference and generic products. The quality evaluator may comment on whether these differences are acceptable

It is anticipated that the quality evaluator will provide comment regarding the adequacy and sufficiency of the bridging study to address the deficiencies in the equilibrium binding study provided in the original submission.

Both the reference and generic products are very large tablets and swallowing is likely to be a problem. There is a small variation in the dimensions of each type of tablet within each batch. There is a difference in cross-sectional area between the reference and generic products of sevelamer hydrochloride of between 6 and 7%. The clinical significance of this difference for the ease of swallowing and the risk of choking in patients with ESRD is unknown.

There is no clinical data included in the responses to the second round Clinical Evaluation Report. The sponsor remains of the opinion that this is not necessary. The clinical safety and efficacy of the generic sevelamer products remain unknown.

The additional information in response to the Clinical Evaluation Report does not change the recommendations in Section 11.

13.7. Draft PI and CMI:

The sponsor has made the editorial changes suggested for the draft PI. This is acceptable.

The sponsor has amended proposed wording for the CMI. The sponsor has removed reference to the 400 mg tablet. The wording of the section headed 'When you must not take it', while improved, could be further amended for clarity. It is noted that the Renagel CMI is also awkwardly worded in this section. The sponsor may also consider re-wording paragraph 3 under the heading 'Storage'.

14. Second round benefit-risk assessment

14.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of the generic version of sevelamer hydrochloride in the proposed usage are unchanged from those identified in the First Round Evaluation.

14.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of the generic version of sevelamer hydrochloride in the proposed usage are unchanged except for the following:

- The mean final dimensions are 19.0431 mm x 9.534 mm x 8.328 mm. This may pose a choking hazard, particularly in the target population who are often elderly, with significant comorbidities. Poor compliance or non-compliance may result from difficulty swallowing the tablet. Although the reference product is very large, the generic product is larger in length and thickness. Using the mean physical dimensions of the generic and reference products provided by the sponsor, the volume of the generic product is greater than the reference product (approximately 791.6 mm^3 and 736.38 mm^3 respectively)[2] and the cross-sectional area of the generic is also larger than the reference product (approximately 62.36mm^2 and 58.28mm^2, respectively)[3]. There is no clinical data to assess the safety and tolerability of the generic product. Whether it is more difficult to swallow and poses a greater choking risk than the reference product is unknown. The sponsor has suggested that it would be willing to consider additional warnings in the PI and CMI regarding this risk, although it is not clear whether this would be sufficient to mitigate any increased risk.
- The sponsor has provided additional information regarding the swelling of the product. In the specification provided for Module 3 the sponsor has indicated the swell index specification is set to 6.0 – 10.0. This is greater than that reported by Plone et al 2002 for the reference product. The quality evaluator will comment further on this, but from a clinical perspective the concern is that the generic product may have an increased risk of constipation and intestinal obstruction if its swell index is greater than the reference

[2] Approximating volume of an ellipsoid figure $V = {}^4/_3 \pi r^1 r^2 r^3$

[3] Approximating cross-sectional area of an ellipse $A = \pi r^1 r^2$

product. If a generic tablet lodged in the airway there is the potential for a larger obstruction to occur, due to the swelling, than with the reference product.

- The sponsor has addressed the issue of the control of the particle size such that monomers and water soluble oligomers are unlikely to be present in the formulation in that the lower limit of the particle size will be controlled and the impurity limit of water soluble oligomers will be no more than 0.2%.

14.3. Second round assessment of benefit-risk balance

The sponsor has chosen in vitro studies to demonstrate the phosphate binding of the generic formulation compared with the reference product. The sponsor has demonstrated that under the conditions of the in vitro studies the generic product binds phosphate ions. The characteristics of the binding differ between the generic and reference products for the affinity constant (k1) of the Langmuir equation, although the binding constants are similar. The kinetic binding study showed both the reference and generic products bind phosphate ions within 15 minutes but because the time points between 0 and 15 minutes have not been measured any difference between the generic and reference products is unknown. The sponsor has also provided evidence that the dose-response relationship for the reference product is complex. This raises uncertainty as to whether the clinical activity of the generic product is adequately characterised by in vitro studies alone.

The sponsor has addressed the issue of the lower limit of the particle size. The particle size distribution is still of concern although the sponsor has provided a justification for not comparing its product to the reference product. The adequacy of this justification will be assessed by the quality evaluator. Particle size is important for phosphate binding but also be important for the binding of other anions.

The sponsor has provided a justification for not performing the phosphate binding studies on the 400 mg product. Although there is quantitative proportionality between the 400 mg and 800 mg doses, the sponsor has provided evidence that the dose-response curve in terms of serum phosphate bound in the target population is flat, suggesting the assumption that the 400 mg tablet should bind half the phosphate of the 800 mg tablet or that two 400 mg tablets should be interchangeable with one 800 mg tablet may not be valid in the patients with renal disease.

The sponsor has further clarified its justification for assuming that the difference in cross-linking is unlikely to be of any clinical consequence but there is no clinical data to support the assumption and its validity is untested. Although, as the sponsor states there is an overlap in the percentage of cross-linking between the polymers the percentage of cross-linking at the upper end of the range of crosslinking for the reference product and the lower end of the generic product. The cross-linking for most polymer molecules is likely to differ between the generic and reference products for the majority of polymer molecules manufactures, and, as previously discussed may be of clinical relevance. Cross-linking is also related to the amount the product swells. The reference product has been associated with constipation and bowel obstruction. Additional swelling adds to the safety concern, particularly for patients with renal failure with an increased risk of slow colonic transit time.

There is acknowledgement by the sponsor that the 800 mg tablet size is large and swallowing difficulties may be encountered and it may be a choking hazard. The tablet must be swallowed whole and the sponsor proposes to add labels to the packaging to remind patients of this. Whether the generic formulation is more difficult to swallow is untested. If so, it is unclear whether additional warnings in the PI and CMI would be sufficient to mitigate the risk.

The benefit-risk balance of this generic version of sevelamer hydrochloride, given the proposed usage, is unfavourable.

15. Second round recommendation regarding authorisation

Following review of the sponsor's responses to the *Clinical questions* the recommendation is for rejection of the application on the following grounds:

- There are physicochemical differences between the generic and reference products which include a difference in the affinity constant for the Langmuir isotherm at 37°C, a difference in cross-linking and the swell index. The relevance of these differences in chemistry have not been [resolved].
- Therapeutic equivalence between the generic and reference products has not been tested in humans and it is unclear whether the generic and reference products are of sufficiently similar safety and efficacy such that they can be used interchangeably as could be the case if the generic formulation is approved.
- There are the differences in chemistry between the reference and generic products which raises the possibility of differences in safety and efficacy in patients with ESRD. The validity of the concerns regarding these potential differences is unknown because of the lack of clinical data. The target population has Stage 4 or 5 ESRD and requires therapy to reduce serum phosphate. This is a complex disorder in patients that are often elderly, with significant co-morbidities and on multiple medications. This lack of clinical information regarding differences in safety and efficacy of the generic product and the reference product poses an unacceptable risk for these patients.

16. References

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