Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Lanthanum carbonate

Proprietary Product Name: Fosrenol

Sponsor: Shire Australia Pty Limited

February 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- 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.

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

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission:	Extension of Indications
Decision:	Withdrawn with Changes to the Product Information
Date of Decision:	8 December 2011
Active ingredient(s):	Lanthanum carbonate
Product Name(s):	Fosrenol
Sponsor's Name and Address:	Shire Australia Pty Limited Level 3, 78 Waterloo Road North Ryde NSW 2113
Dose form(s):	Chewable tablets
Strength(s):	500 mg, 750 mg and 1000 mg
Container(s):	White cylindrical high density polyethylene (HDPE) bottle
Pack size(s):	500 mg: 45 tablets per bottle, 2 bottles per pack 750 mg: 15 tablets per bottle, 6 bottles per pack 1000 mg: 15 tablets per bottle, 6 bottles per pack
Approved Therapeutic use:	No change to the indication which is: Treatment of hyperphosphataemia in adults with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD.
Route(s) of administration:	Oral
Dosage:	Complex, see Product Information
ARTG Number (s)	106964, 106960 and 106962

Product Background

Fosrenol is used for the treatment of hyperphosphataemia in patients with chronic renal failure (CRF) receiving dialysis. This AusPAR describes the evaluation of a submission by Shire Australia Pty Limited (the sponsor) to extend the indications to include not only patients on dialysis but all patients with chronic kidney disease experiencing hyperphosphataemia. .

The indications proposed by the sponsor in the letter of application are:

Treatment of hyperphosphataemia in adults with chronic renal failure.

The current approved indications are as follows:

Treatment of hyperphosphataemia in adults with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD.

The active ingredient in Fosrenol is lanthanum carbonate, the activity of which as a phosphate binder is dependent on the high affinity of lanthanum (La) ions for dietary phosphate. The La ions are released from the carbonate salt in the acid environment of

the upper gastrointestinal tract. Insoluble lanthanum phosphate is formed which reduces the absorption of phosphate from the gastrointestinal tract.

Lanthanum (La) is a rare earth element, is not metabolised, has extremely low bioavailability, that is likely to accumulate when excessive amounts are administered for prolonged periods, is extensively bound to plasma proteins and has been demonstrated to bind to bone, teeth, liver, spleen, stomach and the upper gastrointestinal tract.

The initial registration application in 2005 was based on Phase III studies involving subjects with end stage renal disease, that is, chronic kidney disease (CKD) Stage 5, who were on dialysis. The primary concern raised in relation to La was that little is known about La in humans, particularly in relation to the long term effects of administration. At the time of the initial application for registration, the sponsor had submitted data for a period of up to 2 years in duration but the consequence of accumulation of La in bone and tissue past that point was unclear. Given this, the Australian Drug Evaluation Committee (ADEC, which preceded the Advisory Committee on Prescription Medicines [ACPM]) supported the Delegate's proposal to limit the maximum dosage to 3,000 mg daily and also to limit the duration of administration to 2 years until more evidence was available. It was also noted that the data provided relating to bone were limited. After 12 months administration, median La concentration in bone biopsies taken from La treated renal patients increased sixty fold from baseline. It was also noted that there were no data provided on use in children and that relevant drug interaction data should be clearly stated in the Product Information (PI). The ADEC recommended that the sponsor be strongly encouraged to conduct further studies in these areas.

In 2006, the sponsor made an application to update the registered PI with respect to the 2 year restriction on the duration of administration of Fosrenol which had been imposed due to the lack of long term bone data. Additional data confirmed that the oral bioavailability of La was very low (0.001%). Daily treatment with La resulted in rising bone La concentrations over time. However, sequential bone biopsy samples from patients during treatment and 2 years after stopping treatment with La provided evidence that La is cleared from bone, with a possible half life of 2 to 3.57 years. Bone La levels in patients receiving treatment for 54 months were below levels found in long term animal toxicity studies in which bone histology and anatomy were normal.

The updated study report for LAM-IV-307 showed similar efficacy results to those observed in the earlier submission with > 45% of patients showing controlled phosphate levels in both La and standard groups.[1]

The integrated bone histomorphometry analysis in almost 300 patients showed that La treatment is not associated with any trends suggesting deterioration of renal bone disease.[1] Although the number of bone samples at 2 years and beyond was small, results from biopsies taken in patients treated with La for up to 4 years supported the results observed in the controlled studies. Also, there was no consistent pattern of changes in any of the bone parameters when La was stopped or continued.

[1] Bone biopsies were collected from 3 clinical studies:

- LAM-IV-303: a prospective study to investigate effects on bone of treatment with lanthanum vs calcium carbonate for 1 year with bone biopsies at baseline and after 1 year of treatment; also 21 patients had a third biopsy after they had been off treatment for 18-24 months
- LAM-IV-307: a 2-year comparative study with a bone sub-study in 211 patients with bone biopsies done at baseline and also at the end of 1 and/or 2 years of treatment.
- LAM-301E: long-term extension safety study with bone biopsies obtained from a small group of patients (n = 13) treated with lanthanum for up to 4 years.

Although the observation period was limited, the database was the largest controlled prospective series of bone biopsies collected in renal osteodystrophy patients and appeared to be adequate to detect any significant changes like those typically observed with aluminium based phosphate binders.

The incidence of fractures was too low to enable interpretation of a relationship between La treatment and fractures. Other long term effects on bone were not able to be ruled out from these studies and so the clinical evaluator recommended that the sponsor must continue to monitor for adverse effects (AEs) related to bone toxicity following La treatment. La treatment for 2 years was not associated with any trends suggesting safety risks in terms of cognitive function.

The application to remove the 2 year restriction on the administration of La treatment was approved on 14 August 2007. The following statement was approved as the opening statement in the Precautions section:

Tissue deposition of lanthanum, particularly in bone, liver and the stomach wall, has been shown with Fosrenol in animal studies. Deposition of lanthanum in bone has been studied (see Effects on Bone). Results from long-term studies (Study 301, 303 and 307) demonstrated that bone lanthanum concentration had no apparent effect on bone health or treatment outcome for up to 4.5 years. There is no clinical data examining the potential deposition of lanthanum in other tissues. The long-term clinical effects of lanthanum deposition in tissues are not known. The risk benefit of longer-term therapy with Fosrenol should be considered.

In late 2009 and early 2010, there was correspondence between the sponsor and the TGA with regard to a number of changes related to safety in the PI for Fosrenol.

Regulatory Status

The product received initial ARTG Registration in 2005.

The sponsor stated that applications for a change in the patient group in the indication for Fosrenol had not been submitted in the United States (US) or Canada. However, a similar submission to the current Australian application was approved in the European Union (EU) in September 2009. The EU indication is:

Fosrenol is indicated as a phosphate binding agent for use in the control of hyperphosphataemia in chronic renal failure patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Fosrenol is also indicated in adult patients with chronic kidney disease not on dialysis with serum phosphate levels ≥ 1.78mmol/L in whom a low phosphate diet alone is insufficient to control serum phosphate levels.

On 27 April 2011, the Indications and Usage in the US approved PI were revised to:

Fosrenol is a phosphate binder indicated to reduce serum phosphate in patients with end stage renal disease (ESRD).

Management of elevated serum phosphorous levels in end stage renal disease patients usually includes all of the following: reduction in dietary intake of phosphate, removal of phosphate by dialysis and reduction of intestinal phosphate absorption with phosphate binders.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Fosrenol is presented as chewable tablets. Each tablet contains lanthanum carbonate hydrate corresponding to 500 mg, 750 mg or 1000 mg La. The tablets also contain the excipients dextrates, silicon dioxide and magnesium stearate.

Quality Summary and Conclusions

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical Findings

Introduction

New studies submitted in the current application included:

- two new pharmacodynamic (PD) studies comparing the phosphate binding affinities and capacities of lanthanum and sevelamer[2] under different conditions,
- a secondary PD study examining the effect of lanthanum carbonate (La) on parathyroid hormone (PTH) gene expression, serum PTH, serum calcium (Ca) and phosphorus (P), and liver (enzymes, magnetic resonance imaging [MRI], pathology) in rats with adenine induced renal failure,
- four distribution studies (ranging from acute to 28 days duration) investigating liver kinetics in rats with normal renal function (NRF) and chronic renal failure (CRF), gastrointestinal absorption of La, subcellular hepatic localisation of La, and plasma protein binding of La in rat, dog and human
- four repeat dose toxicity studies with La in rats: 14 day dose ranging dietary, 4 week gavage in normal and uremic animals, 22 week dietary study compared with sevelamer and phosphate deficient diet, 40 day dose ranging study in juvenile animals (10 days to 50 days old).

Only the protein binding study was strictly Good Laboratory Practice (GLP) compliant, although some aspects of bioanalysis and histopathology of the repeat dose studies were also claimed to fully comply.

Overall, the new studies further characterised the pharmacology, tissue deposition and tissue kinetics of La under conditions of NRF and CRF and were appropriate to support an extension of indication. The results from these additional studies were consistent with the pharmacodynamic and toxicological profile of La established in the original Fosrenol application and raised no additional safety issues from a risk benefit perspective.

Efficacy (Pharmacology)

In vitro

New *in vitro* pharmacodynamic (PD) studies showed that the phosphate binding affinity of lanthanum carbonate was greater than that of sevelamer, and that the selectivity of La for binding phosphate in the presence of competing anions (such as bile acids and fatty acids) was greater than that for sevelamer under conditions mimicking the environment of the stomach and small intestine.

[2] Sevelamer hydrochloride is a phosphate binding drug used to prevent hyperphosphataemia in patients with chronic renal failure. It will be referred to as sevelamer for the remainder of this AusPAR.

In vivo

Phosphorus retention and hyperphosphataemia have been recognized as important factors in the pathogenesis of secondary hyperparathyroidism in renal dysfunction. Hyperparathyroidism is associated with renal osteodystrophy and an increased risk of vascular calcification and cardiovascular morbidity and mortality in renal dialysis patients.

Studies investigating the ability of La to reverse hyperphosphataemia and/or hyperparathyroidism were performed in NRF rats or in rats with CRF induced through either a partial (5/6th) nephrectomy (remaining mass only being 1/6 of the original renal mass) or through adenine added to the diet.

Nephrectomy induced renal failure

In recent studies using a rat 5/6th nephrectomy chronic renal failure model, La was found to be an effective agent in reducing phosphorus retention, presumably by binding dietary phosphorus.

In the current submission, 5/6th nephrectomized rats showed decreased body weights, increased kidney remnant weight, increases in serum creatinine and parathyroid hormone, and decreases in heart, lung and liver weight. Lanthanum carbonate treatment for up to 20 weeks orally or 4 weeks intravenously (IV) helped to reverse the hyperparathyroidism. However, efficacy in reversing hyperphosphataemia could not be demonstrated because serum phosphate was not increased in this model of CRF in either of the two studies in this submission.

Adenine induced renal failure

Adenine induced renal failure in rats caused acute hyperphosphataemia, hyperparathyroidism, elevated PTH gene expression, increases in serum creatinine and a lack of weight gain. Dietary La administration to these rats (4 week and 22 week studies) reversed these changes, decreased urinary phosphate excretion and reduced osteodystrophy (22 week study).

A 4 week gavage study also showed that La, but not sevelamer, could reduce PTH levels, decrease urinary phosphorus and improve acidosis in CRF animals.

Efficacy in animals with normal renal function

In animals with normal renal function, modulation of renal phosphate resorption allows maintenance of plasma phosphate levels when the amount of phosphate absorbed from the diet is reduced. Thus, in these animals, urinary phosphorous excretion is a better marker of the degree of phosphate absorption from the gastrointestinal tract. Indeed, a reduction in urinary excretion of phosphorous was shown following La administration to rats with normal renal function in all studies, regardless of the method of induction of renal failure.

In vivo efficacy conclusions

Overall, the effect of ongoing La treatment (between 4 and 22 weeks duration) on plasma phosphate levels in rats was variable. The plasma phosphate levels of the various treatment groups were often not significantly different from controls: adenine induced and nephrectomy induced renal failure often failed to increase plasma phosphate. However, an increase in parathyroid hormone was observed in all CRF animals (regardless of the method of renal failure induction) and this compensatory PTH increase was consistently reversed by La administration in all studies.

Pharmacokinetics

Plasma protein binding

Studies submitted for the original Fosrenol application revealed that absorbed La is extensively bound to plasma proteins (>99%). A new protein binding study in the current submission (ultracentrifugation method) tested a higher concentration range of total La (250 ng/mL up to 25,000 ng/mL) and confirmed that protein binding was greater than 99% in the rat (99.98%), dog (99.62%) and human (99.83%) plasma and was independent of total La concentration over this range.

Kinetics, localisation and toxicity

Liver

In the previous submission, the liver was identified as a major sequestration site for systemically absorbed La in pharmacokinetic studies. However, demonstration of hepatotoxicity required very high systemic single or repeat IV dosing.

Tissue levels are more relevant than plasma levels in determining the potential for La to cause toxicity and repeat dosing in rats, despite not affecting the plasma exposure parameters, clearly caused a progressive rise in tissue levels. Several studies in the original Fosrenol submission demonstrated higher levels of La in the livers of uraemic rats (2 to 3 fold) compared to animals with normal renal function, a finding with possible implications for long term liver toxicity. However, in these studies there was insufficient data to determine whether the increase that was observed in renal failure would be maintained throughout the course of treatment or represented a more rapid attainment of the steady state level. Therefore, new studies in this submission explored the long term hepatotoxic potential of La with respect to its liver kinetics in NRF and CRF rats as well as its gastrointestinal absorption and subcellular hepatic localisation.

Gavage studies of up to 22 weeks duration conducted in NRF and CRF rats used doses of up to 1000 mg/kg/day for 20 weeks in adult rats and 2000 mg/kg/day for 40 days in juvenile rats. The maximum oral dose used in the previous submission in rats was 2000 mg/kg/day, which yielded liver La levels ranging up to 68 µg/g which were not associated with hepatotoxicity. In the present submission, the highest liver La level found in the 22 week oral study with 2% La in the diet was 8.1 µg/g; this was also not associated with hepatotoxicity. La concentrations in the liver were around twice as high in rats with CRF than in NRF rats. It is likely that this is due to increased gastrointestinal absorption of La in CRF as there was no difference in La levels between CRF and NRF rats after IV dosing.

Plasma La concentrations, and liver and femur La levels, were higher in NRF animals receiving La (~850 mg/kg/day) for 4 weeks via oral gavage than levels in NRF animals receiving the same dose in the diet.

No hepatotoxicity (measured by liver weight, MRI scanning, microscopy and liver enzymes) was observed in rats dosed with 2% La in the diet for 22 weeks or 1000 mg/kg/day for up to 20 weeks, irrespective of renal functional status of the rats.

The subcellular localization of La was found to be restricted to the lysosomes of the hepatocyte where it most probably precedes transcellular lysosomal transport and elimination via the bile canaliculi.

Stomach

Repeated oral treatment with La (which is an extremely viscous formulation at the concentrations used in the nonclinical studies) has previously been established to cause stomach changes in mice, rats and rabbits, with thickening of the stomach wall,

hyperkeratosis (limiting ridge), epithelial hyperplasia (limiting ridge, non-glandular and glandular mucosa), mucosal and submucosal inflammation, mineralisation of the glandular mucosa and oedema. Similar local microscopic findings were noted in the new dose ranging study conducted in juvenile animals after oral administration of 2000 mg/kg/day.

Bone

Previous *in vitro* experiments with cultured mouse and rat bone cells showed that La (100–15000 ng/mL) inhibited osteoclast differentiation, stimulated osteoblast differentiation at 100 ng/mL and caused inhibition at higher concentrations but had no effect on bone resorption by osteoclasts, and stimulated bone formation by osteoblasts.

In the current submission, chronic renal failure induced bone histomorphometry changes such as a high accumulation of trabecular bone and increases in woven bone and fibrosis area. These abnormalities were significantly reduced by La treatment.

CRF animals had higher levels of La in bone than NRF animals that did not saturate within the time frame of this study. The issue of whether further La accumulation occurs in bone with longer durations of treatment and whether this has beneficial or adverse clinical effects on bone remains uncertain. Nevertheless, no osteomalacia or fractures were reported in the nonclinical studies and there was no general toxic effect of La on bone consistent with previously submitted repeat dose toxicity studies.

Developmental toxicity/paediatric Use

End stage renal disease and hyperphosphataemia do occur in the paediatric population and the sponsor noted adverse event reports for two children who were exposed to La indicating off label use. The consequence of La deposition in growing bones has been investigated in animals in the previous and current submissions.

Previous long term repeat dose oral toxicity studies in young rats (4 - 7 weeks at the commencement of dosing, up to 2 years treatment) and young dogs (4 - 7 months at commencement of dosing, up to 1 year treatment) showed no functional or microscopic changes reflecting adverse effects on growth plates. The growth plate was also examined in high dose IV studies in rats and dogs, similarly aged and treated for 4 weeks without adverse affects in this tissue. Moreover, these studies showed comparable La concentrations in the growth plate and shaft of long bones indicating no special affinity of La for growth plates.

Administration of La by oral gavage to juvenile rats (aged 10 days at commencement of dosing) in a new dose ranging study resulted in a number of mortalities that were considered to be related to the physical properties of the test material reflected by microscopic findings in the stomach after administration of 2000 mg/kg/day. There were no other treatment related effects of 40 days repeated La dosing up to 2000 mg/kg on body weight gain, food consumption and developmental milestones. Administration of La did not decrease phosphataemia, although it did decrease urinary phosphate excretion.

It should be noted that the current indication for Fosrenol is restricted to adults and that the results from the dose range study in juvenile rats are preliminary in nature and are therefore insufficient to support the off label use of La in very young children.

Nonclinical Summary and Conclusions

Nonclinical studies in this submission further characterized the pharmacology, tissue deposition and tissue kinetics of lanthanum under conditions of normal and impaired renal function and were appropriate to support the proposed extension of indication.

New *in vitro* studies showed that the phosphate binding affinity of lanthanum carbonate (La) was greater than that of sevelamer, and that the selectivity of La for binding phosphate in the presence of competing anions (such as bile acids and fatty acids) was greater than that for sevelamer under conditions mimicking the environment of the stomach and small intestine.

The *in vivo* effect of ongoing La treatment (between 4 and 22 weeks duration) on plasma phosphate levels in rats was variable. Adenine induced and nephrectomy induced renal failure often failed to increase plasma phosphate relative to controls, possibly due to the increase in PTH observed in all CRF animals, irrespective of the method of renal failure induction. Lanthanum carbonate administration reversed this compensatory PTH increase and decreased urinary phosphate excretion in all studies, with no indication of hepatotoxicity.

A new study confirmed that protein binding of La was greater than 99% in the rat, dog and human and was independent of La concentration over a high concentration range (250 ng/mL to 25,000 ng/mL).

No hepatotoxicity (measured by liver weight, MRI scanning, microscopy and liver enzymes) was observed in adult rats dosed with 2 % La in the diet for 22 weeks or 1000 mg/kg/day for up to 20 weeks, or in 10 day old juvenile rats dosed for 40 days at 2000 mg/kg/day, irrespective of renal functional status. La concentrations in the livers of CRF rats were approximately twice as high as those in NRF rats, most likely due to increased gastrointestinal absorption of La as there were no differences in liver levels after intravenous dosing. The subcellular localization of La was found to be restricted to the lysosomes of the hepatocyte where it most probably precedes transcellular lysosomal transport and elimination via the bile canaliculi.

In a non-GLP dose ranging study, forty days of gavage dosing of juvenile (10 day old) rats (2000 mg/kg/day) led to stomach inflammation and hyperplasia, as had been previously observed at high doses in adult rats. There were no other treatment related effects on body weight gain, food consumption and developmental milestones. No La related adverse effects were observed in bone despite it being a principle site of accumulation. In the current submission, chronic renal failure induced bone histomorphometry changes such as a high accumulation of trabecular bone and increases in woven bone and fibrosis area. These abnormalities were significantly reduced by La treatment. Overall, no osteomalacia or fractures were reported in these studies and there was no general toxic effect of La on bone consistent with previously submitted repeat dose toxicity studies.

No animal studies were submitted to address the possible interaction of La and thyroxine hormones, an issue of potential concern previously raised.

Results from these additional studies were consistent with the pharmacodynamic and toxicological profile of La established in the original Fosrenol application and raised no additional safety issues from a risk benefit perspective.

There were no nonclinical objections to the extension of indication for lanthanum carbonate (Fosrenol) to include the treatment of hyperphosphataemia in adults with chronic renal failure.

IV. Clinical Findings

Pharmacokinetics/Pharmacodynamics

No new pharmacokinetic (PK) and pharmacodynamic data were submitted by the sponsor for the use of Fosrenol in patients with CKD who are not on dialysis. The sponsor had stated in the submission document that no new PK studies were conducted in CKD

patients not on dialysis because the PK profile of Fosrenol in these patients is expected to be similar to that in CKD patients on dialysis as Fosrenol is highly protein bound (>99%) and hence dialysis would not result in a significant change in the plasma levels of Fosrenol.

Efficacy

Introduction

A single clinical study report (study SPD405-206) was submitted to support the application for extension of indications for Fosrenol. The approval for the initial registration of Fosrenol was based on Phase III studies involving subjects with end stage renal disease (CKD Stage 5) who were on dialysis. The sponsor stated in the study protocol of study SPD405-206 that this study was intended as a proof of concept study to evaluate the efficacy and safety of Fosrenol in a population in which previous clinical trials had not been conducted, that is, patients with Stage 3 and 4 CKD who were not yet on dialysis.

Clinical Study SPD405-206

Study SPD405-206 was a Phase II, double blind, randomised, placebo controlled study to assess the efficacy and safety of lanthanum carbonate (La) for the reduction of serum phosphorus in subjects with Stage 3 and 4 CKD who have elevated serum phosphorus levels.

Methods

The primary objective was to assess the percentage of subjects with Stage 3 and 4 CKD who had serum phosphate levels controlled to ≤ 4.6 mg/dL after treatment with Fosrenol or placebo.

The secondary objectives were to assess the absolute reduction and maintenance of serum phosphate levels following treatment with Fosrenol, establish the dose of Fosrenol needed to maintain serum phosphate level at ≤ 4.6 mg/dL (1.48 mmol/L), assess the effects of Fosrenol on serum intact parathyroid hormone (iPTH) and calcium phosphate product and evaluate the safety and tolerability of Fosrenol compared to placebo in subjects with Stage 3 and 4 CKD.

Study parameters

This was a multicentre study conducted in 29 centres in the United States. The study period was from 11 January 2006 (first subject randomised) to 1 June 2007 (last subject's last visit).

The main inclusion criteria were males or female subjects ≥ 18 years old who had been in the care of a physician for CKD for > 2 months, who were not expected to begin dialysis for at least 4 months, and who had a screening estimated glomerular filtration rate (eGFR) of 15-59 mL/min/1.73m^2.

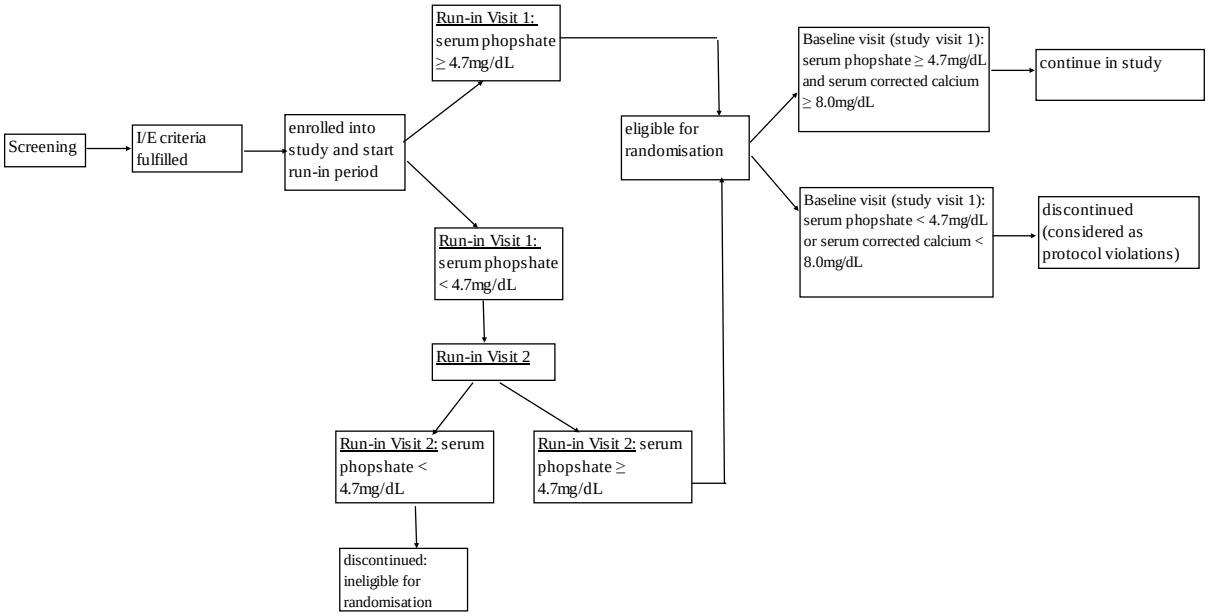
The main exclusion criteria were subjects with: acute renal failure within 12 weeks of screening, rapidly progressing glomerulonephritis, those requiring continuing treatment with cinacalcet or compounds containing phosphate, aluminium, magnesium or calcium (excluding permitted calcium supplements), cirrhosis or other clinically significant liver disease and history of past (treated within the last 5 years) or present gastrointestinal disorders.

The study procedure is outlined in Figure 1. Subjects were screened over a 1 week period. Once eligibility was confirmed in accordance with the inclusion/exclusion criteria described above, subjects were enrolled in the study. Subjects who had been receiving treatment for hyperphosphataemia were then to discontinue their phosphate binder therapy and all subjects entered a run-in period for 3 to 4 weeks. No treatment for

hyperphosphataemia was to be administered during this period. Serum phosphate levels were assessed after 2 weeks of the run-in period at Run-in Visit 1. If the serum phosphate level of a subject at Run-in Visit 1 was ≥4.7 mg/dL (1.52 mmol/L), the subject became eligible for randomisation and would attend the study baseline visit, which would then occur at the end of run-in period Week 3. During the baseline visit, baseline pre-dose serum phosphate and corrected calcium levels were taken. This serum phosphate level had to be ≥4.7 mg/dL in order for the subject to continue in the study (that is, subjects needed to have 2 consecutive baseline serum phosphate levels ≥4.7 mg/dL in order to continue participation in the study).

In addition, subjects had to have a corrected serum calcium level of ≥ 8.0 mg/dL during the baseline visit to continue in the study. If the serum phosphate level of a subject at Run-in Visit 1 was <4.7 mg/dL, a Run-in Visit 2 was performed after 3 weeks of the run-in period. If the serum phosphate level at this Run-in Visit 2 was also <4.7 mg/dL, the enrolled subject became ineligible for randomisation. If the serum phosphate level at this Run-in Visit 2 was ≥4.7 mg/dL, the subject became eligible for randomisation and would attend the study baseline visit, which would then occur at the end of run-in period Week 4. Baseline pre-dose serum phosphate and corrected calcium levels were also taken.

Figure 1: SPD405-206 Study schema



Treatments

The study drug used was Fosrenol administered orally in the formulation of chewable tablets and in dosage strengths of 250 mg and 500 mg. Subjects received either Fosrenol or placebo for a period of 8 weeks. The first 4 weeks were designated the titration period and the remaining 4 weeks were designated the maintenance period. The starting dose of the study drug was 750 mg/day taken in 3 divided doses with meals or immediately following food. Subjects were to remain on this starting dose regimen for the first 2 weeks. The total daily dose was then to be titrated weekly during the titration period in order to achieve serum phosphate levels of < 4.0 mg/dL (1.29 mmol/L), up to a maximum dose of 3000 mg/day.[3]

[3] Normal laboratory range for serum phosphate is 2.7 to 4.6 mg/dL.

During the maintenance period, serum phosphate levels were measured at the end of Week 6 and if the level was > 4.0 mg/dL, the total daily dose was to be increased. The dose was to be decreased if the serum phosphate level was < 2.7 mg/dL (0.87 mmol/L). If the subject was receiving 750 mg/day and required a lower dose, the subject was to be instructed to dose 2 times a day with the heaviest meals, for a total daily dose of 500 mg/day. If the subject was receiving 500 mg/day and required a lower dose, the subject was to be instructed to dose once a day with the heaviest meals, for a total daily dose of 250 mg/day. The dose range of 750 mg to 3000 mg/day, the dosing regimen and the treatment duration were based on previous clinical experience with CKD Stage 5 patients on dialysis.

Outcomes / endpoints

The primary endpoint was the percentage of subjects with serum phosphate levels controlled at ≤ 4.6 mg/dL (1.48 mmol/L). The secondary endpoints included:

- absolute change and maintenance of serum phosphate levels following treatment with Fosrenol,
- total daily dose of Fosrenol required to maintain serum phosphate levels at ≤ 4.6 mg/dL,
- serum intact PTH and calcium phosphate product levels.

Statistical considerations

The sample size was estimated using the results from a Phase III study (LAM-IV-302) involving CKD Stage 5 patients on haemodialysis receiving Fosrenol or placebo. In that study, the control rate of phosphate levels (defined as 5.9 mg/dL [1.90 mmol/L]) for placebo was 23%. To estimate the sample size for this study, the control rate for subjects receiving Fosrenol and placebo was assumed to be 57% and 23% respectively, with an assumed odds ratio of 4.438. A total of 84 subjects (56 on Fosrenol and 28 on placebo) were calculated to be needed for a test with an α level of 0.05 and 80% power.

At the baseline visit, subjects were randomised in a 2:1 ratio to receive either Fosrenol or placebo. Randomisation was based on a centralised randomisation schedule via an interactive voice response system once eligibility for the study had been confirmed. There were no restrictions on the minimum or maximum number of subjects to be enrolled at each study site.

The study was a double blind study. Fosrenol or matching placebo tablets were packaged in identical count bottles. Both subjects and investigators were blinded to the study treatment. No breaking of the blind was necessary in the course of this study.

Primary efficacy analysis

In the primary efficacy analysis, the "intent to treat" (ITT) population was used. The ITT population was denoted in the protocol and study report as the "full analysis population" (FAP), defined as all subjects who had received at least one dose of the study drug or placebo, and for whom at least 1 post-dose observation was recorded for the primary efficacy endpoint. The primary efficacy endpoint was the percentage of subjects with serum phosphate levels controlled at ≤ 4.6 mg/dL at the end of the study. For subjects who completed the study, the serum phosphate level at Week 8 (Visit 7) was used. For subjects who discontinued before completing the study, the last available serum phosphate level was used in the analysis. Treatment differences between Fosrenol and placebo were compared using Fisher's Exact Test.

Secondary efficacy analysis

Secondary efficacy endpoints were analysed in both the ITT and "per protocol" (PP) populations. The last observation carried forward (LOCF) imputation method was used for handling missing or incomplete efficacy data. However, additional analyses were also done without LOCF imputation (that is, using observed case imputation).

The difference between the treatment groups for the absolute change in serum phosphate levels from baseline at each visit was analysed using an analysis of covariance (ANCOVA) model with treatment as a factor and baseline assessment as a covariate. The baseline value was taken to be the last value of serum phosphate obtained prior to the start of the study drug or placebo. This was intended to be the sample taken at the baseline visit prior to the start of the study drug or placebo. For subjects with a missing value at the baseline visit, the latest value obtained at the run-in visit was used as the baseline value. The change from baseline within each treatment group was assessed using a one sample t-test.

Serum iPTH at each visit and calcium phosphate product at Visits 5 and 7 were also analysed using ANCOVA model with treatment as a factor and baseline assessment as a covariate.[4] When an endpoint had a missing value for the final visit of the study (Visit 7), the LOCF method was used to impute the missing data. The total daily dose of Fosrenol required to maintain serum phosphate levels at ≤ 4.6 mg/dL was analysed using an analysis of variance (ANOVA) model with treatment as a factor.

Evaluator comments

The inclusion and exclusion criteria for the study are appropriate. However, the design of the study was such that enrolment was based on only the initial inclusion and exclusion criteria, with additional eligibility for randomisation based on serum phosphate level of ≥4.7 mg/dL during the run-in period after enrolment, and additional eligibility to continue in the study after the baseline visit (Study Visit 1) based on baseline serum phosphate level of ≥4.7 mg/dL and baseline corrected serum calcium level of ≥ 8.0 mg/dL. This study design resulted in a large number of subjects being subsequently discontinued from the study after the baseline visit (and after receiving the initial dose of the study drug or placebo), when their baseline blood results showed serum phosphate levels of <4.7 mg/dL or corrected serum calcium level of < 8.0 mg/dL. They were classified as being discontinued due to protocol violations.

A more optimal study design would have been to include the serum phosphate and calcium levels in the inclusion and exclusion criteria so that only subjects with the appropriate pre-dose serum phosphate and calcium levels were eligible to be enrolled and entered into the study, or to delay dosing until the baseline serum phosphate and corrected calcium levels were known. This would prevent subjects from being unnecessarily exposed to the study drug in the initial period and then discontinued from the study when baseline serum phosphate and calcium levels were found to be lower than the set criteria as had happened with the current study design used. In addition, the current design resulted in some of the subjects who were discontinued from the study after the baseline visit, due to serum phosphate levels of <4.7 mg/dL or corrected serum calcium level of < 8.0 mg/dL at the baseline visit, being included in the efficacy analysis population as they had received one dose of the study drug or placebo and had a post-dose serum phosphate level recorded. This could have confounded the analysis results. This will be discussed further under the efficacy results section of this evaluation report.

[4] Calcium phosphate product was calculated as the product of the individual corrected calcium and phosphate levels at each visit.

The selection of subjects with hypercalcaemia is appropriate as CKD patients with hyperphosphataemia and hypercalcaemia would not be prescribed calcium containing phosphate binders and would be the patient population for whom Fosrenol, a non-calcium containing phosphate binder, would be prescribed in clinical practice.

No reason was given in the study protocol for the unequal randomisation ratio. However, the unequal randomisation was taken into account in the sample size calculation. In the estimation of the sample size required for this study, the control rate for subjects receiving Fosrenol and placebo was assumed to be 57% and 23% respectively. This control rate was based on results of another study (LAM-IV-302) involving CKD Stage 5 patients on haemodialysis receiving Fosrenol or placebo where the control rate of serum phosphate levels for placebo was 23%. However, in study LAM-IV-302, the serum phosphate level used to calculate the above control rate was 5.9 mg/dL. In contrast, the primary efficacy endpoint of the current study was 4.6 mg/dL. It is likely that in the sample size calculation of the current study the sample size required for the primary efficacy endpoint was underestimated resulting in an underpowered study.

The primary and secondary endpoints are appropriate. The serum phosphate level used in the primary endpoint of ≤ 4.6 mg/dL is in line with the target serum phosphate level of the Kidney/Dialysis Quality Outcome Initiative (K/DOQI) guidelines of the National Kidney Foundation (US) for Stages 3 and 4 CKD.[5] The Australia based Caring for Australians with Renal Impairment (CARI) guidelines also recommend the target serum phosphate level to be within the normal reference range (2.7 to 4.6 mg/dL) for Stages 3 and 4 CKD.[6] The secondary endpoints helped to further characterize the reduction in serum phosphate levels below baseline, and also looked at other parameters of bone metabolism in CKD.

Results

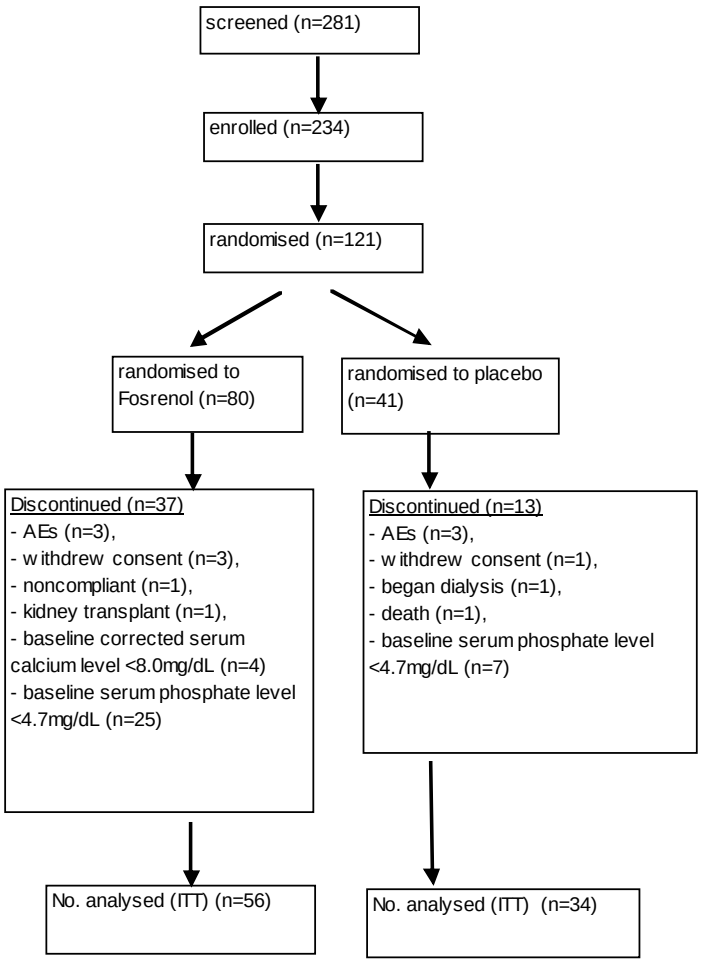
Participant Flow

Overall 281 participants were screened, and 234 were enrolled into the study. Out of these subjects, 121 were randomised, 80 to the Fosrenol group and 41 to the placebo group (see Figure 2).

[5] National Kidney Foundation, Kidney/Dialysis Quality Outcome Initiative (K/DQOI) clinical practice guidelines for bone metabolism and disease in chronic kidney disease, 2003. The K/DQOI guidelines recommend a target serum phosphate level of at or above 2.7 mg/dL and less than 4.6 mg/dL for Stages 3 and 4 CRF, and a target serum phosphate level of between 3.5 mg/dL and less than 5.5 mg/dL for Stage 5 CRF.

[6] Caring for Australians with Renal Impairment, Recommended target for serum phosphate, April 2006. The CARI guidelines recommendation of target serum phosphate level for Stage 5 CRF is ≤ 4.95 mg/dL.

Figure 2: Participant flow



Baseline data

The demographic characteristics of subjects were similar at baseline between the two treatment groups. The median age (range) in the Fosrenol and placebo groups were 63.0 (29 to 87) years and 61.0 (41 to 93) years, respectively. In the Fosrenol group, 51.3% of subjects were male, compared with 51.2% of subjects in the placebo group. In the Fosrenol group, 75.6% of subjects were White, compared with 80.5% of subjects in the placebo group.

The mean baseline serum phosphate levels were similar between the two treatment groups. The mean baseline serum phosphate levels (standard error [SE]) were 5.28 (± 0.090) mg/dL and 5.38 (± 0.119) mg/dL in the Fosrenol and placebo groups, respectively. The primary causes of renal disease were also similar between both treatment groups. The two most common primary causes of renal disease in both treatment groups were diabetes (57.7% and 58.5% of subjects in the Fosrenol and control groups, respectively), and hypertension (26.9% and 22.0% of subjects in the Fosrenol and control groups, respectively).

Protocol deviation and violations

The proportion of subjects with at least one major protocol deviation was similar between the Fosrenol and placebo groups (35.7% [20/56] and 32.4% [11/34], respectively). The most common major protocol deviation in both treatment groups were protocol violations

(19.6% [11/56] and 17.6% [6/34] in the Fosrenol and placebo groups, respectively). All protocol violations were due to baseline serum phosphate or calcium levels not meeting visit criteria.

Among the patients with at least one major protocol deviation, inclusion/exclusion criteria deviations occurred in 8.9% (5/56) of subjects in the Fosrenol group and 5.9% (2/34) of subjects in the placebo group. All 7 subjects had inclusion/exclusion criteria deviation due to having a screening eGFR of <15 mL/min/1.73m^2, 6 had a screening eGFR of 14 mL/min/1.73m^2 and 1 had a screening eGFR of 12 mL/min/1.73m^2. All 7 were allowed to participate in the study under approved protocol waivers.

Out of the 11 subjects with protocol violations in the Fosrenol group, 7 subjects had protocol violations due to baseline serum phosphate levels <4.7 mg/dL, and 4 subjects due to baseline serum calcium levels <8.0 mg/dL (that is, not meeting visit criteria). Of these subjects, 2 subjects with baseline serum phosphate levels <4.7 mg/dL and 3 subjects with baseline serum calcium levels <8.0 mg/dL were allowed to participate in the study under approved protocol waivers. Out of the 6 subjects with protocol violations in the placebo group, 4 subjects had protocol violations due to baseline serum phosphate levels <4.7 mg/dL and 2 subjects due to baseline serum calcium levels <8.0 mg/dL. Of these subjects, 3 subjects with baseline serum phosphate levels <4.7 mg/dL and 2 subjects with baseline serum calcium levels <8.0 mg/dL were allowed to participate in the study under approved protocol waivers.

Numbers analysed

In this study, the ITT population was denoted in the protocol and study report as the "full analysis population" (FAP), defined as all subjects who received at least one dose of the study drug or placebo and for whom at least one post-dose observation was recorded for the primary efficacy endpoint. Primary efficacy analysis was done in only the ITT population, while secondary efficacy analyses were performed on both the ITT and PP population.

Out of 80 subjects randomised to the Fosrenol group, 56 were included in the FAP and 36 in the PP population. Out of 41 subjects randomised to the placebo group, 34 were included in the FAP and 23 in the PP population. All 17 subjects with protocol violations (11 in the Fosrenol group, and 6 in the placebo group) as described above under *Protocol deviation and violations*, were included in the FAP. Although seven out of the 17 subjects (6 in the Fosrenol group, and 1 in the placebo group) were discontinued after the baseline visit due to the protocol violation, they were included in the FAP as they had already received one dose of the study drug or placebo and already had a post-dose serum phosphate level recorded before discontinuation.

Outcomes and estimation

Primary efficacy analysis

A higher percentage of subjects in the Fosrenol group (44.6%, 25/56) than in the placebo group (26.5%, 9/34) had serum phosphate level controlled at ≤4.6 mg/dL at the end of the study. However the difference between the groups was not statistically significant (p=0.1167)

Evaluator comment

The study design incorporating additional criteria for eligibility to continue in the study after the baseline visit instead of having these criteria incorporated in the initial inclusion/exclusion criteria before study enrolment, and the starting dosing in the subjects before the baseline blood results had been evaluated as meeting the criteria,

resulted in 7 out of the 17 subjects (6 in the Fosrenol group, and 1 in the placebo group) who were discontinued after the baseline visit due to baseline serum phosphate or serum calcium levels not meeting the additional criteria, being included for the primary efficacy analysis.

In the primary efficacy analysis of these subjects, the post-dose serum phosphate level used was that taken at Visit 2/Week1 (that is, after only 1 week of starting on the study drug or placebo) as LOCF imputation was used. Due to the small sample size of the study to begin with, the inclusion of these subjects into the analysis would confound the results. An analysis on the PP population, which would exclude subjects with a major protocol deviation, would remove this confounding effect. However, in the secondary efficacy analysis, observed case (OC) imputation (which would remove this confounding effect) was also used to look at the percentages of subjects with serum phosphate levels controlled at ≤ 4.6 mg/dL by visit. It was found that at Visit 7/Week 8 (that is, the end of study visit), the difference between the 2 treatment groups using OC imputation was also not statistically significant.

Secondary efficacy analyses

Secondary efficacy analyses were performed on both the ITT and PP population. Only the results for the ITT population are presented as the analyses in the PP populations for all the secondary efficacy analyses gave similar results to those done in the ITT population.

(i) Percentage of subjects with serum phosphate levels controlled at ≤4.6 mg/dL by visit.

The percentage of subjects with serum phosphate levels controlled at ≤ 4.6 mg/dL by visit for the FAP using both the LOCF and OC imputations are presented in Table 1**.** In both the LOCF and OC analyses, the difference between the treatment groups in favour of Fosrenol was statistically significant only at Visit 6/Week 6. Using the LOCF imputation, at Visit 6/Week 6, 55.4% (31/56) of subjects in the Fosrenol group versus 29.4% (10/34) of subjects in the placebo group had serum phosphate levels controlled at ≤ 4.6mg/dL (p=0.0283). Using the OC imputation, at Visit 6/Week 6, 60.5% (26/43) of subjects in the Fosrenol group versus 28.6% (8/28) of subjects in the placebo group had serum phosphate levels controlled at ≤ 4.6mg/dL (p=0.0145).

However, at Visit 7/Week 8, analyses by both imputation methods in the FAP showed the difference between the two treatment groups to be not statistically significant. The analysis using the LOCF imputation was the same as what was done for the primary efficacy analysis, showing that at Visit 7/Week 8, 44.6% (25/56) of subjects in the Fosrenol group versus 26.5% (9/34) of subjects in the placebo group had serum phosphate levels controlled at ≤ 4.6 mg/dL (p=0.1167). The analysis using OC imputation supported the results done by LOCF imputation, showing that at Visit 7/Week 8, 45.2% (19/42) of subjects in the Fosrenol group versus 25.0% (7/28) of subjects in the placebo group had serum phosphate levels controlled at ≤ 4.6 mg/dL, and that the difference was not statistically significant (p=0.1296).

Table 1: Number and percentage of subjects with serum phosphate level controlled at ≤4.6 g/dL by Visit (FAP), Study SPD405-206

	Lanthanum Carbonate (N=56)		Placebo (N=34)		
	% (Controlled/Total)	95% CI*	% (Controlled/Total)	95% CI*	P-Value†
LOCF Analysis					
Visit 1/Baseline	10.7 (6/56)	(4.0, 21.9)	8.8 (3/34)	(1.9, 23.7)	1.0000
Visit 2/Week 1	40.0 (22/55)	(27.0, 54.1)	37.5 (12/32)	(21.1, 56.3)	1.0000
Visit 3/Week 2	37.7 (20/53)	(24.8, 52.1)	36.4 (12/33)	(20.4, 54.9)	1.0000
Visit 4/Week 3	44.4 (24/54)	(30.9, 58.6)	32.4 (11/34)	(17.4, 50.5)	0.2748
Visit 5/Week 4	48.2 (27/56)	(34.7, 62.0)	35.3 (12/34)	(19.7, 53.5)	0.2761
Visit 6/Week 6	55.4 (31/56)	(41.5, 68.7)	29.4 (10/34)	(15.1, 47.5)	0.0283
Visit 7/Week 8	44.6 (25/56)	(31.3, 58.5)	26.5 (9/34)	(12.9, 44.4)	0.1167
Observed Cases (OC) Analysis					
Visit 1/Baseline	10.7 (6/56)	(4.0, 21.9)	8.8 (3/34)	(1.9, 23.7)	1.0000
Visit 2/Week 1	40.0 (22/55)	(27.0, 54.1)	37.5 (12/32)	(21.1, 56.3)	1.0000
Visit 3/Week 2	34.8 (16/46)	(21.4, 50.2)	35.5 (11/31)	(19.2, 54.6)	1.0000
Visit 4/Week 3	44.4 (20/45)	(29.6, 60.0)	31.3 (10/32)	(16.1, 50.0)	0.3432
Visit 5/Week 4	50.0 (22/44)	(34.6, 65.4)	36.7 (11/30)	(19.9, 56.1)	0.3418
Visit 6/Week 6	60.5 (26/43)	(44.4, 75.0)	28.6 (8/28)	(13.2, 48.7)	0.0145
Visit 7/Week 8	45.2 (19/42)	(29.8, 61.3)	25.0 (7/28)	(10.7, 44.9)	0.1296

* Based on the binomial distribution.
† P-Value is from Fisher's Exact Test.
CI=Confidence interval
Note: P-values are unadjusted for multiplicity.

(ii) Mean serum phosphate levels by visit and mean changes from baseline by visit

The mean serum phosphate levels by visit and mean changes from baseline by visit for the FAP using both the LOCF and OC imputations are presented in Table 2. The mean ± SE baseline serum phosphate levels were similar between the two treatment groups (5.28 ± 0.090 mg/dL and 5.38 ± 0.119 mg/dL in the Fosrenol and placebo groups, respectively). The mean serum phosphate levels in both the Fosrenol and placebo groups did not reach ≤4.6 mg/dL in any of the visits in both the LOCF and OC analyses.

In the Fosrenol group, in both the LOCF and OC analyses, the mean reductions from baseline in the serum phosphate levels was statistically significant (p≤0.05) from Visit 2/Week 1 onwards until Visit 7/Week 8. The mean ± SE reductions in the Fosrenol group ranged from -0.36 ± 0.110 mg/dL to -0.66 ± 0.125 mg/dL in the LOCF analysis, and -0.40 ± 0.121 mg/dL to -0.77 ± 0.143 mg/dL in the OC analysis, with the maximal reductions occurring at Visit 6/Week 6 in both imputation analyses.

In the placebo group, using LOCF imputation, the mean reductions from baseline in the serum phosphate levels was statistically significant (p≤0.05) only in Visit 2/Week 1 and Visit 3/Week 2. Using OC imputation, the mean reductions from baseline in the serum phosphate levels in the placebo group was statistically significant (p≤0.05) only in Visit 2/Week 1, Visit 3/Week 2 and Visit 6/Week 6. The mean ± SE reductions in the placebo group ranged from -0.21 ± 0.139 mg/dL to -0.34 ± 0.126 mg/dL in the LOCF analysis and -0.23 ± 0.122 mg/dL to -0.34 ± 0.134 mg/dL in the OC analysis.

The differences between the two treatment groups in the mean reductions from baseline in the serum phosphate levels was statistically significant (p≤0.05) in favour of the Fosrenol group from Visit 5/Week 4 to Visit 7/Week 8, in both the LOCF and OC analyses.

Table 2: Summary of mean serum phosphate levels (mg/dL) and mean changes from baseline by visit (FAP), Study SPD405-206

	Lanthanum Carbonate (N=56*)		Placebo (N=34*)		
	Mean ± SE	Mean Change ± SE	Mean ± SE	Mean Change ± SE	P-Value†
LOCF Analysis					
Visit 1/Baseline	5.28 ± 0.090		5.38 ± 0.119		
Visit 2/Week 1	4.77 ± 0.095	-0.51 ± 0.100	5.14 ± 0.171	-0.29 ± 0.116	0.0804
P-Value ‡		<0.0001		0.0174	
Visit 3/Week 2	4.91 ± 0.120	-0.36 ± 0.110	5.06 ± 0.171	-0.34 ± 0.126	0.7530
P-Value ‡		0.0018		0.0112	
Visit 4/Week 3	4.81 ± 0.096	-0.46 ± 0.102	5.10 ± 0.174	-0.28 ± 0.163	0.1779
P-Value ‡		<0.0001		0.0930	
Visit 5/Week 4	4.64 ± 0.103	-0.63 ± 0.107	5.15 ± 0.172	-0.23 ± 0.141	0.0094
P-Value ‡		<0.0001		0.1141	
Visit 6/Week 6	4.62 ± 0.102	-0.66 ± 0.125	5.12 ± 0.154	-0.26 ± 0.130	0.0083
P-Value ‡		<0.0001		0.0531	
Visit 7/Week 8	4.74 ± 0.101	-0.54 ± 0.108	5.17 ± 0.161	-0.21 ± 0.139	0.0228
P-Value ‡		<0.0001		0.1486	
Observed Cases (OC) Analysis					
Visit 1/Baseline	5.28 (0.090)		5.38 (0.119)		
Visit 2/Week 1	4.77 ± 0.095	-0.51 ± 0.100	5.14 ± 0.171	-0.29 ± 0.116	0.0804
P-Value ‡		<0.0001		0.0174	
Visit 3/Week 2	4.98 ± 0.133	-0.40 ± 0.121	5.10 ± 0.179	-0.34 ± 0.134	0.6821
P-Value ‡		0.0018		0.0171	
Visit 4/Week 3	4.86 ± 0.108	-0.51 ± 0.115	5.14 ± 0.182	-0.28 ± 0.173	0.1741
P-Value ‡		0.0001		0.1189	
Visit 5/Week 4	4.65 ± 0.120	-0.72 ± 0.115	5.15 ± 0.183	-0.23 ± 0.122	0.0055
P-Value ‡		<0.0001		0.0665	
Visit 6/Week 6	4.61 ± 0.121	-0.77 ± 0.143	5.07 ± 0.155	-0.30 ± 0.102	0.0117
P-Value ‡		<0.0001		0.0070	
Visit 7/Week 8	4.77 ± 0.122	-0.62 ± 0.122	5.14 ± 0.165	-0.23 ± 0.118	0.0284
P-Value ‡		<0.0001		0.0634	

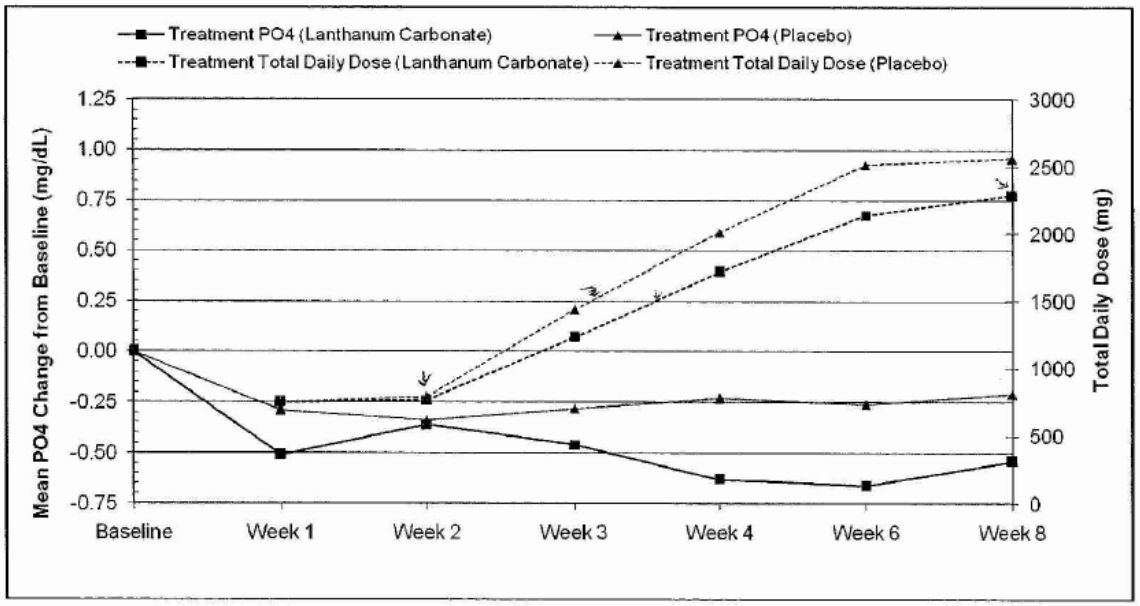
* Overall N for Full Analysis population. Summary data at each visit are based on available data for that visit.
† P-value from ANCOVA model with treatment as a factor and baseline assessment as a covariate.
‡ P-value from one-sample t-test on Change from Baseline.
Note: P-values are unadjusted for multiplicity.

(iii) Mean change in serum phosphate levels and total daily dose

A graphical plot of the mean change in serum phosphate levels against the total daily dose by visit for the FAP (LOCF imputation) is presented in Figure 3. In the Fosrenol group, there appeared to be a dose relationship for mean serum phosphate reductions from

baseline. In the placebo group, a higher daily dose was not associated with a greater mean serum phosphate reduction from baseline.

Figure 3: Plot of mean changes in serum phosphate levels and total daily dose (FAP) Study SPD405-206



(iv) Time to control of serum phosphate level at ≤4.6 mg/dL

The time to control of serum phosphate level at ≤4.6 mg/dL was the number of days from baseline to the first observation of serum phosphate at ≤4.6 mg/dL. The median (range) time to control of serum phosphate level at ≤4.6 mg/dL was 14 days (6 to 56) in the Fosrenol group, and 20 days (6 to 59) in the placebo group. This difference was found to be statistically significant (p=0.0415).

(v) Percentage of subjects with serum calcium phosphate product levels controlled at ≤55 mg^2/dL^2 by visit

Serum calcium phosphate product levels were done at Visit 1/Baseline, Visit 5/Week 4 and Visit 7/Week 8. In the Fosrenol group, the percentage of subjects with serum calcium phosphate product levels controlled at ≤ 55mg^2/dL^2 was 94.6% (53/56) at Visit 1/Baseline, and remained at 94.6% at Visit 5/Week4 and Visit 7/Week 8**.** In the placebo group, the percentage of subjects with serum calcium phosphate product levels controlled at ≤ 55 mg^2/dL^2 was 85.3% (29/34) at Visit 1/Baseline and remained at 85.3%% at Visit 5/Week 4 and was 88.2% (30/34) at Visit 7/Week 8. The differences between the treatment groups were not statistically significant.

Evaluator comments

Serum calcium phosphate product is used in CKD patients as an indicator of the risk of mineral crystallisation in soft tissues which can lead to cardiovascular calcification. The K/DQOI guidelines recommend a target serum calcium phosphate product of < 55 mg^2/dL^2 for Stages 3 to 5 CKD patients. The results showed that in the Fosrenol group, there was no change in the proportion of subjects with a serum calcium phosphate product ≤ 55 mg^2/dL^2 from the baseline visit (pre-dose levels) to the end of the study at Week 8. This could be due to the fact that at baseline, only 3 subjects had serum calcium phosphate product levels > 55 mg^2/dL^2.

(vi) Mean serum calcium phosphate product levels by visit and changes from baseline

The mean ± SE baseline serum calcium phosphate product levels were 46.57 ± 0.728 mg^2/dL^2 and 48.11 ± 0.968 mg^2/dL^2 in the Fosrenol and placebo groups, respectively. In the Fosrenol group (LOCF analysis) the mean reductions from baseline in the serum calcium phosphate product levels were statistically significant ($p \leq 0.05$) at both Visit 5/Week 4 (-5.05 ± 0.988 mg^2/dL^2) and Visit 7/Week 8 (-4.00 ± 1.020 mg^2/dL^2). In the placebo group (LOCF analysis) the mean reductions from baseline in the serum calcium phosphate product levels were not statistically significant ($p > 0.05$) at Visit 5/Week 4 (-2.39 ± 1.304 mg^2/dL^2) or Visit 7/Week 8 (-2.47 ± 1.278 mg^2/dL^2). The difference between the treatment groups was statistically significant ($p \leq 0.05$) at Visit 5/Week 4 but not at Visit 7/Week 8.

(vii) Mean change in serum calcium phosphate product levels and total daily dose

In both the Fosrenol and placebo group, a higher daily dose was not associated with a greater mean serum calcium-phosphate product reduction from baseline.

(viii) Mean iPTH levels by visit and changes from baseline

The mean serum iPTH levels by visit and mean changes from baseline by visit for the FAP (LOCF analysis) are presented in Table 4**.**

Figure 4: Summary of mean serum intact PTH levels (pg/mL) and mean changes from baseline by visit (LOCF, FAP), Study SPD405-206

	Lanthanum Carbonate (N=56*)		Placebo (N=34*)		
	Mean ± SE	Mean Change ± SE	Mean ± SE	Mean Change ± SE	P-Value†
Visit 1/Baseline	183.5 ± 19.48		179.3 ± 24.36		
Visit 2/Week 1	163.4 ± 16.54	-26.3 ± 9.59	183.9 ± 25.49	3.4 ± 8.33	0.0274
P-Value ‡		0.0083		0.6836	
Visit 3/Week 2	172.7 ± 20.38	-15.2 ± 8.21	187.8 ± 24.01	8.4 ± 9.50	0.0698
P-Value ‡		0.0694		0.3807	
Visit 4/Week 3	160.9 ± 19.33	-26.0 ± 6.02	190.2 ± 24.78	8.3 ± 8.66	0.0011
P-Value ‡		0.0001		0.3450	
Visit 5/Week 4	160.6 ± 19.72	-28.3 ± 10.70	191.8 ± 27.48	0.5 ± 12.03	0.0796
P-Value ‡		0.0109		0.9683	
Visit 6/Week 6	170.0 ± 17.49	-19.5 ± 9.94	190.4 ± 25.72	11.1 ± 12.49	0.0580
P-Value ‡		0.0552		0.3825	
Visit 7/Week 8	159.5 ± 18.97	-24.0 ± 9.48	188.4 ± 25.79	9.1 ± 9.25	0.0212
P-Value ‡		0.0143		0.3347	

* Overall N for Full Analysis population. Summary data at each visit are based on available data for that visit.
† P-value from ANCOVA model with treatment as a factor and baseline assessment as a covariate.
‡ P-value from one-sample t-test on Change from Baseline.
Note: P-values are unadjusted for multiplicity.

The mean ± SE baseline serum iPTH levels were 183.5 ± 19.48 pg/mL and 179.3 ± 24.36 pg/mL in the Fosrenol and placebo groups, respectively. In the Fosrenol group (LOCF analysis) the mean reductions from baseline in the serum iPTH levels were statistically significant ($p \leq 0.05$) only at Visit 2/Week 1, Visit 4/Week 3, Visit 5/Week 4 and Visit

7/Week 8. The mean reductions from baseline were not statistically significant at Visit 3/Week 2 and Visit 6/Week 6. The mean ± SE reductions in the Fosrenol group ranged from -15.2 ± 8.21 pg/mL to -28.3 ± 10.70 pg/mL. The lowest mean iPTH level reached in the Fosrenol group was at Visit 7/Week 8 (159.5 ± 18.97 pg/mL). In the placebo group (LOCF analysis) there were mean increases from baseline in the serum iPTH levels at all the visits but the increases from baseline were not statistically significant ($p>0.05$). The difference between the treatment groups was statistically significant ($p\leq0.05$) at only Visit 2/Week 1, Visit 4/Week 3 and Visit 7/Week 8.

Evaluator comments

K/DQOI guidelines recommend target serum iPTH levels of 35-70 pg/mL for Stage 3 CKD, 70-110 pg/mL for Stage 4 CKD and 150-300 pg/mL for Stage 5 CKD. The results showed that although the difference between the treatment groups was statistically significant in favour of Fosrenol at the end of study visit (Visit 7/Week 8), the reductions from baseline in the Fosrenol group were only modest with a maximal mean reduction of minus 28.3 pg/mL and a mean nadir level of 159.5 pg/mL.

(ix) Mean change in iPTH levels and total daily dose

In both the Fosrenol and placebo group, a higher daily dose was not associated with a greater mean serum iPTH reduction from baseline.

(x) Total prescribed daily dose by visit

The mean total prescribed daily dose by visit for the FAP increased in both treatment groups over the course of the study. For the FAP (LOCF analysis), in the Fosrenol group, the mean ± SE total prescribed daily dose increased from 750.0 ± 0.00 mg/day at Visit 2/Week 1 to 2285.7 ± 123.6 mg/day at Visit 7/Week 8. For the FAP (LOCF analysis), in the placebo group, the mean ± SE total prescribed daily dose increased from 750.0 ± 0.00 mg/day at Visit 2/Week 1 to 2558.8 ± 138.45 mg/day at Visit 7/Week 8. The lower mean total prescribed daily dose by visit for the FAP (LOCF) for subjects in the Fosrenol group compared to the placebo group was statistically significant at Visit 4/Week 3, Visit 5/Week 4 and Visit 6/Week 6. Using the OC imputation analysis, the results were similar, except that the lower mean total prescribed daily dose by visit for the FAP for subjects in the Fosrenol group compared to the placebo group was statistically significant only at Visit 4/Week3.

(xi) Total prescribed dose levels by visit

At Visit 7/Week 8, 57.1% (32/56) of subjects in the Fosrenol group were taking 3000 mg dose, compared with 70.6% (24/34) of subjects in the placebo group. When analysed based on the number of unique subjects at Visit 7/Week 8 instead of the FAP, 74.4% (32/43) of subjects in the Fosrenol group was taking 3000 mg dose, compared with 85.7% (24/28) of subjects in the placebo group. These differences were not analysed for statistical significance.

Product Information (PI)

Recommendations regarding changes to the PI are usually beyond the scope of an AusPAR. However, the evaluator recommended some changes to the PI with regard to the term "chronic renal failure".

The evaluator noted that the more internationally accepted term is CKD rather than CRF. K/DOQI guidelines and internationally accepted definition of CKD is that it is either a glomerular filtration rate (GFR) of < 60 mL/min/1.73m^2 that is present for ≥ 3 months with or without evidence of kidney damage, or the evidence of kidney damage with or without decreased GFR that is present for ≥ 3 months as evidenced by any of the following:

microalbuminuria, proteinuria, glomerular haematuria, pathological abnormalities (for example, abnormal renal biopsy), or anatomical abnormalities (for example, scarring seen on imaging or polycystic kidneys).

CKD is divided into different stages:

Stages	Description	GFR (mL/min/1.73m^2)
Stage 1 CKD	kidney damage with normal kidney function	≥ 90
Stage 2 CKD	kidney damage with mild ↓ GFR	60-89
Stage 3 CKD	kidney damage with moderate ↓ GFR	30-59
Stage 4 CKD	kidney damage with severe ↓ GFR	15-29
Stage 5 CKD	kidney failure	<15 (or dialysis)

The use of the term "CKD" alone without indicating the stages, in the text for indications of Fosrenol, would encompass CKD Stages 1 to 5, and would be inappropriate as the results of the study submitted for this evaluation (SPD405-206) cannot be generalised to include all CKD patients who are not on dialysis. The sponsor had stated that there was "no intention to broaden the indication beyond chronic renal failure (CRF); only to remove reference to dialysis". However, the term "CRF" is usually taken to mean Stage 5 CKD. No clinical study results are submitted to support extending the indication to Stage 5 CKD patients who are not on dialysis.

The clinical results of the Phase III studies, upon which the initial registration of Fosrenol was based, supported the indication for use in Stage 5 CKD patients (CRF patients) who are on dialysis. The clinical results of study SPD405-206 supported the indication to include patients with CKD Stage 3 or 4 who are not on dialysis. The evaluator agreed with the sponsor that the pathophysiology of hyperphosphataemia in CKD patients, and hence the principle of management, is the same regardless of whether they are on dialysis or not. It is thus reasonable to assume that the results of the Phase III trials can be extrapolated to Stage 5 CKD patients who are not on dialysis. However, this is outside the scope of this evaluation. The study SPD405-206 submitted for this evaluation supported the indication to include patients with CKD Stages 3 and 4 who are not on dialysis, but there is no clinical study data submitted for this evaluation regarding the use of Fosrenol in Stage 5 CKD patients who are not on dialysis. The results of study SPD405-206 cannot be extrapolated to Stage 5 CKD patients who are not on dialysis, as patients with Stage 5 CKD are likely to present with higher baseline serum phosphate levels than patients with Stages 3 or 4 CKD, and their target serum phosphate level is different from those with Stage 3 and 4 CKD. It was recommended that results from the Phase III trials are more appropriate in the consideration of any extrapolation of results to Stage 5 CKD patients who are not on dialysis. It was thus recommended that, based on this submission, the indication should be amended to:

> *Treatment of hyperphosphataemia in adults with Chronic Kidney Disease Stage 5 on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). It is also indicated for the treatment of hyperphosphataemia in adults with Chronic Kidney Disease Stages 3 and 4.*

Evaluator's overall conclusions on clinical efficacy

The design of the study as a randomised placebo controlled trial is appropriate for the primary objective. The sample size of the study is small but appropriate for a proof of

concept study. Overall the baseline demographics and disease characteristics were similar between the two treatment groups.

A flaw in the study design was the placement of eligibility criteria of baseline serum phosphate and calcium levels after study enrolment instead of within the study inclusion and exclusion criteria before enrolment. If this had not been feasible due to the necessity of the run-in period as a wash out period for any prior phosphate binding treatment, an alternative study design could have been to delay dosing of subjects until the baseline serum phosphate and corrected calcium levels had been evaluated as meeting continuation criteria. The current study design resulted in a large number of subjects (25 out of 80 subjects randomised to the Fosrenol group and 7 out of 41 subjects randomised to the placebo group) being subsequently discontinued from the study after the baseline visit due to serum phosphate levels of <4.7 mg/dL or corrected serum calcium level of < 8.0 mg/dL at the baseline visit. This led to unnecessary exposure of these subjects to the study drug.

In addition, 17 of these subjects (11 in the Fosrenol group and 6 in the placebo group) were included in the FAP as they had received one dose of the study drug or placebo and had a post-dose serum phosphate level recorded and they were classified as having protocol violations. This resulted in a very small sample size for the PP population, which excluded subjects with major protocol deviations. Due to the study design, 20 subjects in the Fosrenol group had to be excluded for the PP population, out of whom 11 were due to the protocol violations as described above. Eleven subjects in the placebo group had to be excluded for the PP population, out of whom 6 were due to protocol violations as described above. This left a PP population sample size of only n=59, 36 in the Fosrenol group, and 23 in the placebo group.

Ten out of these 17 subjects were allowed to continue in the study under approved protocol waivers. The remaining 7 subjects (6 in the Fosrenol group and 1 in the placebo group) were discontinued after the baseline visit but were included in the FAP as they had already received one dose of the study drug or placebo and had a post-dose serum phosphate level recorded. This means that, in the primary efficacy analysis of these subjects, the "end of study" serum phosphate level used for these 7 subjects was that taken at Visit 2/Week 1 (that is, after only 1 week of starting on the study drug or placebo). Due to the small sample size of the study to begin with, the inclusion of these subjects into the analysis would confound the results.

The serum phosphate level used in the primary endpoint of ≤ 4.6 mg/dL is in line with the target serum phosphate level of the K/DOQI and CARI guidelines for Stages 3 and 4 CKD. It was noted that the endpoint serum phosphate level used in the Phase III trials, as described in the PI, was ≤ 1.8 mmol/L (5.6 mg/dL). However, the subject populations in the Phase III trials were patients with Stage 5 CKD, for whom the target serum phosphate levels were 5.5 mg/dL and 4.95 mg/dL by the K/DOQI and CARI guidelines, respectively. Primary efficacy analysis showed that there was no statistically significant difference in the percentage of subjects with serum phosphate level controlled at ≤4.6 mg/dL at the end of the study, between the Fosrenol group and the placebo group. This result could have been confounded by the study design, as described in the preceding paragraph. In addition, the study could have been underpowered as the sample size was calculated based on an estimated effect size derived from a Phase III study where the effect size was for a serum phosphate level of 5.9 mg/dL and not 4.6 mg/dL.

Overall, the secondary efficacy analyses showed that Fosrenol was associated with a reduction in the serum phosphate levels compared to placebo but efficacy to reach the target serum phosphate level of ≤ 4.6 mg/dL after 8 weeks of treatment was not demonstrated. There was also no clinically significant effect on serum calcium phosphate

product and iPTH levels. The secondary efficacy analyses showed the difference between the Fosrenol and placebo groups for the percentages of subjects with serum phosphate levels controlled at ≤ 4.6 mg/dL was statistically significant only at Visit 6/Week 6 (55.4% in the Fosrenol group vs 29.4% in the placebo group, [LOCF imputation]). Subsequently, at Visit 7/Week 8, as per the primary efficacy analysis results, the difference between the 2 treatment groups was not statistically significant.

Looking at mean reductions from baseline in the serum phosphate levels instead of efficacy in reaching a specific target serum phosphate level, it was found that the differences between the two treatment groups in the mean reductions from baseline in the serum phosphate levels was statistically significant in favour of the Fosrenol group from Visit 5/Week 4 to Visit 7/Week 8. However, the mean serum phosphate levels in the Fosrenol group did not reach ≤4.6 mg/dL in any of the visits, the mean (SE) nadir being 4.62 (± 0.102) mg/dL (LOCF imputation), reached at Visit 6/Week 6. There appeared to be a dose relationship for mean serum phosphate reductions from baseline in the Fosrenol group.

There was no change in the proportion of subjects with a serum calcium phosphate product ≤ 55 mg^2/dL^2 from the baseline visit to the end of the study at Week 8. The endpoint of ≤ 55 mg^2/dL^2 is in line with the target serum calcium phosphate product level recommended by the K/DQOI guidelines. The result may be due to the fact that at baseline, the majority of subjects in the Fosrenol group (94.6%) already had serum calcium phosphate product levels controlled at ≤ 55 mg^2/dL^2 and only 3 subjects had baseline calcium phosphate product levels >55 mg^2/dL^2. The difference between the treatment groups for the proportion of subjects with a serum calcium phosphate product ≤ 55 mg^2/dL^2 was also not statistically significant.

There were some reductions from baseline in the serum calcium phosphate product levels in the Fosrenol group, with a maximal mean reduction of -5.05 mg^2/dL^2. The clinical significance of a reduction of -5.05 mg^2/dL^2 is unclear. The difference between the treatment groups for reductions from baseline in the serum calcium phosphate product levels was statistically significant ($p \leq 0.05$) only at Visit 5/Week 4, but not at Visit 7/Week 8. There was also no obvious dose relationship with mean serum calcium phosphate product reductions from baseline. Overall, the secondary analyses on the serum calcium phosphate product levels showed that Fosrenol was not associated with a clinically significant or meaningful reduction in serum calcium-phosphate product levels.

Analyses on the serum iPTH levels showed that the difference between the treatment groups for reductions of serum iPTH from baseline was statistically significant in favour of Fosrenol at the end of study visit (Visit 7/Week 8). However, the reductions from baseline in the Fosrenol group were only modest, with a maximal mean reduction of -28.3 pg/mL and a mean nadir level of 159.5 pg/mL. K/DQOI guidelines recommend a target serum iPTH level of 35-70 pg/mL for Stage 3 CKD, 70-110 pg/mL for Stage 4 CKD and 150-300 pg/mL for Stage 5 CKD.

Overall, the clinical efficacy analyses showed that there was some reduction of serum phosphate levels in CKD Stages 3 and 4 patients who were not on dialysis, after 8 weeks of Fosrenol. However, the results failed the proof of concept that the use of Fosrenol in these patients would be associated with a reduction of serum phosphate level down to the target serum phosphate level of ≤ 4.6 mg/dL recommended by K/DQOI and CARI guidelines for this patient population. There was also no added clinically significant beneficial effect on serum calcium phosphate product and iPTH levels.

Safety

Introduction

The safety data of study SPD405-206 was drawn from a total of 119 subjects: 78 out of 80 subjects randomised in the Fosrenol group and all 41 subjects randomised in the placebo group. These subjects had taken at least one dose of the study drug or placebo. Two randomised subjects in the Fosrenol group were excluded from the safety analysis population as they did not receive any dose of the study drug.

Patient exposure

The mean ± SE total daily dose in the Fosrenol and placebo groups were 1272.4±56.61 mg/day and 1497.3±78.97 mg/day, respectively. The mean±SE length of exposure in the Fosrenol and placebo groups was 34.3±2.77 days and 43.1 ±3.24 days, respectively. Overall, 56.5% (44/78) of subjects in the Fosrenol group and 73.2% (30/41) of subjects in the placebo group received treatment for at least 29 days.

Evaluator comment

Overall the exposure is adequate for a Phase II trial to assess if the safety data had any major deviation from the safety results of the major Phase III trials conducted previously with Fosrenol.

Adverse events

In the clinical study report, only treatment emergent adverse events (TEAEs) were summarised. AEs were considered TEAEs if the AE start date occurred on or after the first dosing date. AEs with missing dates were assumed to be treatment emergent.

An overview of TEAEs in study SPD405-206 is presented in Table 3. Overall 109 TEAEs were reported by 37 subjects in the Fosrenol group, compared with 66 TEAEs reported by 25 subjects in the placebo group. The percentage of subjects reporting at least one TEAE was lower in the Fosrenol group (47.4%, 37/78) compared to the placebo group (61%, 25/41). In the Fosrenol group, 15.4% of subjects (12/78) reported at least one drug related TEAE compared to 22% of subjects (9/41) in the placebo group.

Table 3: Overview of TEAEs (Safety Population), study SPD405-206

	Lanthanum Carbonate (N = 78)		Placebo (N = 41)	
	n (%)	Events	n (%)	Events
Any TEAE	37 (47.4)	109	25 (61.0)	66
Any Severe TEAE*	6 (7.7)	11	3 (7.3)	5
Any Drug-Related TEAE†	12 (15.4)	21	9 (22.0)	11
Any Treatment-emergent SAE	7 (9.0)	12	2 (4.9)§	3
Deaths	0 (0.0)	0	1 (2.4)	1
Any TEAE Leading to Discontinuation	2 (2.6)	7	4 (9.8)§	4

* Includes TEAEs with severity equal to severe or missing.
† Includes TEAEs with a relationship equal to suspected or missing.
§ Includes the subject that died.

TEAEs reported by at least two subjects in either treatment group are presented in Table 4. In the Fosrenol group, the most commonly reported TEAEs by System Organ Classification (SOC) were *Gastrointestinal Disorders* (20.5% vs 26.8 % in the placebo group) and *Metabolism and Nutrition Disorders* (12.8% vs 12.2% in the placebo group).

Table 4: TEAEs reported by at least two subjects in either treatment group (Safety Population), study SPD405-206

MedDRA System Organ Class Preferred Term	Lanthanum Carbonate (N = 78) n (%)	Placebo (N = 41) n (%)
Any TEAE	37 (47.4)	25 (61.0)
Gastrointestinal Disorders	16 (20.5)	11 (26.8)
Nausea	7 (9.0)	4 (9.8)
Vomiting	5 (6.4)	1 (2.4)
Diarrhea	3 (3.8)	1 (2.4)
Constipation	2 (2.6)	2 (4.9)
Flatulence	1 (1.3)	2 (4.9)
Metabolism and Nutrition Disorders	10 (12.8)	5 (12.2)
Hyperkalemia	3 (3.8)	0 (0.0)
Hypoglycemia	1 (1.3)	2 (4.9)
Metabolic acidosis	1 (1.3)	2 (4.9)
Respiratory, Thoracic and Mediastinal Disorders	8 (10.3)	5 (12.2)
Epistaxis	2 (2.6)	3 (7.3)
Dyspnea exacerbated	2 (2.6)	0 (0.0)
General Disorders and Administration Site Conditions	6 (7.7)	7 (17.1)
Peripheral edema	2 (2.6)	3 (7.3)
Edema	2 (2.6)	1 (2.4)
Infections and Infestations	6 (7.7)	5 (12.2)
Nasopharyngitis	2 (2.6)	1 (2.4)
Injury, Poisoning and Procedural Complications	6 (7.7)	4 (9.8)
Excoriation	2 (2.6)	0 (0.0)
Procedural pain	3 (3.8)	1 (2.4)
Nervous System Disorders	5 (6.4)	1 (2.4)
Dizziness	2 (2.6)	1 (2.4)
Renal and Urinary Disorders	3 (3.8)	4 (9.8)
Renal failure chronic*	1 (1.3)	3 (7.3)
Cardiac Disorders	3 (3.8)	1 (2.4)
Cardiac failure congestive	2 (2.6)	0 (0.0)
Skin and Subcutaneous Tissue Disorders	3 (3.8)	3 (7.3)
Pruritus	1 (1.3)	2 (4.9)
Blood and Lymphatic System Disorders	2 (2.6)	1 (2.4)
Anemia	2 (2.6)	1 (2.4)
Psychiatric Disorders	1 (1.3)	2 (4.9)
Anxiety	1 (1.3)	2 (4.9)

* Reported verbatim terms suggested a worsening of CKD.

In the Fosrenol group, the most commonly reported TEAEs (reported by ≥ 5% of subjects) by preferred term were nausea (9.0% vs 9.8% in the placebo group) and vomiting (6.4% vs 2.4% in the placebo group). The most common drug related TEAE by SOC was

Gastrointestinal Disorders (10.3% vs 17.1 % in the placebo group). The most commonly reported drug related TEAE in both treatment groups by preferred term was nausea (3.8% in the Fosrenol group vs 7.3% in the placebo group). TEAEs were also analysed against the dose at onset. Results showed that there was no obvious relationship between the incidence of TEAEs and the dose level at the time of onset of TEAEs in either treatment group. In the Fosrenol group, the percentage of subjects who reported any TEAE while receiving doses of 750, 1500, 2250 and 3000 mg was 29.5%, 11.5%, 10.3% and 20.5%, respectively. The corresponding percentages in the placebo group were 43.9%, 9.8%. 17.1% and 29.3%, respectively.

Serious adverse events and deaths

Overall no deaths were reported in the Fosrenol group. One subject in the placebo group died from respiratory failure. This was judged by the investigator as not related to the study drug.

A total of 12 treatment emergent SAEs were reported by 7 subjects in the Fosrenol group. In the placebo group, 3 treatment emergent SAEs (including the event of death in one subject) were reported in 2 subjects. In the Fosrenol group the most common treatment emergent SAEs were *Cardiac Disorders* (2 SAEs of congestive cardiac failure and 1 SAE of myocardial infarction) and *Respiratory, Thoracic and Mediastinal Disorders* (1 SAE each of pneumothorax, acute pulmonary oedema and dyspnoea exacerbated). Other treatment emergent SAEs in the Fosrenol group were 2 SAEs of anaemia and 1 each of catheter site pain, bacterial arthritis, impaired gastric emptying and perinephric abscess. None of these treatment emergent SAEs in the Fosrenol group were judged by the investigator to be related to the study drug. In the placebo group, all 3 treatment emergent SAEs were of *Respiratory, Thoracic and Mediastinal Disorders*: 1 each of pneumonia, chronic obstructive pulmonary disease, and respiratory failure. None of these treatment emergent SAEs in the placebo group were judged by the investigator to be related to the study drug.

Laboratory findings

There were no significant laboratory findings of safety concern. Overall, there were 11 clinical laboratory abnormalities reported as AEs in 9 subjects in the Fosrenol group. In the placebo group, there were 4 clinical laboratory abnormalities reported as AEs in 4 subjects. In the Fosrenol group, the 11 clinical laboratory abnormalities reported as AEs were 4 episodes of hyperkalaemia, 3 episodes of hypoglycaemia and 1 each of hypocalcaemia, hyperphosphataemia, hyperglycaemia and hypercholesterolaemia. Only the AE of hyperphosphataemia was judged to be possibly related to the study drug. In the placebo group, the 4 clinical laboratory abnormalities were 3 episodes of hypoglycaemia and 1 of hypocalcaemia. Only the AE of hypocalcaemia was judged to be possibly related to the study drug.

Discontinuation due to Adverse Events

Overall, 2 (2.6%) subjects in the Fosrenol group and 4 (9.8%) subjects in the placebo group were discontinued from the study due to TEAEs. In the Fosrenol group, only 1 TEAE (itching abdomen sides) in 1 of the 2 subjects was judged to be possibly related to the study drug. The severity of this TEAE was graded mild.

Evaluator's overall conclusions on clinical safety

The safety results of study SPD405-206 showed that the most common AEs were nausea and vomiting. This is consistent with the safety results from the Phase III trials presented in the PI. The sample size of the study was small but the safety results did not show any safety concerns inconsistent with the safety results from the Phase III trials reported in the proposed PI.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

Efficacy

1. Overall, the clinical efficacy analyses results showed that Fosrenol was associated with some reduction of serum phosphate level in the targeted patient population. However, it failed the proof of concept on the efficacy to reach the target serum phosphate level of ≤ 4.6 mg/dL recommended by K/DQOI and CARI guidelines for this patient population after 8 weeks of treatment. It was stated in the sponsor application cover letter that although the target serum phosphate level used in the study was in line with the K/DQOI guidelines, the Australian guidelines (CARI guidelines) uses a target serum phosphate level of ≤ 4.95 mg/dL and hence the secondary efficacy analyses results would be more relevant than the primary efficacy analysis result. However, a look through the CARI guidelines showed that the guidelines recommendation of target serum phosphate level ≤ 4.95 mg/dL is for Stage 5 CKD patients. The target serum phosphate level recommended by the CARI guidelines for Stage 3 and 4 CKD is for it to be within the normal reference range (2.7 to 4.6 mg/dL). Given the clinical efficacy results of the study submitted, is the sponsor able to provide research evidence on the clinical benefit of achieving some reduction of serum phosphate level in Stage 3 and 4 CKD patients with hyperphosphataemia, even if the reduction does not manage to reach the recommended target level?

2. What is the basis for extrapolating the efficacy results of the Phase II study submitted (study SPD405-206) involving Stage 3 and 4 CKD patients to Stage 5 CKD patients who are not on dialysis?

The proposed change in indication for Fosrenol is a change from "Treatment of hyperphosphataemia in adults with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD)." to "Treatment of hyperphosphataemia in adults with chronic renal failure." The sponsor had also stated that there was "no intention to broaden the indication beyond chronic renal failure (CRF); only to remove reference to dialysis".

The term "CRF" is usually taken to mean Stage 5 CKD. However, no clinical study results are submitted to support extending the indication to Stage 5 CKD patients who are not on dialysis. The clinical results of the Phase III studies, upon which the initial registration of Fosrenol was based, supported the indication for use in Stage 5 CKD patients (CRF patients) who are on dialysis. The clinical results of study SPD405-206 supported the indication to include patients with CKD Stage 3 or 4 who are not on dialysis. The evaluator agrees with the sponsor that the pathophysiology of hyperphosphataemia in CKD patients, and hence the principle of management, is the same regardless of whether they are on dialysis or not. It is thus reasonable to assume that the results of the Phase III trials may be extrapolated to Stage 5 CKD patients who are not on dialysis.

However, there is no clinical study data or other supporting evidence submitted for this evaluation regarding the rationale for the extrapolation of current study results to Stage 5 CKD patients who are not on dialysis. The study SPD405-206 submitted for this evaluation supported the indication to include patients with CKD Stages 3 and 4 who are not on dialysis but results of study SPD405-206 cannot be extrapolated to Stage 5 CKD patients who are not on dialysis, as patients with Stage 5 CKD are likely to present with higher baseline serum phosphate levels than patients with Stages 3 or 4 CKD, and their target serum phosphate level is different

from those with Stage 3 and 4 CKD. It is recommended that the sponsor clarifies the basis and provides supporting evidence for the extrapolation of the results to Stage 5 CKD patients who are not on dialysis.

There were also questions relating to the PI/Consumer medicines Information (CMI) but these are beyond the scope of this AusPAR.

Clinical Summary and Conclusions

Clinical aspects

Clinical efficacy

Overall, the clinical efficacy analyses results failed the proof of concept that the use of Fosrenol for 8 weeks was associated with a reduction of serum phosphate level down to ≤4.6 mg/dL in patients with Stage 3 and 4 CKD who were not on dialysis. The results showed that Fosrenol was associated with some reduction of serum phosphate level in the targeted patient population but efficacy to reach the target serum phosphate level of ≤ 4.6 mg/dL recommended by K/DQOI and CARI guidelines for this patient population after 8 weeks of treatment was not demonstrated. There was also no added clinically significant beneficial effect on serum calcium phosphate product and iPTH levels.

Primary efficacy analysis showed that there was no statistically significant difference between the Fosrenol group and the placebo group for the percentage of subjects with serum phosphate level controlled at ≤4.6 mg/dL at the end of the study. This result could have been confounded by the study design, which resulted in 7 out of the 17 subjects (6 in the Fosrenol group, and 1 in the placebo group) who were discontinued after the baseline visit due to baseline serum phosphate or serum calcium levels not meeting the study continuation criteria, being included in the primary endpoint analysis. In the primary efficacy analysis of these subjects, the "end of study" serum phosphate level used was that taken at Visit 2/Week1 (that is, after only 1 week of starting on the study drug or placebo) as LOCF imputation was used. Due to the small sample size of the study to begin with, the inclusion of these subjects into the analysis would confound the results.

However, in the secondary efficacy analysis, OC imputation was also used to look at the percentages of subjects with serum phosphate levels controlled at ≤ 4.6 mg/dL by visit. The OC imputation would exclude these 7 subjects when the proportions of subjects with serum phosphate levels controlled at ≤ 4.6 mg/dL in each group was calculated at Visit 7/Week 8 (end of study visit). It was found that at Visit 7/Week 8 the difference between the two treatment groups using OC imputation was also not statistically significant.

The primary efficacy results could also have been affected by the possibility that study was underpowered. The sample size was calculated based on an estimated effect size derived from a Phase III study, where the effect size was for a serum phosphate level of 5.9 mg/dL and not 4.6 mg/dL. The sample size for this study could have been underestimated, resulting in an underpowered study.

Looking at mean reductions from baseline in the serum phosphate levels instead of efficacy in reaching a specific target serum phosphate level, it was found that the differences between the two treatment groups in the mean reductions from baseline in the serum phosphate levels was statistically significant in favour of the Fosrenol group from Visit 5/Week 4 to Visit 7/Week 8. However, the mean serum phosphate levels in the Fosrenol group did not reach ≤4.6 mg/dL in any of the visits, the mean nadir being 4.62 mg/dL (LOCF imputation), reached at Visit 6/Week 6.

There also appeared to be a dose relationship for mean serum phosphate reductions from baseline in the Fosrenol group, as compared to in the placebo group, where a higher daily dose was not associated with a greater mean serum phosphate reduction from baseline.

This helped support the hypothesis that Fosrenol was associated with a reduction in serum phosphate levels in Stage 3 and 4 CKD patients.

A search through the literature showed that there was a study on another non-calcium containing phosphate binder, sevelamer, in CKD patients who were not on dialysis.[7] The study looked at the efficacy of sevelamer in treating hyperphosphataemia in Stage 4 and 5 CKD patients who were not on dialysis. A comparison of the main study design parameters and the results between study SPD405-206 and this study is presented in Table 5.

Table 5: Comparison of design parameters between SPD405-206 and sevelamer study

	Fosrenol study (SPD405-206)	**Sevelamer study**
Target subject population	Stages 3 and 4 CKD, not on dialysis	Stages 4 and 5 CKD, not on dialysis
Study design	Double blind, randomised, placebo controlled	Open label, single arm
Eligible baseline phosphate levels	≥4.7 mg/dL	≥5.5 mg/dL
Run-in period and treatment period	3-4 weeks run-in period; 8 weeks treatment period	2 weeks run-in period; 8 weeks treatment period
Target serum phosphate level	≤ 4.6 mg/dL	≥2.7 mg/dL and ≤ 4.6 mg/dL for subjects with Stage 4 CKD; ≤ 5.5 mg/dL for subjects with Stage 5 CKD
Primary efficacy endpoint	Percentage of subjects with serum phosphate levels controlled at ≤ 4.6 mg/dL.	Change in serum phosphate levels from baseline to the end of the treatment period
Sample size analysed	56 in Fosrenol group, 34 in placebo group (ITT population)	46 (ITT population)
RESULTS		
Mean age (SD)	61.8 (12.89) years (Fosrenol group); 63.0 (1.67) years (placebo group)	61.8 (11.9) years
Mean baseline serum phosphate level ± SE	5.28 ± 0.090 mg/dL (Fosrenol group); 5.38 ± 0.119mg/dL (placebo group)	6.2 ± 0.8 mg/dL
Mean serum phosphate level at end of the treatment period ± SE	4.74 ± 0.101 mg/dL (Fosrenol group); 5.17 ± 0.161 mg/dL (placebo group)	4.8 ± 1.0 mg/dL
Mean change in serum phosphate levels from baseline at end of the treatment period ± SE	-0.54 ± 0.108 mg/dL (Fosrenol group) (p<0.0001); -0.21 ± 0.139 mg/dL (placebo group) (p=0.1486)	-1.4 ± 1.0 mg/dL (p<0.001)
Percentage of subjects with serum phosphate levels controlled at study-specified target level at end of treatment period	44.6% (Fosrenol group); 26.5% (placebo group) (difference between treatment groups not statistically significant (p=0.1167))	75% of patients with Stage 4 CKD (target level of ≥2.7 mg/dL and ≤ 4.6 mg/dL); 70% of patients with Stage 5 CKD (target level of ≤ 5.5 mg/dl)

[7] Ketteler M, Rix M, Fan S et al. Efficacy and tolerability of sevelamer carbonate in hyperphosphatemic patients who have chronic kidney disease and are not on dialysis. Clin J Am Soc Nephrol 2008; 3: 125–1130.

In both studies, the non-calcium containing phosphate binder being tested led to a statistically significant reduction of serum phosphate levels from baseline to end of 8 week treatment period. In addition, in study SPD405-206, the difference between the Fosrenol and placebo groups for the reductions of serum phosphate levels from baseline to end of study was statistically significant. Although a larger percentage of patients in the Sevelamer study achieved the target serum phosphate levels compared to in the Fosrenol study, this was not tested for statistical significance against a placebo.

Clinical safety

Overall, the safety results did not show any safety concerns inconsistent with the safety results from the Phase III trials reported in the proposed PI. The safety results of study SPD405-206 showed that the most common AEs were nausea and vomiting. This is consistent with the safety results from the Phase III trials presented in the PI.

The mean±SE length of exposure in the Fosrenol group was 34.3±2.77 days. In the study, 56.5% (44/78) of subjects in the Fosrenol group received treatment for at least 29 days.

Overall the exposure is adequate for a Phase II trial to assess if the safety data has any major deviation from the safety results of the major Phase III trials.

Overall 109 TEAEs were reported by 37 subjects in the Fosrenol group, compared with 66 TEAEs reported by 25 subjects in the placebo group. The percentage of subjects reporting at least one TEAE was lower in the Fosrenol group (47.4%, 37/78) compared to the placebo group (61%, 25/41). In the Fosrenol group, the most commonly reported TEAEs by SOC were *Gastrointestinal Disorders* (20.5% vs 26.8 % in the placebo group) and the most commonly reported TEAEs (reported by ≥ 5% of subjects) by preferred term were nausea (9.0% vs 9.8% in the placebo group) and vomiting (6.4% vs 2.4% in the placebo group). In the Fosrenol group, the most common drug related TEAE by SOC was *Gastrointestinal Disorders* (10.3% vs 17.1 % in the placebo group). The most commonly reported drug related TEAE by preferred term was nausea (3.8% in the Fosrenol group vs 7.3% in the placebo group).

No deaths were reported in the Fosrenol group. A total of 12 treatment emergent SAEs were reported by 7 subjects in the Fosrenol group, compared with 3 treatment emergent SAEs reported in 2 subjects in the placebo group. In the Fosrenol group the most common treatment emergent SAEs were *Cardiac Disorders* (2 SAEs of congestive cardiac failure and 1 SAE of myocardial infarction) and *Respiratory, Thoracic and Mediastinal Disorders* (1 SAE each of pneumothorax, acute pulmonary oedema, and dyspnoea exacerbated). None of the treatment emergent SAEs in the Fosrenol group were judged by the investigator to be related to the study drug.

There were no significant laboratory findings of safety concern.

Benefit risk assessment

Benefits

Patients with CKD can develop hyperphosphataemia as renal function deteriorates and their CKD progresses through to the late stages. Hyperphosphataemia exacerbates hyperparathyroidism and is associated with cardiovascular morbidity and mortality. Hyperphosphataemia in these CKD patients is treated with dietary restrictions and phosphate binding agents when diet alone is insufficient to bring the serum phosphate levels down. Different phosphate binding agents are available for the treatment of hyperphosphataemia in CKD patients. The most common phosphate binding agents used are calcium containing agents. However, if the patients have concurrent hypercalcaemia, the phosphate binding agents of choice would be those that are non-calcium containing.

There are currently two non-calcium containing phosphate binding agents available in Australia: Fosrenol (lanthanum carbonate) and Renagel (sevelamer). Fosrenol is currently registered in Australia for the indications of "treatment of hyperphosphataemia in adults with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD)." Renagel is currently registered in Australia for the indications of "management of hyperphosphataemia in adult patients with Stage 4 and 5 chronic kidney disease".[8]

While Stage 5 CKD patients would likely be on dialysis, there are patients with later stages of CKD who are not on dialysis but have hyperphosphataemia and hypercalcaemia. At the current time, Renagel is the only non-calcium containing phosphate binding agent indicated for the treatment of hyperphosphataemia in these patients. There is benefit in having an additional drug that is able to treat hyperphosphataemia in these patients.

The approval for the initial registration of Fosrenol was based on Phase III studies involving subjects with end stage renal disease (CKD Stage 5) who were on dialysis. The sponsor had stated in the study protocol of study SPD405-206 that this study was intended as a proof of concept study to evaluate the efficacy and safety of Fosrenol in a population in which previous clinical trials had not been conducted, that is, patients with Stage 3 and 4 CKD who were not yet on dialysis.

Overall, the clinical efficacy analyses results showed that Fosrenol was associated with some reduction of serum phosphate level in the targeted patient population. However, it failed the proof of concept on the efficacy to reach the target serum phosphate level of ≤ 4.6 mg/dL recommended by K/DQOI and CARI guidelines for this patient population after 8 weeks of treatment. The sponsor had tried to mitigate this by stating in the application cover letter that although the target serum phosphate level used in the study was in line with the K/DQOI guidelines, the Australian guidelines (CARI guidelines) uses a target serum phosphate level of ≤ 4.95 mg/dL and hence the secondary efficacy analyses results would be more relevant than the primary efficacy analysis result. However, a look through the CARI guidelines showed that the guidelines recommendation of target serum phosphate level ≤ 4.95 mg/dL is for Stage 5 CKD patients. The target serum phosphate level recommended by the CARI guidelines for Stage 3 and 4 CKD is for it to be within the normal reference range (2.7 to 4.6 mg/dL).

The efficacy results of study SPD405-206 showing that Fosrenol was associated with a reduction in serum phosphate levels in patients with Stage 3 and 4 CKD who were not on dialysis is within expectations, as the pathophysiology of hyperphosphataemia in CKD patients, and hence the principle of management, is the same regardless of whether they are on dialysis or not. What the study failed to demonstrate is the efficacy of Fosrenol in reducing serum phosphate levels down to the target level. This may be a true result due to drug efficacy factors, or may be due to the small sample size, the study design and the possible underpowering of the study, as described earlier.

Research and major international guidelines have concentrated mainly on refining the target serum phosphate levels associated with reducing morbidity and mortality in CKD patients. Based on research evidence alone, it is unclear if some reduction of serum phosphate level is still associated with reduced morbidity and mortality even if it is not achieving the target level. However, based on the pathophysiology of hyperphosphataemia in CKD patients and the pathophysiology of consequent secondary hyperparathyroidism and vascular calcification, it is reasonable to expect that some reduction of serum phosphate level, even if it does not reach the target level, will confer some clinical benefit.

[8] Product Information, Sevelamer. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-PI-01839-3 (accessed 20th May 2011).

Risks

The safety results on the use of Fosrenol in patients with Stage 3 and 4 CKD who were not on dialysis did not show any safety concerns inconsistent with the safety results in CKD Stage 5 patients who were on dialysis from the Phase III trials reported in the proposed PI. The most common AEs in patients with Stage 3 and 4 CKD who were not on dialysis were nausea and vomiting. This is consistent with the safety results from the Phase III trials presented in the PI.

Balance

Overall, the benefit risk balance of Fosrenol for the treatment of hyperphosphataemia in patients with CKD Stages 3 and 4 who are not on dialysis is positive.

The clinical efficacy analyses results demonstrated efficacy of Fosrenol in reducing serum phosphate level in CKD Stages 3 and 4 patients who were not on dialysis, although it failed to demonstrate efficacy to reach the target serum phosphate level of ≤ 4.6 mg/dL recommended by K/DQOI and CARI guidelines for this patient population after 8 weeks of treatment. This may be due to the study design and sample size of the study, and more studies evaluating the efficacy of Fosrenol in reducing serum phosphate level down to the recommended target level need to be done. There is benefit in having an additional drug that is able to treat hyperphosphataemia in CKD patients who are not on dialysis, and in whom calcium containing phosphate binding agents are contraindicated due to the presence of hypercalcaemia.

The safety results on the use of Fosrenol in patients with Stage 3 and 4 CKD who were not on dialysis did not show any safety concerns inconsistent with the safety results in CKD Stage 5 patients who were on dialysis from the Phase III trials reported in the proposed PI. Hence Fosrenol can provide the benefit of reducing the serum phosphate levels in CKD Stages 3 and 4 patients who are not on dialysis, for whom dietary restriction is insufficient to bring the serum phosphate levels down, and in whom calcium containing phosphate binding agents are contraindicated due to the presence of hypercalcaemia, without causing additional risk.

The results, however, cannot be generalised to include all CKD patients who are not on dialysis. The sponsor had stated that there was “no intention to broaden the indication beyond chronic renal failure (CRF); only to remove reference to dialysis”. The proposed indication was amended to “Treatment of hyperphosphataemia in adults with chronic renal failure”. However, the term “CRF” is usually taken to mean Stage 5 CKD. No clinical study results are submitted to support extending the indication to Stage 5 CKD patients who are not on dialysis.

The clinical results of the Phase III studies, upon which the initial registration of Fosrenol was based, supported the indication for use in Stage 5 CKD patients (CRF patients) who are on dialysis. The clinical results of study SPD405-206 supported the indication to include patients with CKD Stage 3 or 4 who are not on dialysis. The evaluator agreed with the sponsor that the pathophysiology of hyperphosphataemia in CKD patients, and hence the principle of management, is the same regardless of whether they are on dialysis or not. It is thus reasonable to assume that the results of the Phase III trials can be extrapolated to Stage 5 CKD patients who are not on dialysis. However, this is outside the scope of this evaluation. The study SPD405-206 submitted for this evaluation supported the indication to include patients with CKD Stages 3 and 4 who are not on dialysis, but there is no clinical study data submitted for this evaluation regarding the use of Fosrenol in Stage 5 CKD patients who are not on dialysis. The results of study SPD405-206 cannot be extrapolated to Stage 5 CKD patients who are not on dialysis, as patients with Stage 5 CKD are likely to present with higher baseline serum phosphate levels than patients with Stages 3 or 4 CKD,

and their target serum phosphate level is different from those with Stage 3 and 4 CKD. It is recommended that results from the Phase III trials are more appropriate in the consideration of any extrapolation of results to Stage 5 CKD patients who are not on dialysis. It is thus recommended that, based on this submission, the indication be amended to:

> *Treatment of hyperphosphataemia in adults with Chronic Kidney Disease Stage 5 on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). It is also indicated for the treatment of hyperphosphataemia in adults with Chronic Kidney Disease Stages 3 and 4*

V. Pharmacovigilance Findings

Risk Management Plan

The TGA's Office of Product Review (OPR) assessed this submission and concluded that no specific Risk management Plan (RMP) evaluation was required unless the Delegate raised specific issues.

Safety Specification

The Safety Specification was reviewed by both the nonclinical and the clinical evaluators. The nonclinical evaluator commented that all potentially clinically relevant toxicological findings have been adequately identified and described in the Safety Specification. The clinical evaluator noted the Safety Specification in the Risk Management Plan submitted appropriately represents the safety of the product.

VI. Overall Conclusion and Risk/Benefit Assessment

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

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

New *in vitro* studies showed that the phosphate binding affinity of La was greater than that of sevelamer and that the selectivity of La for binding phosphate in the presence of competing anions (such as bile acids and fatty acids) was greater than that of sevelamer under conditions mimicking the environment of the stomach and small intestine.

The *in vivo* effect of ongoing La treatment of between 4 and 22 weeks duration on plasma phosphate levels in rats was variable. Adenine induced and nephrectomy induced renal failure often failed to increase plasma phosphate relative to controls, possibly due to the increase in PTH observed in all animals with chronic renal failure, irrespective of the method of renal failure induction. Lanthanum carbonate administration reversed this compensatory PTH increase and brought about a decrease in urinary phosphate excretion in all studies, with no indication of hepatotoxicity.

A new study confirmed that protein binding of La was greater than 99% in the rat, dog and human and was independent of La concentration over a high concentration range (250 ng/mL to 25,000 ng/mL).

No hepatotoxicity, as measured by liver weight, MRI scanning, microscopy or liver enzymes, was observed in adult rats dosed with 2% La in the diet for 22 weeks or 1000 mg/kg/day for up to 20 weeks or in 10 day old juvenile rats dosed for 40 days at 2000

mg/kg/day. These findings were all irrespective of renal function. La concentrations in the livers of rats with chronic renal failure were approximately twice as high as those in rats with normal renal function. This was most likely due to increased gastrointestinal absorption of La as there were no differences in such liver levels after intravenous dosing. The subcellular localization of La was found to be restricted to the lysosomes of the hepatocyte, where it most probably precedes transcellular lysosomal transport and elimination via the bile canaliculi.

In a non-GLP dose ranging study, forty days of gavage dosing of juvenile, 10 day old rats at 2000 mg/kg/day led to stomach inflammation and hyperplasia, as has been previously observed at high doses in adult rats. There were no other treatment related effects on body weight gain, food consumption or developmental milestones. La is not indicated for use in children.

No La related adverse effects were observed in bone, despite its being a principal site of accumulation. In the current submission, chronic renal failure induced bone histomorphometry changes such as a high accumulation of trabecular bone and increases in woven bone and area of fibrosis. These abnormalities were significantly reduced by La treatment. Overall, no osteomalacia or fractures were reported in these studies and there was no general toxic effect of La on bone. This was consistent with previously submitted repeat dose toxicity studies.

No animal studies were submitted to address the possible interaction of La and thyroxine hormones, a potential issue of concern previously raised in a clinical evaluation of the PSUR for the period 19 March 2007 to 18 March 2008. During that reporting period, there had been 4 reports of possible drug interactions with La, 3 of which involved a possible interaction between La and thyroxine hormones which resulted in patients requiring higher doses of thyroxine hormones.

There were no nonclinical objections to the extension of indication for lanthanum carbonate to include the treatment of hyperphosphataemia in adults with chronic renal failure.

Clinical

Clinical evaluation

The clinical evaluator provided a report on the submitted data which relies on a single pivotal study SPD405-206. In the protocol of this study, the sponsor stated that this study was intended as a proof of concept study to evaluate the efficacy and safety of Fosrenol in a population in which previous clinical trials had not been conducted, that is, in patients with Stage 3 and 4 CKD who were not yet on dialysis.

The clinical evaluator recommended approval of the application for the extension of indications for Fosrenol subject to satisfactory responses to the list of questions and comments in the evaluation report and to the recommendations for changes to the PI. The clinical evaluator also recommended that the text of the indications in the PI should be changed to:

> *Treatment of hyperphosphataemia in adults with Chronic Kidney Disease Stage 5 on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). It is also indicated for the treatment of hyperphosphataemia in adults with Chronic Kidney Disease Stages 3 and 4.*

Efficacy

SPD405-206, the pivotal and only study in the submission, was a Phase II, double blind, randomised, placebo controlled study to assess the efficacy and safety of lanthanum

carbonate for the reduction of serum phosphorus in subjects with Stage 3 and 4 chronic kidney disease who have elevated serum phosphorus levels. It was conducted in 29 centres in the USA between January 2006 and June 2007.

The primary efficacy endpoint was the percentage of subjects with serum phosphate levels controlled at ≤ 4.6 mg/dL (1.48 mmol/L).

The secondary efficacy endpoints included:

- Percentage of subjects with serum phosphate levels controlled at ≤ 4.6 mg/dL by visit
- Mean serum phosphate levels by visit and mean changes from baseline by visit
- Mean change in serum phosphate levels and total daily dose
- Time to control of serum phosphate level at ≤ 4.6 mg/dL
- Percentage of subjects with serum calcium phosphate product levels controlled at ≤ 55 mg^2/dL^2 by visit
- Mean serum calcium phosphate product levels by visit and changes from baseline
- Mean change in serum calcium phosphate products levels and total daily dose
- Mean iPTH levels by visit and changes from baseline
- Mean change in iPTH levels and total daily dose
- Total prescribed daily dose by visit
- Total prescribed dose levels by visit

Overall 281 subjects were screened and 234 enrolled into the study;out of these subjects 121 were randomised, 80 to the Fosrenol group and 41 to the placebo group. Figure 2 indicates that there were a large number of discontinuations from the study after randomisation, 37 from the Fosrenol group and 13 from the placebo group.

The numbers analysed according to ITT criteria were 56 in the Fosrenol group and 34 in the placebo group. Over half of the discontinuations from each treatment group arose from the fact that baseline serum phosphate levels were less than 4.7 mg/dL and this issue is discussed at length in the clinical evaluation report (CER). The clinical evaluator pointed out that a flaw in the study design was the placement of eligibility criteria relating to baseline serum phosphate and calcium levels after study enrolment instead of within the study inclusion and exclusion criteria before enrolment. This study design resulted in a large number of subjects (25 out of 80 subjects randomised to the Fosrenol group and 7 out of 41 subjects randomised to the placebo group) being subsequently discontinued from the study after the baseline visit due to a serum phosphate level of less than 4.7 mg/dL being found at that baseline visit. In fact this meant that about two thirds of the discontinuations in the Fosrenol group (25/37) and just over half in placebo group (7/13) were due to this problem of a low baseline serum phosphate level.

There were also 4 subjects who were discontinued from the Fosrenol group because their baseline corrected serum calcium levels were < 8.0 mg/dL. It was not clear whether all this group of calcium violators were also phosphate violators. Were there more than 25 discontinuations from the Fosrenol group due to either a baseline serum phosphate level < 4.7 mg/dL or a baseline corrected serum calcium level < 8.0 mg/dL? *The sponsor was*

asked to clarify this point. As noted by the evaluator, this led to unnecessary exposure of these subjects to the study drug.

As well, 17 of these subjects (11 in the Fosrenol group and 6 in the placebo group) were included in the FAP as they had received one dose of the study drug or placebo and had a post-dose serum phosphate level recorded. These 17 subjects were classified as having protocol violations. As noted by the clinical evaluator, this resulted in a very small sample size for the per protocol (PP) population which excluded subjects with major protocol violations. There were 20 subjects in the Fosrenol group who were excluded from the PP population and of these 20, there were 11 excluded due to protocol violations as described above. There were 11 subjects in the placebo group who were excluded from the PP population and of these 11, there were 6 excluded due to protocol violations as described above. The resultant PP population consisted of only a total of 59 subjects, 36 in the Fosrenol group and 23 in the placebo group.

The Delegate noted that it was fortuitous that the numbers analysed according to the ITT criteria were 56 in the Fosrenol group and 34 in the placebo group, the number in the Fosrenol group just satisfying the sample size requirements. *Had the sponsor anticipated a large number of discontinuations because of the placement of eligibility criteria of baseline serum phosphate and calcium levels after study enrolment?*

The clinical evaluator further noted that 10 out of the 17 subjects deemed as protocol violators were allowed to continue in the study under approved protocol waivers. The remaining 7 subjects (6 in the Fosrenol group and 1 in the placebo group) were discontinued after the baseline visit but were included in the FAP as they had already received one dose of the study drug or placebo and had a post-dose serum phosphate level recorded. The clinical evaluator noted that this meant that, in the primary efficacy analysis of these subjects, the "end of study" serum phosphate level used for these 7 subjects was that taken at Visit 2/Week 1, that is, after only one week of starting on the study drug or placebo. The Delegate noted with concern that these 17 protocol violators were included in the FAP despite their either having a serum phosphate level of less than 4.7 mg/dL or a corrected calcium level of less than 8.0 mg/dL at the baseline visit. Some of these 17 protocol violators appear to have been included in the FAP despite having baseline serum phosphate levels which already satisfied the primary efficacy endpoint.

This must be clarified in detail by the sponsor. *The Delegate requested that the sponsor provide the number and percentage of the subjects in the FAP, in each treatment arm, whose baseline serum phosphate levels were ≤ 4.6 mg/dL, ≤ 4.7 mg/dL, ≤ 4.8 mg/dL, ≤ 4.9 mg/dL, ≤ 5.0 mg/dL, ≤ 5.1 mg/dL, ≤ 5.2 mg/dL, ≤ 5.3 mg/dL, ≤ 5.4 mg/dL, ≤ 5.5 mg/dL, ≤ 5.6 mg/dL and > 5.6 mg/dL. The sponsor was also requested to give the range [min, max], interquartile range and median of the baseline serum phosphate levels of the subjects in the FAP, by treatment arm.*

The results of the primary endpoint analysis showed that while a higher percentage of subjects in the Fosrenol group (25/56, 44.6%) than in the placebo group (9/34, 26.5%) had serum phosphate levels controlled at ≤ 4.6 mg/dL at the end of the study, the difference between the two groups was not statistically significant (p = 0.1167):

Not only was this result not statistically significant but the Delegate was concerned at the possible extent of the contribution to this result from subjects whose baseline serum phosphate level was either below the primary efficacy endpoint of 4.6 mg/dL or quite close to it.

As noted in the clinical evaluation report(CER), the failure to demonstrate a statistically significant difference with regard to the primary efficacy endpoint meant a failure of the proof of concept for the study. The evaluator reiterated the issue of having additional

criteria for eligibility to continue in the study after the baseline visit instead of having these criteria incorporated in the initial inclusion/exclusion criteria before study enrolment. The evaluator noted that an analysis of the primary efficacy endpoint based on the PP population would exclude patients with major protocol deviations and thereby remove the consequent confounding effects of the inclusion of such patients.

The sponsor was requested, in its pre-ACPM response, to provide the results of the analysis of the primary efficacy endpoint based on the PP population. The sponsor was also requested, in its pre-ACPM response, to provide the results of the following analysis of the data: the number and percentage of subjects in each treatment arm of the Full Analysis Population who achieved the primary efficacy endpoint, firstly for those subjects whose baseline serum phosphate level was below or at the level of the median baseline serum phosphate level for their treatment arm and secondly for those subjects whose baseline serum phosphate level was above the level of the median baseline serum phosphate level for their treatment arm.

The results for the secondary efficacy endpoints were somewhat variable.

The analysis using OC imputation was consistent with that using LOCF imputation, that is, the difference in the percentages of subjects in each group at Visit 7/Week 8 with serum phosphate levels controlled at ≤ 4.6 mg/dL was not statistically significant

The differences between the two treatment groups in the mean reductions from baseline in the serum phosphate levels were statistically significant ($p \leq 0.05$) in favour of the Fosrenol group from Visit 5/Week 4 to Visit 7/Week 8, in both the LOCF and OC analyses.

In the Fosrenol group, there appeared to be a dose relationship for mean serum phosphate reductions from baseline. No such relationship was observed in the placebo group.

The median (range) time to control of serum phosphate level at ≤ 4.6 mg/dL was 14 (6 – 56) days in the Fosrenol group and 20 (6 – 59) days in the placebo group. This difference was found to be statistically significant ($p = 0.0415$).

With regard to the serum calcium phosphate product levels, the results showed that there was no change in the proportion of subjects with serum calcium phosphate product levels ≤ 55 mg^2/dL^2 from the baseline visit (pre-dose levels) to the end of the study at Week 8, the proportion, 53/56 or 94.6% remaining constant. As noted by the evaluator, this may have something to do with the fact that there were only 3/56 subjects at baseline with serum calcium phosphate product levels > 55 mg^2/dL^2.

The Delegate requested the sponsor to comment on this observation and also to indicate whether such a proportion (3/56 or 5.4%) is what one would expect in a population of subjects with Stage 3 or 4 CKD and with elevated serum phosphate values. The Delegate also asked the sponsor to comment on the possibility that such an observation is the result of the relatively small subject numbers in this clinical trial.

Interestingly, the proportion of subjects in the placebo group with serum calcium phosphate product levels ≤ 55 mg^2/dL^2 rose from 85.3% at baseline to 88.2% at Visit 7/Week 8.

With regard to the mean reductions from baseline in the serum calcium phosphate product levels, the difference between the two treatment groups was statistically significant ($p \leq 0.05$) at Visit 5/Week 4 but not at Visit 7/Week 8.

In both the Fosrenol and placebo groups, a higher daily dose was not associated with a greater mean serum calcium phosphate reduction from baseline.

With regard to mean iPTH levels, the results showed that although the difference between the treatment groups was statistically significant in favour of Fosrenol at the end of study

visit (Visit 7/Week 8), the reductions from baseline in the Fosrenol group were only modest.

In both the Fosrenol and placebo groups, a higher daily dose was not associated with a greater mean serum iPTH reduction from baseline.

Overall conclusions with regard to efficacy

As noted by the clinical evaluator, the sample size for the study was small but probably appropriate for a proof of concept study. Although Fosrenol was associated with a reduction in serum phosphate levels compared with placebo, the primary efficacy analysis showed that there was no statistically significant difference between the Fosrenol and placebo groups in the percentage of subjects with serum phosphate controlled at ≤ 4.6 mg/dL. This result may have been somewhat clouded/confounded by the study design.

Also the study may have been underpowered to begin with by the fact that the sample size was based on an estimated effect derived from a Phase III study where the effect size was for a target phosphate level of 5.6 mg/dL and not 4.6 mg/dL. The results of the secondary efficacy analyses were variable. There was no clinically significant effect, neither on serum calcium phosphate product levels nor on iPTH levels. In the Fosrenol group, there appeared to be a dose relationship for mean serum phosphate reductions from baseline. No such relationship was observed in the placebo group. The time to control of serum phosphate was significantly shorter in the Fosrenol group.

Safety

The safety data of study SPD405-206 were drawn from a total of 199 subjects, 78 out of 80 subjects randomised to the Fosrenol group and all 41 subjects randomised to the placebo group. Overall, 56.5% (44/78) of subjects in the Fosrenol group and 73.2% (30/41) of subjects in the placebo group received treatment for at least 29 days.

In the Fosrenol group, the most commonly reported TEAEs by SOC were *Gastrointestinal Disorders* (20.5% vs 26.8 % in the placebo group) and *Metabolism and Nutrition Disorders* (12.8% vs 12.2% in the placebo group). In the Fosrenol group, the most commonly reported TEAEs (reported by ≥ 5% of subjects) by preferred term were nausea (9.0% vs 9.8% in the placebo group) and vomiting (6.4% vs 2.4% in the placebo group). The most common drug related TEAE by SOC was *Gastrointestinal Disorders* (10.3% vs 17.1 % in the placebo group). The most commonly reported drug related TEAE in both treatment groups by preferred term was nausea (3.8% in the Fosrenol group vs 7.3% in the placebo group).

Overall no deaths were reported in the Fosrenol group. A total of 12 treatment emergent SAEs were reported by 7 subjects in the Fosrenol group. In the Fosrenol group the most common treatment emergent SAEs were *Cardiac Disorders* (2 SAEs of congestive cardiac failure and 1 SAE of myocardial infarction) and *Respiratory, Thoracic and Mediastinal Disorders* (1 SAE each of pneumothorax, acute pulmonary oedema and dyspnoea exacerbated). Other treatment emergent SAEs in the Fosrenol group were 2 SAEs of anaemia, and 1 each of catheter site pain, bacterial arthritis, impaired gastric emptying and perinephric abscess. None of these treatment emergent SAEs in the Fosrenol group was judged by the investigator to be related to the study drug.

There were no significant laboratory findings of safety concern.

Overall, 2 (2.6%) subjects in the Fosrenol group and 4 (9.8%) subjects in the placebo group were discontinued from the study due to TEAEs. In the Fosrenol group, only 1 TEAE (itching abdomen sides) in 1 of the 2 subjects was judged to be possibly related to the study drug. The severity of this TEAE was graded mild.

Overall conclusions with regard to safety

The safety results of study SPD405-206 showed that the most common AEs were nausea and vomiting. This is consistent with the safety results from the Phase III trials presented in the PI. The sample size of the study was small, but the safety results did not show any safety concerns inconsistent with the safety results from the Phase III trials reported in the proposed PI.

Postmarketing experience

The Delegate also examined briefly the most recent PSUR lodged with the TGA by the sponsor, that for the period 19 March 2008 to 18 March 2009 or PSUR no. 007. Three cases of gadolinium associated Nephrogenic Systemic Fibrosis (NSF) were reported within one literature abstract.[9] Two of the cases had a fatal outcome due to causes not directly related to NSF progression. In its discussion in the PSUR, the sponsor was of the opinion that the event of NSF in all 3 cases reported in the literature abstract was likely to be due to the exposure to gadolinium, in patients with impaired excretion due to end stage renal disease. However, as noted by the sponsor, the literature article also discussed a possible contributory role of La. In the sponsor's opinion, the latter remains speculative. Although La belongs to the same periodic class as gadolinium, it differs substantially in its pharmacokinetics, metabolism and toxicity. In the opinion of the sponsor, systemic exposure after gadolinium (0.1 mmol/kg body weight [BW]) cannot be compared to the systemic exposure to La with an oral bioavailability of 0.00127%, a difference of orders of magnitude, even after having taken long term use and accumulation into account. The assumption that the risks established for high dose gadolinium based contrast agents can be extrapolated to the low level absorption of La has not been demonstrated by either clinical association studies or by experimental animal studies.

Another hypothesis for the development of NSF is related to the dechelation of gadolinium leading to free gadolinium ions which then initiate inflammation and fibrosis. The dechelation is hypothesized to be due to an interaction with gadolinium complexes by the process of transmetallation between gadolinium and other metals like iron. Again the sponsor posits that the extremely low free La concentrations present in human serum (La > 99.7% protein bound with free La serum concentrations in the order of approximately 20 pM) make it an unlikely participant in the displacement of gadolinium from its chelate. Also, the sponsor stated that it has been suggested from experimental models that it is the excess of chelate which is responsible for the initiation of the NSF and the metal itself.

To date there have been no further cases of gadolinium induced NSF in patients treated with La reported to the sponsor's Global Safety Database. In particular, there is no case of NSF reported in patients not exposed to gadolinium, but only to La. Gadolinium is currently contraindicated in dialysis patients. Taking into account all of the foregoing, the sponsor was of the opinion that there is not sufficient evidence to assume that La might contribute to gadolinium induced NSF at this point in time. The sponsor maintained that it remains vigilant of all cases of NSF.

Risk Management Plan

The Office of Product Review assessed this submission at the filter stage and concluded that no specific RMP evaluation was required unless the clinical delegate raised specific issues.

[9] Swaminathan et al, Are patients on lanthanum carbonate at high risk for gadolinium-associated nephrogenic systemic fibrosis? – ASN online October 2008.

Risk-Benefit Analysis

Initial Delegate Considerations

Overall, the clinical efficacy analyses results failed the proof of concept that the use of Fosrenol for 8 weeks was associated with a reduction of serum phosphate level down to ≤4.6 mg/dL in patients with Stage 3 and 4 CKD who were not on dialysis. The results showed that Fosrenol was associated with some reduction of serum phosphate level in the targeted patient population but efficacy to reach the target serum phosphate level of ≤ 4.6mg/dL recommended by K/DQOI and CARI guidelines for this patient population after 8 weeks of treatment was not demonstrated. There was also no added clinically significant beneficial effect on serum calcium-phosphate product and iPTH levels.

There was considerable discussion in the clinical evaluation report as to whether there could have been a contribution to the failure of the primary efficacy analysis by the study design. The latter meant that 7 out of the 17 subjects (6 in the Fosrenol group, and 1 in the placebo group) who were discontinued after the baseline visit due to baseline serum phosphate or serum calcium levels not meeting the study continuation criteria, were included in the primary endpoint analysis. In the primary efficacy analysis of these subjects, the "end of study" serum phosphate level used was that taken at Visit 2/Week 1 (after only 1 week of starting on the study drug or placebo) as LOCF imputation was used. Due to the small sample size of the study to begin with, the inclusion of these subjects into the analysis would confound the results and the Delegate agreed.

The Delegate also agreed with the clinical evaluator's point that the study may have been underpowered to begin with by the fact that the sample size was based on an estimated effect derived from a Phase III study where the effect size was for a target phosphate level of 5.6 mg/dL and not 4.6 mg/dL.

Because of the foregoing issues, the Delegate was unsure whether the study population can be truly regarded as being representative of patients with Stages 3 or 4 CKD who are not on dialysis and who have raised serum phosphate levels. The Delegate requested specific advice from the ACPM on this issue. It is also why the Delegate asked the sponsor to provide data on the specific make-up of the FAP with regard to serum phosphate and to provide extra analyses of the data, the latter hopefully to show internal consistency of the results.

Overall, the safety results did not show any safety concerns inconsistent with the safety results from the Phase III trials reported in the proposed PI. The safety results of study SPD405-206 showed that the most common AEs were nausea and vomiting. This is consistent with the safety results from the Phase III trials presented in the PI.

In order to effect a change in the indications of a medicine, the burden of proof, particularly of efficacy, must be set quite high. The Delegate was reluctant to recommend a change to the indications of a medicine from the results of a proof of concept study. However, the Delegate was even more reluctant to recommend a change to the indications on the basis of such a study which has failed to achieve the primary efficacy endpoint. The results of the clinical efficacy analyses did show that Fosrenol was associated with some reduction of serum phosphate levels in the targeted patient population. However, it failed the proof of concept on the efficacy to reach the target serum phosphate level of ≤ 4.6 mg/dL recommended by K/DQOI and CARI guidelines for this patient population after 8 weeks of treatment, that is, patients with Stages 3 or 4 CKD. The secondary efficacy results were variable. Furthermore, there are concerns as to the degree to the results of the study SPD405-206 can be extrapolated to patients with Stage 5 CKD who may not yet be on dialysis and also the degree to the present dosage recommendations in the approved PI can be extrapolated to the new patient population. At this stage, the Delegate remained

unconvinced as to the robustness of the efficacy results of the study SPD405-206 and could not recommend approval of the submission for an extension of indications. However, the Delegate would have no objection to fair and balanced reporting of the study outcomes in the Clinical Trials section of the PI.

In addition to the specific requests by the Delegate, the sponsor was also requested to address the following issues:

The sponsor was asked to explain why this application for a change in the patient group in the indication for Fosrenol has not been submitted in the USA or Canada.

The sponsor was asked to confirm whether or not the dataset for this application, in particular the results for the study SPD405-206, have been submitted to and evaluated by the EMA.

The sponsor was requested to confirm whether or not the results for the pivotal study SPD405-206 have been published in a peer reviewed journal.

The sponsor was requested to confirm that there have been no further cases of gadolinium induced NSF in patients treated with La reported to Shire's Global Safety Database since the assessment done in the PSUR no. 007 (for the period 19 March 2008 to 18 March 2009) and that it maintains its position that there is no causative role which can be attributed to lanthanum carbonate in the aetiology of this condition.

Sponsor's response to the Delegate

The sponsor addressed the questions asked by the clinical evaluator and began by giving some background to the issue of hyperphosphataemia and its treatment in patients with CKD (in both dialysis and non-dialysis patients). The sponsor acknowledged that little data exist with respect to improved dialysis and non-dialysis patient outcomes resulting from reducing an elevated serum phosphate with phosphate binders. However, there appear to be some promising early results from a clinical epidemiology study by Isakova et al 2008 and two other studies, those of Kovesdy et al 2010 and Di Lullo et al 2011.[10,11,12]

The sponsor also noted that there are no randomized controlled data which specifically address the clinical benefits achieved by a reduction of serum phosphate levels in Stage 3 and 4 CKD patients with hyperphosphataemia, even if the reduction does not manage to reach the recommended target level. The sponsor argued that CKD is a continuum of stages up to and including CKD Stage 5 and that the compensatory mechanisms associated with CKD are essentially the same no matter the stage of CKD except for varying in degree according to the particular stage. *The ACPM was asked to indicate whether it agrees with this proposition.*

As noted by the sponsor, there does not appear to be a single accepted target phosphate level specified in Australia, with the upper limit ranging between 1.4 and 1.5 mmol/L. Therefore, a reduction in the phosphate level may be more appropriate than the actual target level. *The ACPM was asked to indicate whether it agrees with this proposition.*

The sponsor was asked by the clinical evaluator to explain the basis for extrapolating the efficacy results of the study submitted, SPD405-206 involving Stage 3 and 4 CKD patients

[10] Isakova T, Gutierrez O, Shah A et al. Postprandial mineral metabolism and secondary hyperparathyroidism in early CKD. J Am Soc Nephrol008; 19: 615-623.

[11] Kovesdy CP, Kuchmak O, Lu JL, Kalantar-Zadeh K. Outcomes associated with phosphorus binders in men with non–dialysis-dependent CKD. Am J Kidney Dis 2010; 56: 842-851.

[12] Di LulloDi Lullo L, Antonio Gorini A, Cecilia A et al. Clinical benefits on secondary hyperparathyroidism and chronic kidney disease progression of lanthanum carbonate treatment on pre-dialysis patients with stage iii-iv ckd: a randomized trial. Presented at ERA-EDTA 25 June 2011

to Stage 5 CKD patients not yet on dialysis. The sponsor began by pointing out that experimental evidence to date does not suggest that patients on dialysis have a different response from patients not yet on dialysis. The sponsor also pointed out that there were 7 patients in SPD405-206 who had CKD Stage 5 and were not yet on dialysis (5 on lanthanum carbonate and 2 on placebo). The mean baseline serum phosphate level of these 7 patients was 5.3 mg/dL (1.77 mmol/L) which was the median baseline serum phosphate level in the placebo group (the median value in the La group was 5.2 mg/dL). In a re-analysis requested by the Delegate, the sponsor demonstrated that, in patients whose baseline serum phosphate concentrations were at least 5.3 mg/dL (1.77 mmol/L), the least squares (LS) mean reductions in serum phosphate from baseline at Weeks 4 to 8 ranged from 0.87 mg/dL to 1.09 mg/dL (0.28 to 0.35 mmol/L), while the placebo group had LS mean reductions of 0.33 to 0.36 mg/dL (0.11 to 0.12 mmol/L) at the same time points. The sponsor argued that this confirms the potential for reduction of total body phosphorus burden prior to the initiation of dialysis. The Delegate noted these results with interest but was unaware as to the actual outcomes of these particular 7 patients.

The sponsor was requested to provide the actual reductions in serum phosphate at study endpoint for each of the 5 patients in the La group and the 2 patients in the placebo group and state the proportion of each group which achieved the target primary endpoint.

The sponsor confirmed that there were 17 patients who were protocol violators included in the FAP and these were included in order to be consistent with the principles of the ITT analysis. The Delegate requested the results for the PP Population. The latter were consistent with those from the FAP. In the FAP at Week 8, there were 44.6% patients in the La group with phosphate levels controlled compared with 44.4% in the PP Population. In the placebo group, the corresponding percentages were 26.5% and 26.1%, respectively. Thus the placebo subtracted difference was, in each case, about 18%.

The sponsor was requested to supply the results of the re-analysis of the data for the primary efficacy endpoint of SPD405-206, stratified according to whether the subject's baseline serum phosphate level was either at or below the median baseline serum phosphate level or above the median. In reply, the sponsor provided the study results for the subset of patients whose baseline serum phosphate level was equal to or greater than the baseline median phosphate value for the enrolled population (5.3 mg/dL or 1.77 mmol/L) as well as for the subset of patients whose baseline serum phosphate level was less than this median value of 5.3 mg/dL.

Firstly, in the subgroup of patients with baseline serum phosphate levels ≥ 5.3 mg/dL (1.77 mmol/L), 10/26 (38.5%) patients in the La group versus 2/19 (10.5%) patients in the placebo group had controlled serum phosphate at the end of treatment (Week 8). Once again, these results would appear to be consistent with the results of the FAP with preservation of a placebo subtracted difference of about 18%.

Secondly, in the subgroup of patients with baseline serum phosphate levels < 5.3 mg/dL (1.77 mmol/L), 15/30 (50.0%) patients in the La group versus 7/15 (46.7%) patients in the placebo group had controlled serum phosphate at the end of treatment (Week 8). In other words, there was virtually no difference between these proportions, that is, lanthanum carbonate was no better than placebo.

This appears to be the explanation as to why the EMA approved the extension of indication to those adult patients with chronic kidney disease not on dialysis with serum phosphate levels ≥ 1.78 mmol/L (the latter is very close to 1.77 mmol/L [5.3 mg/dL]).

The sponsor presented an up to date report on the cases of gadolinium induced NSF in patients treated with La. From the discussion, the sponsor's opinion that there is no

causative role attributable to lanthanum carbonate with respect to this condition was considered reasonable.

Following receipt of the clinical evaluation report, the sponsor proposed the following wording for the indications:

Treatment of hyperphosphataemia in adults with chronic kidney disease stage 5 on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). It is also indicated for the treatment of hyperphosphataemia in adults with chronic kidney disease stages 3 to 5.

Further Delegate Considerations

The Delegate noted that there was no additional evidence which would provide any compelling reasons to change his opinion. The Delegate reiterated that the pivotal study was a Phase II, proof of concept study which failed to achieve its primary endpoint. On the basis of the extra sub-analyses performed by the sponsor, it can observed that, for those patients whose baseline serum phosphate level was above 5.3 mg/dL (1.77 mmol/L), the results were consistent with those of the FAP. The Delegate noted that this value is very close to the value which has been approved as the serum phosphate threshold by the EMA. However, it can also be observed that, for those patients whose baseline serum phosphate level was below 5.3 mg/dL (1.77 mmol/L), there was no efficacy benefit with almost equal proportions of patients in the La and placebo groups achieving the target. The latter subgroup of patients whose baseline serum phosphate level was below 5.3 mg/dL (1.77 mmol/L) constituted 50% of the patient population of the study.

There were two important observations to be made. Firstly, the failure to demonstrate a benefit occurred in patients whose baseline serum phosphate level was < 5.3 mg/dL (1.77 mmol/L) and these patients form a substantial part of the target population of patients with CKD Stages 3 to 5. Secondly, the failure of the study to achieve its primary efficacy endpoint means that no further conclusions can be drawn and that all other results, including those of sub-analyses, can only be regarded as hypothesis generating.

Thus, although approval could be considered in those patients whose baseline phosphate levels lie above 5.3 mg/dL (1.77 mmol/L), or as in the EU SmPC, above 1.78 mmol/L, there can be no justification in accepting the results of a sub-analysis of a study which is a failed study, for a change in the indications. Such observations do not take into account the obvious difficulties caused by the high number of discontinuations and important protocol violations. The Delegate indicated continuing concerns as to the degree to which the results of the study SPD405-206 can be extrapolated to patients with Stage 5 CKD who may not yet be on dialysis and has asked the sponsor a question about the 7 patients in the study who had Stage 5 CKD but were not yet on dialysis. In the opinion of the Delegate, the evidence to support the proposed extension of indications was simply not robust enough and the only satisfactory way of garnering the required evidence would be to replicate the results in an appropriately designed and powered Phase III clinical efficacy and safety trial.

The Delegate proposed to reject the submission.

In addition to the question asked of the sponsor, the Delegate asked the following questions of the ACPM:

- Does the ACPM agree with the sponsor that CKD is a continuum of stages up to and including CKD Stage 5 (and dialysis dependent) and that the compensatory mechanisms associated with CKD are essentially the same no matter the stage of CKD except for varying in degree according to the particular stage?

- Does the ACPM agree with the sponsor that there does not appear to be a single accepted target phosphate level specified in Australia for the treatment of CKD? Current recommendations vary, with the upper limit ranging between 1.4 and 1.5 mmol/L and so the sponsor argues that a reduction in the phosphate level may be more appropriate than the actual target level.
- Does the ACPM agree with the Delegate that a study which is both a proof of concept study and one which has failed to achieve its primary efficacy endpoint may not be used as the basis for extending the indications?
- Does the ACPM share the concerns of the Delegate about the small size of the pivotal study SPD405-206 and the possible confounding of the study's results by the large number of protocol violations?
- Does the ACPM have any view concerning the generalisability of the study's results to the population of subjects with Stage 3 or 4 CKD not yet on dialysis?

Response from Sponsor

Introduction

Chronic kidney disease (CKD) at Stage 3 and beyond is associated with progressive deterioration of renal function which culminates in the need for renal replacement therapy (either dialysis or renal transplant) (Levey 2011).[13] As kidney function declines, the kidney loses its ability to maintain phosphate balance and excrete excess phosphate. As a result, phosphate balance becomes positive and phosphate accumulates.

Excess phosphate accumulates primarily in tissues, including cells. Because serum phosphate accounts for <1% of total body phosphate, serum phosphate levels rise only when tissues and cells become saturated. Hyperphosphataemia is therefore a late indicator of excess body phosphate burden and is associated with adverse outcomes both in patients on dialysis and those not yet on dialysis, and may hasten the rate of renal deterioration in the latter (Voormolen 2007).[14] In addition, in patients not on dialysis, increased serum phosphate has been found to correlate with increased cardiac risk (Tonelli et al, 2005; Kestenbaum et al, 2005; Menon et al, 2005; Voormolen et al, 2007), coronary artery calcification (Russo et al, 2007), and increased mortality (Kestenbaum et al, 2005).[14,15,16,17,18] As such, clinical guidelines have been developed, including the Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines (Eknoyan, 2003);[19] Caring for Australasians with Renal Impairment (CARI) guidelines (Elder G,

[13] Levey AS et al: Chronic kidney disease: definition, classification, and prognosis. Kidney International 2011: 80:17-28.

[14] Voormolen, N., Noordzij, M., Grootendorst, D.C., et al. High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. Nephrol Dial Transplant 2007.

[15] Tonelli M, Sacks F, Pfeffer M et al. Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. Circulation 2005; 112: 2627-2633.

[16] Kestenbaum, B et al: Serum phosphate levels and mortality risk among people with chronic kidney disease. JASN 2005; 16: 520-528.

[17] Menon V, Greene T, Pereira AA et al. Relationship of Phosphorus and Calcium-Phosphorus Product With Mortality in CKD. Am J Kidney Dis 46:455-463.

[18] Russo D, Miranda I, Ruocco C et al. The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer Kidney Int. 2007; 72: 1255-1261.

[19] Eknoyan,G., Levin,A., and Levin,N. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Am J Kidney Dis 2003; 42 Suppl 3: 1-201.

2006);[20] and Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines in 2009 all of which recommend reduction of phosphate levels in both dialysis and pre-dialysis patients.[21]

Use of calcium-based binders is recognised as contributing to the cardiovascular risk associated with CKD and therefore their use is restricted in the presence of persistent/recurrent hypercalcaemia, arterial calcification, adynamic bone disease and/or persistently low serum iPTH levels is recommended (KDIGO, K/DOQI).[19,21] It is generally accepted that there is a higher risk of vascular calcification with calcium based phosphate binders than with non-calcium phosphate binders in dialysis patients (Block et al. 2005, Chertow et al. 2002).[22, 23]Additionally there are now data supporting the same higher risk in CKD patients not on dialysis (Russo et al 2007).[18] A recent review authored by the Chair of the CARI Guidelines Working Group has further highlighted these risks (Elder G, 2011).[24]

One prospective randomised trial of 13 patients with CKD on haemodialysis compared standard therapy (calcium based binders, sevelamer or both) to La. At 12 months there was a significant reduction in progression of coronary artery calcification in patients on La compared to calcium based binders (-2% vs 77%, p=0.003) (Kalil 2009).[25] A further randomised trial conducted in Australia involved 45 haemodialysis patients and also demonstrated attenuation of vascular calcification with La. This study revealed less progression of aortic calcification in those patients administered La compared to calcium-based phosphate binders over an 18 month period despite similar phosphate control (Toussaint 2011).[26]

These considerations related to calcium-based binders, together with the known toxicity of aluminium-based binders (K/DOQI, CARI, KDIGO), translates to a clear medical need for non-calcium/non-aluminium phosphate binders. However, sevelamer is the only non-calcium/non-aluminium binder available for use in non-dialysed CKD patients Stages 4 and 5.

As will be discussed later in this document, there is a paucity of evidence supporting the use of calcium based salts, aluminium based salts and sevelamer in non-dialysed CKD patients. As such, Shire believes this application, consisting of a single double blind placebo controlled study (SPD405-206)(recently published (Sprague, 2008)) which demonstrates a statistically significant reduction in phosphate levels (both serum and

[20] Elder G, Faull R, Branley P, Hawley C; Caring for Australasians with Renal Impairment (CARI). The CARI guidelines. Management of bone disease, calcium, phosphate and parathyroid hormone. Nephrology 2006; Suppl 1: S230-261.

[21] Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD–MBD). Kidney International 2009; 76 Suppl 113: S1–S130.

[22] Block GA, Spiegel DM, Ehrlich R et al. Effects of sevelamer and calcium on coronary artery calcification in patients to new hemodialysis. Kidney International 2005; 68: 1815–1824.

[23] Chertow GM, Burke SK, Raggi P et al. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney International 2002; 62: 245-252.

[24] Elder G. Calcium supplementation: lessons from the general population for chronic kidney disease and back. Current Opinion in Nephrology and Hypertension 2011, 20:369–375 Endocrinology Therapeutic Guidelines 2009. Therapeutic Guidelines Ltd.

[25] Kalil RS, Flanigan MG, Stanford W, Haynes WG. The effect of lanthanum carbonate (Fosrenol) on coronary artery calcification and endothelial function in hemodialysis patients. A pilot, prospective study American Society of Nephrology (ASN) Annual Scientific Meeting 2009 Poster 1252.

[26] Toussaint ND, Lau KK, Polkinghorne KR, Kerr PG. Attenuation of aortic calcification with lanthanum carbonate vs calcium-based phosphate binders in haemodialysis – a randomized controlled trial. Nephrology 2011; 16: 290–298.

urinary) is sufficient to address this inequity.[27] The Delegate has recommended rejection because the evidence is "not robust enough" but is seeking advice from the ACPM on a number of issues and the sponsor addressed each individually. In addition, the sponsor presented expert opinions from two independent internationally recognised experts in the field.

The issues for consideration are:

Is CKD a continuum of stages up to and including CKD Stage 5 (with/without dialysis)?

As discussed in the Introduction, CKD at Stage 3 and beyond correlates with progressive deterioration of renal function and is associated with an increase in cardiovascular and all cause mortality. CKD is a continuum of stages associated with a progressively increased relative risk for all cause and cardiovascular mortality as well as end stage renal disease and progressive CKD is addressed in the recent publication of Levey et al which proposes a revision of the current chronic kidney disease classification based on this continuum (Levey 2011).[13] This is also supported in the clinical evaluation report (CER). The evaluator agreed with the sponsor that the pathophysiology of hyperphosphataemia in CKD patients, and hence the principle of management, is the same regardless of whether they are on dialysis or not.

Serum phosphate levels rise when tissues and cells become saturated with phosphate and the only mechanism available to maintain balance is to increase filtered phosphate at the glomerulus which leads to an increase in total phosphate excretion in the urine. Before hyperphosphataemia occurs, compensatory mechanisms such as increased levels of fibroblast growth factor 23 (FGF-23), iPTH and decreased active vitamin D, act to increase renal clearance of phosphate and reduce gastrointestinal (GI) phosphate absorption. As the kidney progressively fails, compensatory mechanisms gradually work at capacity upon the kidney.

Phosphate binders decrease the availability of phosphate by inhibiting GI phosphate absorption. They supplement the removal of phosphate by dialysis or by native kidneys to the same extent. Thus, studies in patients on dialysis, and studies in patients with pre-dialysis CKD with hyperphosphataemia measure the same response. Experimental evidence to date does not suggest that patients on dialysis have a different response from patients not on dialysis. In patients on dialysis, shorter duration studies show similar effects as long duration (>2 years) studies on the endpoint of serum phosphate reduction (Hutchison A, 2008, Finn WF 2005).[28,29]

An application to extend the indications for Fosrenol to pre-dialysis patients, based on the same data presented with this application, was recently approved in Europe (October 2009). In the Public Assessment Report (Swedish MPA, 2009), it was concluded: "Considering that dialysis represents a treatment option in the latter stages of a continuum of disease progression in the same patient population, corresponding efficacy would be expected for the pre-dialysis CKD population".[30] Following approval of this application in Europe, the indication was extended to:

[27] Sprague SM, Abboud H, Qiu P et al. Lanthanum carbonate reduces phosphorus burden in patients with CKD stages 3 and 4: A randomized trial. Clin J Am Soc Nephrol 2009; 4: 178-185.

[28] Hutchison AJ, Barnett ME, Krause R et al. Long-Term Efficacy and Safety Profile of Lanthanum Carbonate: Results for up to 6 Years of Treatment. Nephron Clin Pract 2008; 110: c15-c23.

[29] Finn WF, Joy MS. A long-term, open-label extension study on the safety of treatment with lanthanum carbonate, a new phosphate binder, in patients receiving hemodialysis. Current Medical Research and Opinion 2005; 21: 657-664.

[30] CHMP Assessment Report for Fosrenol, March 2009.

Control of hyperphosphataemia in chronic renal failure patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Fosrenol is also indicated in adult patients with chronic kidney disease not on dialysis with serum phosphate levels .1.78 mmol/L in whom a low phosphate diet alone is insufficient to control serum phosphate levels.

It should be noted that the minimum baseline phosphate level for pre-dialysed patients was included in the Fosrenol indication in order for the Fosrenol European SmPC to be in line with sevelamer (Renvela) which was approved in Europe in June 2009.[31] This product is not currently approved in Australia.

Target vs reduction in phosphate levels

At the time Study SPD405-206 was designed, the K/DOQI guidelines (the only guidelines available) recommended a target phosphate level of ≤4.6 mg/dL (1.49 mmol/L). The later published CARI and KDIGO guidelines make no recommendation for a particular numeric phosphate level – only that phosphate levels be kept within the normal range. Subsequent to the KDIGO guidelines, the K/DOQI guidelines also adopted this terminology (Uhlig, 2010).[32]

In Australia, the upper limit for normal serum phosphate ranges between 1.4 mmol/L (Endocrinology Therapeutic Guidelines 2009) and 1.5 mmol/L (Royal College of Pathologists of Australasia Manual, 2004).[33] Only one Australian publication giving a numeric serum phosphate limit for CKD patients was found following a literature search (Embase, Medline); the authors recommended an upper limit of 1.65 mmol/L (Tan K, 2008).[34] As such, it is clear there is no single accepted target phosphate level specified in Australia. Furthermore, Kestenbaum et al 2005 found that serum phosphate levels above 3.5 mg/dL were associated with significantly increased risk for death in CKD patients not on dialysis.[16] When serum phosphate was 4.5 to 4.999 mg/dL and > 5.0 mg/dL, the adjusted risk of mortality was increased by 83% and 90% respectively, compared to 2.5-2.999 mg/dL (Figure 5). Additionally, Block et al 2004 showed in patients on dialysis, serum phosphate levels >5.0 mg/dL were associated with an increased relative risk of death (see Figure 6).[35] Given the lack of agreement on a target serum phosphate level and the evidence that increasing phosphate levels increases the risk of mortality, it is very relevant to consider the secondary endpoint from Study SPD405-206 of change in serum phosphate.

[31] CHMP Assessment Report for Renvela, March 2009; available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000993/WC500052615.pdf.

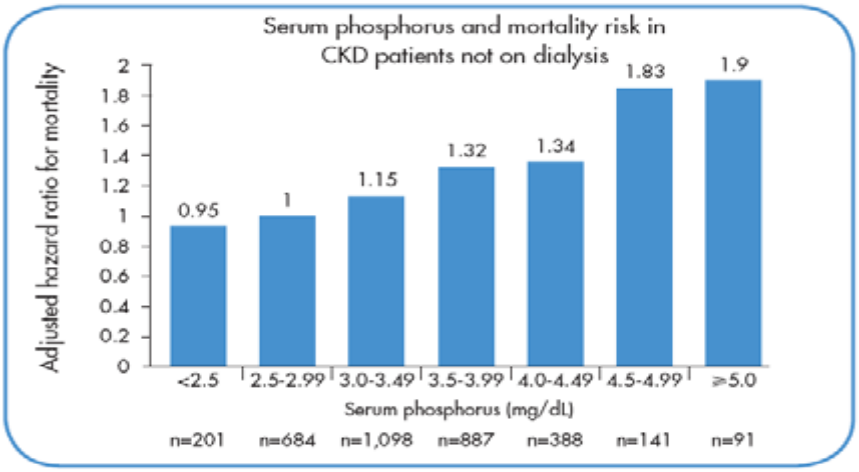
[32] Uhlig, K., Berns, J.S., Kestenbaum, B., et al. KDOQI US Commentary on the 2009 KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of CKD–Mineral and Bone Disorder (CKD-MBD). Am J Kidney Dis 2010; 55: 773-799.

[33] Royal College of Pathologists of Australasia Manual, 2004 (http://rcpamanual.edu.au/index.php?option=com_pttests&task=show_test&id=547&Itemid=77 accessed 28/7/11).

[34] Tan K & Johnson DW. Managing the cardiovascular complications of chronic kidney disease. Australian Prescriber 2008;31:154–8.

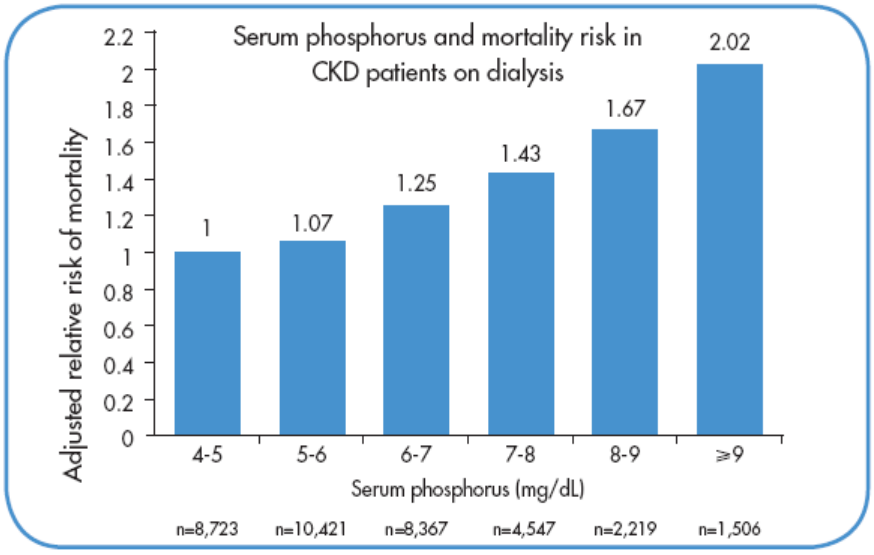
[35] Block, G. A., Klassen, P. S., Lazarus, J. M., et al. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis." J Am Soc Nephrol 2004; 15: 2208-18.

Figure 5: Figure adapted from Kestenbaum B et al 2005



*Adjusted for baseline age, sex, race, cerebrovascular disease, diabetes, ischemic heart disease, HF, acute renal failure, calcium intake from medications, serum calcium, inverse of baseline creatinine, time-averaged creatinine, slope of creatinine, maximal creatinine concentration, haemoglobin CKD (CrCl 50.4–39.5 mL/min)

Figure 6: Figure adapted from Block et al 2004 to show only patients with serum phosphate levels above 4 mg/dL.



Adjusted for age, gender, race or ethnicity, diabetes, dialysis vintage, body weight, URR, serum albumin, creatinine pre-dialysis, BUN, bicarbonate, cholesterol, haemoglobin, ferritin, aluminium and calcium and parathyroid hormone.

In addition, other measures such as urinary phosphate, FGF23 and iPTH should also be considered as well as the dose response to the individual phosphate binder.

Percentage of patients achieving target serum phosphate

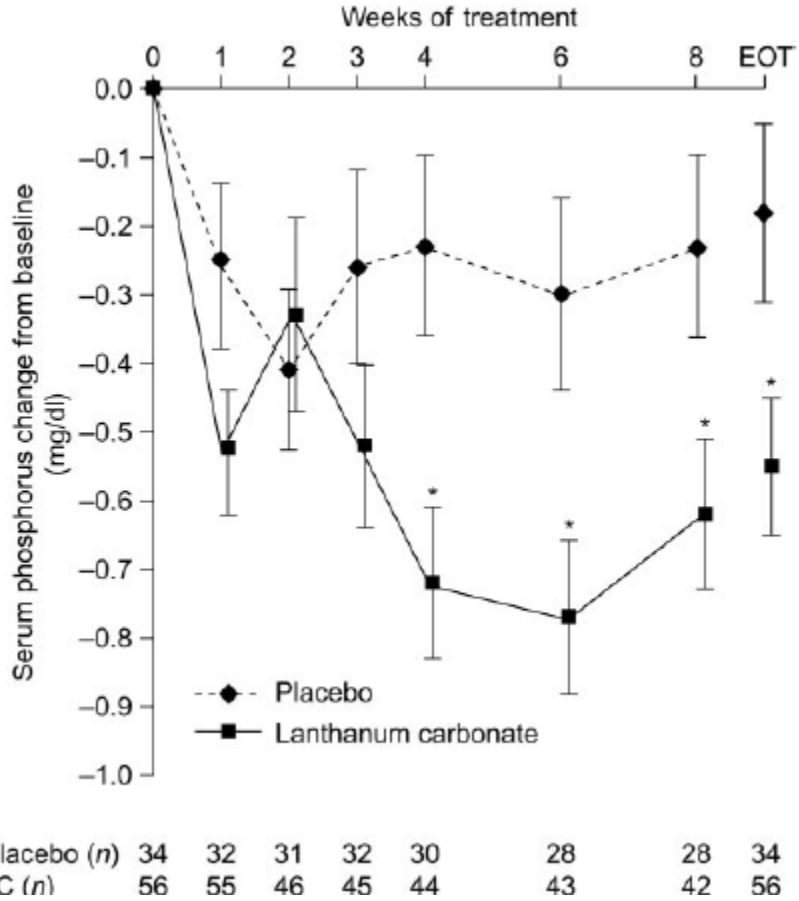
It should be noted that a higher percentage of subjects in study SPD405-206 in the Fosrenol group than in the placebo group achieved controlled serum phosphate levels starting at Week 3 of treatment which continued through Week 8, with the differences between the treatment groups reaching significance at Week 6 in the ITT population. At Week 6, 55.4% (31/56) of subjects in the Fosrenol group versus 29.4% (10/34) of subjects in the placebo group achieved controlled serum phosphate levels (p=0.0283). At the end of treatment, 44.6% (25/56) subjects in the Fosrenol group versus 26.5% (9/34)

subjects in the placebo group had controlled serum phosphate levels (difference 18.1%, p = 0.1167).

Reduction in serum phosphate

Statistically significant differences in serum phosphate levels were observed between Fosrenol and placebo in the change from baseline starting at Week 3 of treatment and continuing through Week 8 (p = 0.0228) in the ITT analysis. At the end of treatment, mean serum phosphate levels had decreased from baseline by 0.55 mg/dL (0.18 mmol/L) in the Fosrenol group compared to 0.18 mg/dL (0.06 mmol/L) in the placebo group. These results are shown in Figure 7. It should be noted that reduction in serum phosphate has been the primary endpoint for both sevelamer studies sponsored by Genzyme.

Figure 7: Change in serum phosphate values (observed cases and end of treatment)



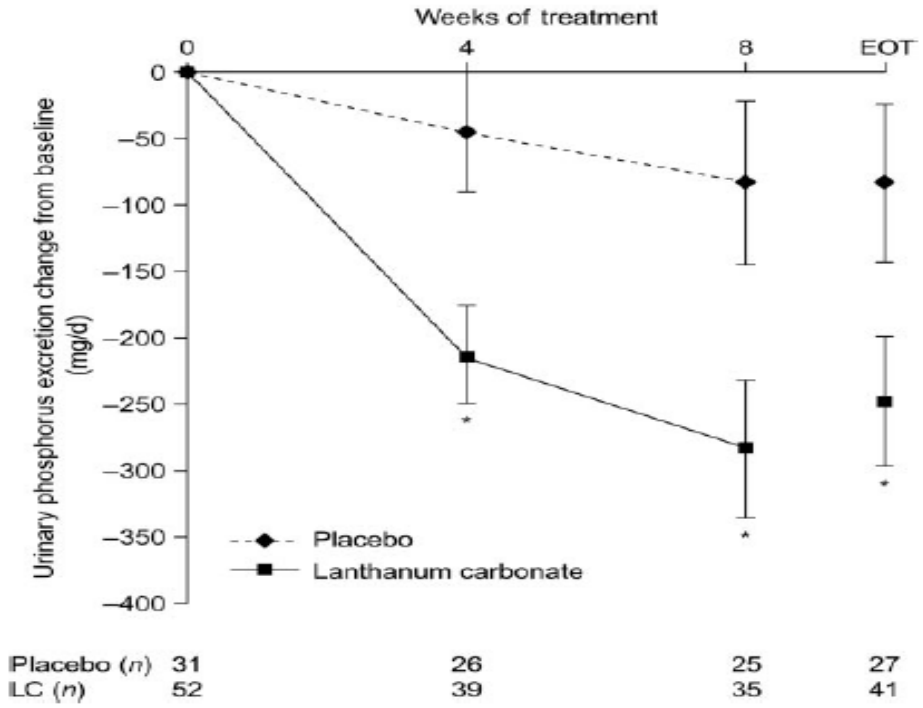
Reduction in urinary phosphate

Fosrenol substantially reduced urinary phosphate excretion, starting at the first post-dose visit and this persisted to the end of study, compared with little change in the placebo group (p=0.04) in the ITT population. These results are shown in Figure 5 and are comparable to the findings of another recently completed study with Fosrenol in Stage 3 CKD patients with "normal" serum phosphate levels (Gonzalez-Parra E, 2011).[36] Unlike CKD patients on dialysis, patients with Stage 3-4 CKD maintain urine output and the ability to excrete a proportion of any phosphorous absorbed. In the "steady state" condition, the amount excreted in the urine is proportional to the amount absorbed; therefore,

[36] Gonzalez-Parra E, Gonzalez-casaus ML, Galan A et al. Lanthanum carbonate reduces FGF23 in chronic kidney disease stage 3 patients. Nephrol Dial Transplant 2011; 26: 2567–2571.

measurement of urinary phosphate can be used as a marker of intestinal phosphorous absorption (Russo 2007, Burke 1997).[18] In the study by Russo et al, patients were randomised to receive calcium carbonate, sevelamer or placebo. After 2 years, the mean serum phosphate levels had actually increased in the calcium carbonate and sevelamer groups by 0.1 and 0.3 mg/dL, respectively (no change in the control group). However, the authors considered the compounds efficacious because both significantly decreased urinary phosphate. The mean 24 hour urinary phosphate in the calcium carbonate and sevelamer groups had decreased by 83 mg ($p<0.05$) and 80 mg ($p<0.01$), respectively, while it had increased in the control group by 147 mg ($p<0.05$).

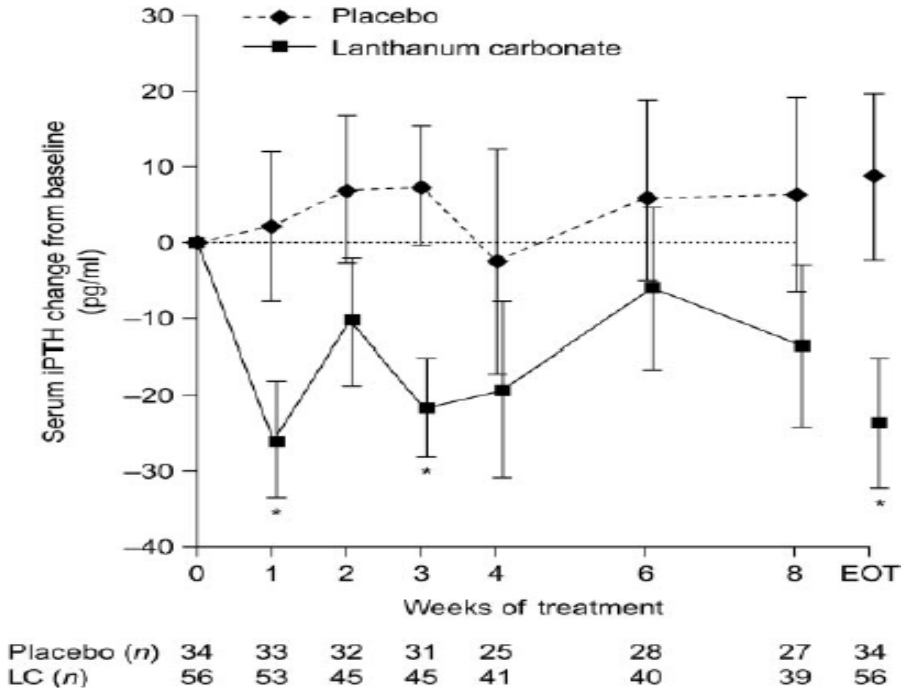
Figure 8: Change in urinary phosphate values (observed cases and end of treatment)



Reduction in iPTH

Reductions from baseline in iPTH levels occurred after treatment with Fosrenol starting at Week 1 and continued through to Week 8 with significant ($p<0.05$) within group differences occurring at all visits from Week 3 to Week 8. In contrast, iPTH levels in the placebo group actually increased from baseline, starting at Week 1 and remained increased through Week 8. The differences between the treatment groups in the mean changes from baseline in iPTH levels were significant ($p<0.05$) at Week 1, Week 3 and Week 8. At Week 8, the mean reduction in iPTH levels in the Fosrenol group was 24.0 pg/mL while the mean increase in the placebo group was 9.1 pg/mL ($p=0.0212$). These results are shown in Figure 9.

Figure 9: Change in intact parathyroid hormone (observed cases and end of treatment)

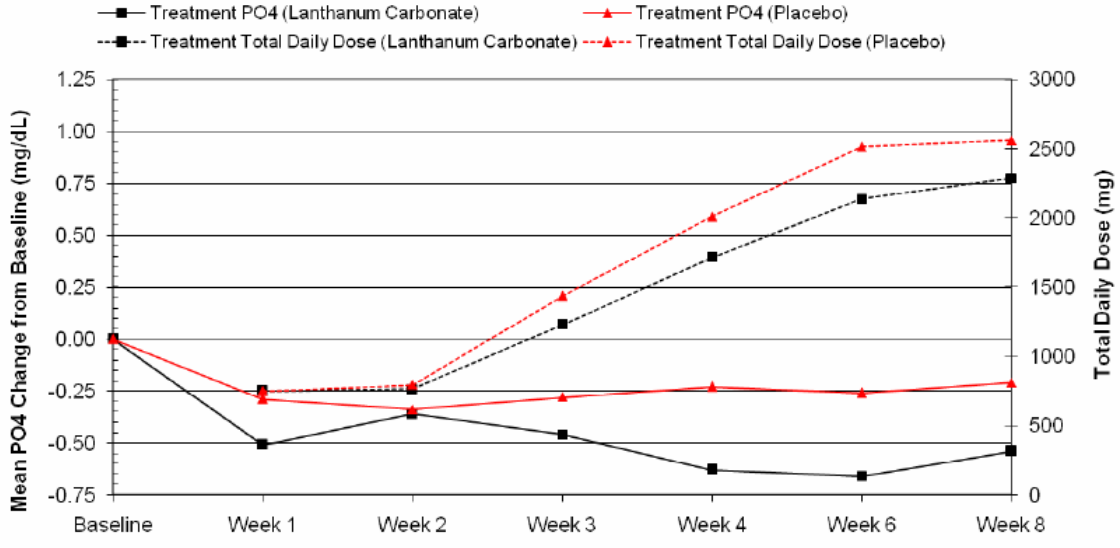


Dose response

A dose response in serum phosphate reduction was demonstrated for the Fosrenol treatment group, although the response was not proportional to the increase in the Fosrenol dose.

Conversely, the reduction in serum phosphate levels remained relatively unchanged in the placebo treatment group during treatment despite an increase in dose. These results are shown in Figure 10.

Figure 10: Change in serum phosphate and daily dose (last observation carried forward)



Size of the study and impact of protocol violators

The sponsor acknowledged the small size of the study; however, as previously discussed, this should not be a hindrance to approval considering the argument that CKD is a continuum of stages up to Stage 5D and the extensive investigations of Fosrenol conducted by the sponsor in dialysis patients. Further the Delegate acknowledged the consistency of the results between the full analysis (ITT) population and the PP population.

Comparison of Study SPD405-206 results to other phosphate binder studies

Differences in study design mean that direct comparisons of results between SPD405-206 and studies using other phosphate binders in non-dialysed patients are difficult. As far as the sponsor was aware there are two similar studies for the other non-calcium based binder, sevelamer; one for sevelamer (GTC-45-204) and one for sevelamer carbonate (SVCARB00105) (the previously discussed Russo 2007 study is not discussed further here as it was a 2 year study with markedly different aims). GTC-45-204 is a non-published, open label, single arm, 12 week study (n=79).[37] SVCARB00105, which was referenced by the clinical evaluator, investigated the use of sevelamer carbonate over 8 weeks (Ketteler 2008).[7] As with GTC-45-204, this was a Genzyme sponsored open label, single arm study (n=46). Both studies had a primary endpoint of change in serum phosphate from baseline to end of study.

The two sevelamer studies were single arm studies and the lack of a comparator group does not allow for control of potential biases or for an estimation of other factors that can contribute to a placebo effect. In contrast, SPD405-206 was a double blind, placebo controlled study designed to minimise bias which may have resulted in a smaller observed treatment effect. With regard to the patient population, an inclusion criterion for SPD405-206 was baseline serum phosphate ≥ 4.7 mg/dL (1.52 mmol/l), compared with ≥5.5 mg/dL (1.78 mmol/L) in SVCARB00105 and ≥5.0 mg/dL (1.55 mmol/L) in GTC-45-204. In addition SPD405-206 had an inclusion criterion of screening eGFR of 15 – 59 mL/min/1.73m^2 whereas there was no similar criterion in the sevelamer studies. As a result of the different inclusion criteria the percentage of patients at each CKD stage or the mean eGFR at baseline was different. The mean serum phosphate levels at baseline were higher in SVCARB00105 than in SPD405-206 (6.2 mg/dL (2.00 mmol/L) vs 5.28 mg/dL (1.71 mmol/L)), the mean baseline serum phosphate was not given for GTC-45-204. The magnitude of the reduction in serum phosphate is known to be correlated with the baseline phosphate, that is, higher baseline serum phosphate levels are associated with larger reductions in serum phosphate. Therefore the patients in SVCARB00105 would be expected to have a greater absolute decrease than those in SPD405-206. The percentage of subjects achieving response was similar in all three studies, 44.6%, 50% and 50% for SPD405-206, SVCARB00105 and GTC-45-204 respectively.

The sponsor was aware of one similar clinical trial with a calcium binder, calcium acetate, in non-dialysed CKD patients (Quinibi W, 2011).[38]

Data on CKD Stage 5 patients

As requested by the Delegate, the sponsor presented data on the CKD Stage 5 patients. Due to the small number of patients, no conclusions can be made from the results.

[37] http://www.genzymeclinicalresearch.com/home/ search_clinical_trial_results/renagel_study13.asp.

[38] Quinibi W, Winkelmayer WC, Solomon R et al. A randomized, double-blind, placebo-controlled trial of calcium acetate on serum phosphorus concentrations in patients with advanced nondialysis-dependent chronic kidney disease. BMC Nephrology 2011; 129: 1-12.

Product Information

The originally proposed indication was:

> *Treatment of hyperphosphataemia in adults with chronic renal failure.*

However following receipt of the clinical evaluation report, the sponsor proposed the alternate indication:

> *Treatment of hyperphosphataemia in adults with Chronic Kidney Disease Stage 5 on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).*
>
> *It is also indicated for the treatment of hyperphosphataemia in adults with Chronic Kidney Disease Stages 3 to 5.*

This wording is in line with the clinical evaluator's recommendation for the indication except that it includes Stage 5 CKD patients. As previously discussed and the clinical evaluator's comments regarding the utility of the previously evaluated Phase III studies in dialysis patients to support use in Stage 5 CKD, the sponsor believed the expanded indication was justified.

Conclusion

SPD405-206 provided a number of important findings and confirmed the understanding of the complexity and heterogeneity of mineral metabolism in CKD. Additionally, treatments aimed at affecting one metabolic bone parameter also invariably influence other metabolic bone parameters, making it difficult to assess the therapeutic benefit of an intervention on other than the primary target of the intervention in a given study. Serum phosphate is a late marker of phosphorous burden in CKD patients not on dialysis and is influenced by a number of factors including dietary protein intake, food additives, vitamin D status, iPTH and FGF-23 levels. In such patients, serum phosphate should be considered in the context of dietary protein and phosphorus intake along with urinary phosphate excretion and iPTH. Although the primary endpoint in this study was not met, Fosrenol treatment resulted in a substantial decrease in intestinal phosphate absorption, as demonstrated by significant reductions in serum phosphate and urinary phosphate levels compared to placebo. This indicates that Fosrenol reduces phosphate burden and offers a potential treatment option for hyperphosphataemia in CKD patients not yet initiated on dialysis. Further, no safety issues of concern were raised by either clinical or nonclinical evaluators which would preclude use of Fosrenol in these patients.

As stated by the clinical evaluator, "Renagel is the only non calcium-containing phosphate binding agent indicated for the treatment of hyperphosphataemia [in patients with later stages of CKD who are not on dialysis]. There is benefit in having an additional drug that is able to treat hyperphosphataemia in these patients". The benefits of Fosrenol and its place in therapy in this patient group were supported by two experts whose opinions were included in the sponsor's response.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised that the submission has not satisfactorily demonstrated adequate efficacy in the proposed indication for the following reasons:

Efficacy

The ACPM noted that, despite observational data and strong clinical acceptance, there are very limited data to show survival benefit in dialysis and non-dialysis patients resulting from reducing an elevated serum phosphate with phosphate binders.

Overall, the clinical efficacy analyses results failed the proof of concept that the use of Fosrenol for 8 weeks was associated with a reduction of serum phosphate level down to the pre-defined and guidelines recommended level in patients with Stage 3 or 4 CKD who were not on dialysis. The results showed that Fosrenol was associated with some reduction of serum phosphate level in the targeted patient population. There was also no added clinically significant beneficial effect on serum calcium phosphate product and iPTH levels.

This study may have been underpowered to begin with, which was compounded by the problem of the number of protocol violators. The study submitted, was a phase II proof of concept study in Stage 3 and 4 CKD patients not on dialysis whereas the indication sought included CKD 5 (not on dialysis) patients and the results would require extrapolation.

Similarly, the basis upon which the dosage guidelines in the Product Information (at present those for Stage 5 CKD patients on dialysis) may be extrapolated to cover patients with Stages 3 or 4 CKD not on dialysis has not been clarified.

Safety

Although the sample size of the study was small the safety results of study SPD405-206 showed that the most common adverse events were nausea and vomiting. This is consistent with the safety results from the phase III trials presented in the PI.

The ACPM was of the view that as the study did not contribute pertinent evidence for use in the currently approved indication then it should not be incorporated into the Product Information (PI). Nonetheless, the committee endorsed the remaining amendments to the PI which had been made by the various evaluators and by the Delegate.

Outcome

The sponsor withdrew the application and the TGA approved changes to the product information.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

FOSRENOL®

500 mg, 750 mg and 1000 mg chewable tablets

NAME OF THE MEDICINE

Lanthanum carbonate hydrate
$La_2(CO_3)_3.xH_2O$ = 457.85 (anhydrous), on average x = 4.5 moles of water.
CAS Registry Number: 54451-24-0

DESCRIPTION

FOSRENOL (lanthanum carbonate hydrate) has been developed as a dietary phosphate-binding agent. Phosphate absorption from the gastrointestinal tract is effectively decreased by the formation of highly insoluble complexes that are largely unable to pass through the wall of the gastrointestinal tract and are eliminated by excretion.

FOSRENOL is presented as chewable tablets. Each tablet contains lanthanum carbonate hydrate corresponding to 500 mg, 750 mg or 1000 mg lanthanum. The tablets also contain the excipients dextrates, silicon dioxide and magnesium stearate.

PHARMACOLOGY

Pharmacodynamic Properties
FOSRENOL is indicated for the treatment of hyperphosphataemia. FOSRENOL contains lanthanum carbonate hydrate. The activity of lanthanum carbonate as a phosphate binder is dependent on the high affinity of lanthanum ions, which are released from the carbonate salt in the acid environment of the upper gastrointestinal tract, for dietary phosphate. Insoluble lanthanum phosphate is formed which reduces the absorption of phosphate from the gastro-intestinal tract.

Several studies have shown that lanthanum can be used to control hyperphosphataemia associated with chronic renal failure through dose titration and that effect is maintained with long-term use. A lower incidence of hypercalcaemia was reported with FOSRENOL (0.4%) compared with calcium-based binders (20.2%) in comparative studies.

Serum PTH concentrations may fluctuate depending on a patient's serum calcium, phosphate and vitamin D status. FOSRENOL has not been shown to have any direct effects on PTH secretion.

Pharmacokinetic Properties
As binding between lanthanum and dietary phosphorus occurs in the lumen of the stomach and upper small intestine, the therapeutic effectiveness of FOSRENOL is not dependent on levels of lanthanum in the plasma.

Lanthanum is present in the environment. Measurement of background levels in non-lanthanum treated chronic renal failure patients during Phase III clinical trials revealed

concentrations of <0.05 to 0.90 ng/mL in plasma, and <0.006 to 1.02 μg/g in bone biopsy samples.

Absorption
Lanthanum carbonate has low aqueous solubility (<0.01 mg/mL at pH 7.5) and is minimally absorbed following oral administration. Absolute oral bioavailability is estimated to be <0.002% in humans.

In healthy subjects, plasma AUC and C_{max} increased as a function of dose, but in a less than proportional manner, after single oral doses of 250 to 1000 mg lanthanum, consistent with dissolution-limited absorption. The apparent plasma elimination half-life in healthy subjects was 36 hours.

In renal dialysis patients dosed for 10 days with 1000 mg lanthanum 3 times daily, the mean (± sd) peak plasma concentration was 1.06 (± 1.04) ng/mL, and mean AUC_{last} was 31.1 (± 40.5) ng.h/mL. Regular blood level monitoring in 1707 renal dialysis patients taking lanthanum carbonate for up to 2 years showed no increase in plasma lanthanum concentrations over this time period.

Distribution
Orally administered lanthanum is distributed predominantly within the gastrointestinal tract. The small fraction absorbed is extensively bound to human plasma proteins (>99.7%), and binding is high capacity and non-specific. In long-term animal studies, at oral doses up to 17 times a human dose of 3000 mg/day, lanthanum concentrations in the majority of tissues were less than 1 μg/g. Concentrations in brain and cerebrospinal fluid (CSF) were below or around the assay quantification limit (0.01 μg/g for brain and 0.05 ng/mL for CSF) and median steady state concentrations were up to 8.2 μg/g in bone, 11.1 μg/g in liver and 2.2 mg/g in the stomach wall. Rodents, but not dogs, treated at doses 4 times the human dose of 3000 mg/day showed submucosal inflammation and epithelial hyperplasia of the stomach. No other adverse effects were associated with these concentrations. Lanthanum levels in these tissues dissipated very slowly after the cessation of oral dosing, with a half-life >26 weeks.

Metabolism
Lanthanum is not metabolised. Studies in chronic renal failure patients with hepatic impairment have not been conducted. In patients with co-existing hepatic disorders at the time of entry into Phase III clinical studies, there was no evidence of increased plasma exposure to lanthanum or worsening hepatic function after treatment with FOSRENOL for periods up to 2 years.

Elimination
Lanthanum is excreted mainly in the faeces (>90%) with only around 0.000031% of an oral dose excreted via the urine in healthy subjects.

CLINICAL TRIALS

A total of 1130 patients with chronic renal failure treated with maintenance haemodialysis or CAPD were studied in two phase II and two phase III studies (LAM-IV-202, 204, 301 and 302). Three studies were placebo controlled (1 fixed dose and 2 titrated dose designs) and one included calcium carbonate as an active comparator. During these studies, 1016 patients received lanthanum carbonate, 267 received calcium carbonate and 95 received placebo.

The first phase III study (301) was a two-part study designed to assess the reduction of serum phosphate by FOSRENOL compared to calcium carbonate. The study had 2 parts: Part 1 was a 5-week titration phase after randomization to FOSRENOL or calcium carbonate where

patients were titrated to a target phosphate level of 1.8 mmol/L. Part 2 was a 20-week maintenance phase where patients maintained their doses of binder and plasma phosphate levels assessed. The study endpoints were % patients achieving target phosphate levels at the end of the titration and maintenance periods. The plasma phosphate levels from this study are presented in Table 1. Serum phosphate levels were reduced to target levels of 1.8 mmol/L at the end of the 5 week titration period, in 58% of the lanthanum group compared with 70% of the calcium carbonate group. Following 25 weeks of treatment, the proportions controlled were 66% (lanthanum carbonate) and 64% (calcium carbonate).

Table 1: Plasma phosphate (mmol/L) levels in clinical study 301.

		Treatment Group			
Weeks on treatment	**Visit**	**Lanthanum**		**Calcium**	
		N	Mean (SD)	N	Mean (SD)
0	1	504	2.67 (0.66)	254	2.69 (0.63)
5 (Endpoint 1)[1]	6	453	1.87 (0.52)	209	1.66 (0.48)
25 (Endpoint 2)[2]	11	222	1.73 (0.46)	122	1.72 (0.48)

[1] Primary endpoint, after completion of titration phase
[2] Secondary endpoint, after completion of maintenance phase

The second Phase III study (302) was a double-blind, placebo controlled study designed to assess the maintenance in reduction in serum phosphate levels after an open-label titration phase with FOSRENOL to achieve a target phosphate concentration of 1.8 mmol/L. This was followed by a 4-week double-blind phase where patients were randomised to continue to receive FOSRENOL or a comparable number of placebo tablets. The endpoint of this study was the plasma phosphate concentrations after 4 weeks of treatment on FOSRENOL or placebo. A total of 93 patients completed the open-label phase and were randomised to FOSRENOL or placebo. The plasma phosphate levels at the end of the open-label titration and at each week of the double-blind study are presented in Table 2.

Table 2: Plasma phosphate levels (mmol/L) in clinical study 302.

	Treatment Group			
	Lanthanum		**Placebo**	
	N	Mean (SD)	N	Mean (SD)
End of Titration[1]	46	1.81 (0.54)	43	1.77 (0.48)
RMP Week 1	46	1.87 (0.54)	43	2.23 (0.54)
RMP Week 2	44	1.86 (0.48)	43	2.41 (0.55)
RMP Week 3	41	1.78 (0.45)	39	2.46 (0.65)
RMP Week 4	41	1.89 (0.50)	38	2.49 (0.61)
Study Endpoint[2]	**44**	**1.91 (0.53)**	**43**	**2.54 (0.63)**

[1] End of open-label titration phase (Randomisation)
[2] Study endpoint (LOCF) double-blind, placebo phase.
RMP = Randomised Maintenance Phase

A Phase II randomised, double-blind, placebo-controlled study (SPD405-206) was also conducted in chronic kidney disease stage 3 and 4 patients not undergoing dialysis but requiring treatment with phosphate binders. The primary endpoint was achievement of a target serum phosphate concentration of ≤1.49 mmol/L. Eighty patients were randomised to receive FOSRENOL vs 41 patients on placebo. The ITT population consisted of 56 patients on FOSRENOL vs 34 patients on placebo (there was a large number of discontinuations mainly due to patients' baseline not being above the target serum phosphate level after the washout phase). Patients were treated for up to 8 weeks. At the end of the study the mean dose of FOSRENOL was 2645.3 mg/day. 44.6% of FOSRENOL patients had achieved the target phosphate concentration compared to 26.5% of patients on placebo. The difference was not statistically significant (p=0.12). The mean change from baseline to end of treatment for serum

phosphate in the Fosrenol group was -0.18 mmol/L compared to -0.06 mmol/L in the placebo group.

Hyperphosphataemia
Lanthanum has been demonstrated to be an effective binder of dietary phosphate for use in controlling the hyperphosphataemia of chronic renal failure. Multiple studies have shown that lanthanum can reliably be used to achieve serum phosphate reductions to target levels through dose titration and to effectively maintain control of serum phosphate levels with long-term use. Maintenance of target phosphate levels was shown to be similar between lanthanum and calcium treatments.

The lowest effective dose of lanthanum that is effective in the control of serum phosphate levels was established to be approximately 750 mg/day. Doses of up to 3000 mg lanthanum resulted in a reduction of serum phosphate to within target control levels in most patients.

No difference in level of control was observed between those patients on haemodialysis and those receiving CAPD. In addition no difference in the effectiveness of lanthanum carbonate administration was noted between patients under or over 65 years of age.

Effects on Bone
Overall, FOSRENOL and standard treatments, including calcium carbonate, produced similar effects on the bones of dialysis patients.

Results from histology and histomorphometry of human biopsy samples evaluated to date from the three clinical studies (Study 301 where patients had been treated with lanthanum carbonate for up to 4.5 years, Studies 303 and 307) showed no evidence of osteomalacia or other adverse bone pathology. In Study 303, a randomised study to investigate the effect of FOSRENOL with calcium carbonate, results showed that FOSRENOL produced marginally greater improvements towards normal values than calcium carbonate for many of the bone primary and secondary response variables in addition to the general improvements in bone growth and turnover parameters. In Study 307, a study where patients had been treated for 2 years, no statistical differences in bone parameters between patients randomised to receive standard therapy or FOSRENOL were observed. Analysis of data from paired bone biopsies (at baseline and at one or two years) in patients randomised to either FOSRENOL or calcium carbonate in Study 303 and patients randomised to either FOSRENOL or alternative therapy in Study 307, showed no differences in the development of mineralisation defects between the groups. An analysis of adverse events in the bone study participants in these studies did not show any increase in adverse events related to the musculoskeletal system, including fractures. FOSRENOL, therefore, does not appear to harm bone following treatment for up to 4.5 years.

INDICATIONS

Treatment of hyperphosphataemia in adults with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

CONTRAINDICATIONS

Hypersensitivity to lanthanum or any of the excipients in the product.
Hypophosphataemia.

PRECAUTIONS

Tissue deposition of lanthanum, particularly in bone, liver and the stomach wall, has been shown with FOSRENOL in animal studies. Deposition of lanthanum in bone has been studied (see Effects on Bone). Results from long-term studies (Studies 301, 303 and 307) demonstrated that bone lanthanum concentration had no apparent effect on bone health or treatment outcome for up to 4.5 years. There is no clinical data examining the potential deposition of lanthanum in other tissues. The long term clinical effects of lanthanum deposition in tissues are not known. The risk benefit of longer-term therapy with FOSRENOL should be considered.

The efficacy and safety of FOSRENOL has not been studied in children, therefore, the consequence of lanthanum deposition in growing bones is not known.

Patients with renal insufficiency may develop hypocalcaemia. FOSRENOL does not contain calcium. Serum calcium levels should therefore be monitored at the usual time intervals for this patient population and appropriate supplements given.

Lanthanum is not metabolised by liver enzymes but it is most likely excreted in the bile. Conditions resulting in a marked reduction of bile flow may be associated with incrementally slower elimination of lanthanum, which may result in higher plasma levels and increased tissue deposition of lanthanum (see PHARMACOLOGY, Pharmacokinetic Properties). Caution should therefore be exercised in these patients and monitoring of liver fucntion may be required.

Patients with acute peptic ulcer, ulcerative colitis, Crohn's disease or bowel obstruction were not included in clinical studies with FOSRENOL. Fosrenol is known to cause constipation (see Adverse Effects section) and therefore caution should be exercised in patients predisposed to bowel obstruction (e.g. previous abdominal surgery, peritonitis, etc).

Abdominal x-rays of patients taking lanthanum carbonate may have a radio-opaque appearance typical of an imaging agent.

Effects on Fertility

There are no human data on the effects of lanthanum carbonate on fertility. Lanthanum carbonate administered to female and male rats prior to and throughout mating at oral doses up to 2000 mg/kg/day (half the clinical exposure based on AUC at 3000 mg/day) did not alter mating or fertility.

Use in Pregnancy

Pregnancy Category B3

There was no evidence of teratogenicity in rats or rabbits following oral administration of lanthanum carbonate during the period of organogenesis at doses up to 2000 (rat) and 1500 (rabbit) mg/kg/day (0.5-1.2 times the clinical exposure based on AUC at 3000 mg/day). Increased implantation loss, and delayed skeletal ossification occurred in rabbits at ≥1500 mg/kg/day, in association with maternal toxicity. There are no adequate data from the use of FOSRENOL in pregnant women. The safety of lanthanum carbonate in human pregnancy has not been established. FOSRENOL should not be used during pregnancy unless the potential benefit justifies the potential risk.

Use in Lactation

There is some evidence that lanthanum can be excreted in human breast milk. The excretion of lanthanum in milk following oral treatment with lanthanum carbonate has not been studied in animals. Post-natal development was delayed in the offspring of rats receiving oral doses of lanthanum carbonate at 2000 mg/kg/day. Women taking FOSRENOL should stop breastfeeding.

Carcinogenicity
Lanthanum carbonate, at doses 13-times higher than the clinical dose of 3000 mg/day, caused a slight increase in gastric adenomas in mice. This response was considered to be an exacerbation of spontaneous stomach pathology and secondary to changes in the gastric environment caused by lanthanum carbonate administration. Gastric pathology was confined to rodents.

Genotoxicity
In vitro assays for gene mutations (bacteria and CHO cells) and *in vivo* studies for chromosomal or DNA damage did not provide evidence of genotoxic potential. An *in vitro* chromosome aberration assay in CHO cells had an equivocal outcome.

Interactions with other Medicines
The drug interaction profile of FOSRENOL is characterised by the potential of lanthanum to bind to drugs with anionic functions (e.g. carboxyl, carbonyl and hydroxyl groups).

Lanthanum carbonate may increase gastrointestinal pH.

It is recommended that compounds, which are known to interact with antacids, should not be taken within 2 hours of dosing with FOSRENOL (e.g. chloroquine, hydroxychloroquine and ketoconazole).

Serum levels of fat-soluble vitamins A, D, E and K, were not affected by FOSRENOL administration in clinical studies.

Lanthanum carbonate is not a substrate for cytochrome P450. *In vitro* tests indicate that no significant inhibition of the activities of the major human cytochrome P450 isoenzymes, CYP1A2, CYP2D6, CYP3A4, CYP2C9 or CYP2C19 is expected at therapeutic concentrations. Lanthanum is extensively bound in human plasma and isolated human plasma protein preparations, including albumin, transferrin and alpha-1-acid glycoprotein (99.7 to >99.9%).

Interaction with drugs such as tetracycline and doxycycline are theoretically possible and if these compounds are to be co-administered, it is recommended that they are not to be taken within 2 hours of dosing with FOSRENOL.

***In Vitro*- Interactions with other Medicines**
Gastric Fluid: The potential for a physico-chemical interaction (precipitation) between lanthanum and six commonly used medications (warfarin, digoxin, furosemide, phenytoin, metoprolol, and enalapril) was investigated in simulated gastric fluid. The results suggest that precipitation in the stomach of insoluble complexes of these drugs with lanthanum is unlikely.

The therapeutic activity of FOSRENOL depends on the acidity of the gastric environment. The potential for drugs which alter gastric acidity (for example proton-pump inhibitors) to alter the therapeutic activity of FOSRENOL has not been examined in trials but should be considered.

***In Vivo*- Interactions with other Medicines**
In healthy subjects, the absorption and pharmacokinetics of a single dose of 1000 mg of FOSRENOL is unaffected by co-administration of citrate. No clinically-relevant effects of lanthanum were found on the absorption and pharmacokinetic profiles of digoxin (0.5 mg),

metoprolol (100 mg), or warfarin (10 mg) in healthy subjects co-administered lanthanum carbonate (three doses of 1000 mg on the day prior to exposure and one dose of 1000 mg on the day of coadministration). Potential pharmacodynamic interactions between lanthanum and these drugs (e.g. bleeding time or prothrombin time) were not evaluated. None of the drug interaction studies was done with the maximum recommended therapeutic dose of lanthanum carbonate. No drug interaction studies assessed the effects of drugs on phosphate binding by lanthanum carbonate.

Co-administration of FOSRENOL with quinolone antibiotics may reduce the extent of absorption as a result of complex formation. The bioavailability of oral ciprofloxacin was decreased by approximately 50% when taken with FOSRENOL in a single dose study in healthy volunteers. It is recommended that oral quinolone formulations are taken at least 2 hours before or 4 hours after FOSRENOL.

Phosphate binders (including FOSRENOL) have been shown to reduce the absorption of levothyroxine. The bioavailability of levothyroxine was decreased by approximately 40% when taken together with FOSRENOL. Consequently, thyroid hormone replacement therapy should not be taken within 2 hours of dosing with FOSRENOL and closer monitoring of TSH levels is recommended in patients receiving both medicinal products.

Effects on Ability to Drive and use Machines
Fosrenol may induce dizziness and vertigo, which may impair the ability to drive and use machinery.

ADVERSE EFFECTS

The safety of FOSRENOL for use in patients with end-stage renal failure (ESRF) in both hemodialysis and peritoneal dialysis patients was initially examined in three short-term, placebo-controlled, double-blind studies, three long-term, comparator-controlled studies, and three long- term open-label studies. These studies have provided a total safety database of 1754 patients treated with lanthanum carbonate hydrate and represents a mean exposure of 272.1 days (median 184.0 days, range 1-1123 days).

The most common adverse events (≥5% in either treatment group) in two long-term open-label phase III trials that included 1215 patients treated with lanthanum carbonate hydrate and 944 with alternative therapy are detailed in Table 3.

The adverse events in the long-term, open label, active controlled, study of FOSRENOL vs. alternative therapy (Study 307) have been adjusted for mean exposure differences between the treatment groups (with a mean exposure of 1.0 years on lanthanum and 1.4 years on alternative therapy). The adjustment for mean exposure was achieved by multiplying the observed adverse event rates in the alternative therapy group by 0.74.

Table 3. Incidence of Treatment-Emergent Adverse Events that occurred in ≥5% of Patients (in Either Treatment Group) and in Both Comparative Studies 307 and 301.

	Study 307 %		**Study 301** %	
	FOSRENOL (N=682)	Alternative Therapy* Adjusted Rates (N=677)	FOSRENOL (N=533)	Calcium Carbonate (N=267)
Nausea	37	29	16	13
Vomiting	27	22	18	11
Dialysis graft complication	25	24	3	5

	Study 307 %		Study 301 %	
	FOSRENOL (N=682)	Alternative Therapy* Adjusted Rates (N=677)	FOSRENOL (N=533)	Calcium Carbonate (N=267)
Diarrhoea	24	24	13	10
Headache	22	21	5	6
Dialysis graft occlusion	21	21	4	6
Abdominal pain	17	18	5	3
Hypotension	16	18	8	9
Constipation	15	14	6	7
Bronchitis	5	7	5	6
Rhinitis	4	6	7	6
Hypercalcaemia	4	8	0	20

***** alternative therapy included calcium carbonate, calcium acetate, sevelamer, aluminium based phosphate binders

Overall, approximately 24% of all ESRF patients who participated in these_clinical studies reported a drug related adverse reaction, as determined by the investigator. No individual ADR was reported at a frequency greater than 10%. The most commonly reported adverse drug reactions, with the exception of headache, are gastrointestinal in nature. Gastrointestinal reactions were the most common leading to discontinuation. Gastrointestinal reactions can be minimized by taking FOSRENOL with food and generally abated with time with continued dosing (see Dosage and Administration).

Table 4 presents the very common (≥1/10), common (>1/100, <1/10) and uncommon (>1/1,000 to <1/100) reactions reported~~:~~ with FOSRENOL in clinical trials to date.

Table 4. Adverse Drug Reactions Associated with FOSRENOL

Organ System	Very Common Reactions	Common Reactions	Uncommon Reactions
Infections and Infestations			Gastroenteritis, laryngitis
Blood and lymphatic system disorders			Eosinophilia
Endocrine disorders			Hyperparathyroidism
Metabolism and nutrition disorders		Hypocalcaemia	Hypercalcaemia, hyperglycaemia, hyperphosphataemia, hypophosphataemia, anorexia, appetite increased
Nervous system disorders	Headache		Dizziness, taste alteration
Ear and Labyrinth disorders			Vertigo
Gastrointestinal disorders	Abdominal pain, diarrhoea, nausea, vomiting	Constipation, dyspepsia, flatulence,	Eructation, indigestion, irritable bowel syndrome, dry mouth, oesophagitis, stomatitis, stools loose, tooth disorder, gastro-intestinal disorder NOS*

Organ System	Very Common Reactions	Common Reactions	Uncommon Reactions
Skin and subcutaneous tissue disorders			Alopecia, sweating increased
Musculoskeletal and connective tissue disorders			Arthralgia, myalgia, osteoporosis
General disorders			Asthenia, chest pain, fatigue, malaise, peripheral oedema , pain, thirst
Investigations			Elevated Aluminum, increase in GGT, increases in hepatic transaminases, alkaline phosphatase increased, weight decrease

* Not otherwise specified

Post marketing experience: During post-approval use of Fosrenol, cases of allergic skin reactions (including skin rashes, urticaria and pruritus) have been reported which show a close temporal relationship to lanthanum carbonate therapy. In clinical trials, allergic skin reactions were seen in both Fosrenol and placebo/active comparator groups at a frequency of very common (≥1/10).

Although there have been a number of additional isolated reactions reported, none of these reactions are considered unexpected in this patient population.

Transient QT changes have been observed but these were not associated with any adverse events.

DOSAGE AND ADMINISTRATION

Patients should adhere to recommended diets in order to control phosphate and fluid intake.

FOSRENOL tablets must be chewed completely before swallowing. The tablets may be crushed as an aid to chewing. Intact tablets must not be swallowed whole.

Adults, including elderly (>65 years)
For patients taking FOSRENOL for the first time, the starting dose may be determined individually based on serum phosphate concentration as indicated below:

Pre-treatment serum phosphate level	Recommended initial daily dose of FOSRENOL
>1.8 and ≤2.4 mmol/L	750 mg
>2.4 and ≤2.9 mmol/L	1500 mg
>2.9 mmol/L	2250 mg

FOSRENOL should be taken with or immediately after food, with the daily dose divided between meals, i.e. three times daily. Serum phosphate levels should be monitored and the dose of FOSRENOL titrated every 2-3 weeks until an acceptable serum phosphate level is reached, with regular monitoring thereafter.

Control of serum phosphate level has been demonstrated at doses from 750 mg with most patients achieving acceptable serum phosphate levels at 1500 – 3000 mg lanthanum per day.

Hepatic impairment
The effect of hepatic impairment on FOSRENOL pharmacokinetics has not been formally assessed. Due to its mechanism of action and the lack of liver metabolism, doses in hepatic impairment should not be modified, but patients should be monitored carefully (see PRECAUTIONS and PHARMACOLOGY, Pharmacokinetic Properties).

Children
The safety and efficacy of FOSRENOL has not been established in patients below the age of 18 years.

OVERDOSAGE

The symptoms associated with overdose are known adverse reactions such as headache, nausea and vomiting. As FOSRENOL is only pharmacologically active within the gut, supportive therapy is recommended for overdose.

For advice on the management of overdosage, please contact the Poisons Information Centre (telephone 13 11 26).

PRESENTATION

FOSRENOL is supplied as chewable tablets in white cylindrical HDPE bottles fitted with polypropylene caps and is available in the following presentation and pack sizes:

FOSRENOL 500 mg: White, round, bevel-edged flat tablets embossed with ‘S405/500’ on one side; 45 tablets per bottle; 2 bottles per pack (pack of 90 tablets).

FOSRENOL 750 mg: White to off-white round, flat bevel-edged tablets embossed on one side with ‘S405’ above ‘750’; 15 tablets per bottle; 6 bottles per pack (pack of 90 tablets).

FOSRENOL 1000 mg: White to off-white round, flat bevel-edged tablets embossed on one side with ‘S405’ above ‘1000’; 15 tablets per bottle; 6 bottles per pack (pack of 90 tablets).

STORAGE CONDITIONS

Store below 25˚C.

NAME AND ADDRESS OF THE SPONSOR

Shire Australia Pty. Limited
Level 3
78 Waterloo Rd
North Ryde NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF APPROVAL

Date of TGA approval: 8 December 2011

Therapeutic Goods Administration

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Reference/Publication #