CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204734Orig1s000

MEDICAL REVIEW(S)

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 204734

Submission Date(s): 02/28/2013, 04/10/2013, 7/31/2014

Applicant: Shire Development Inc.

Product: Fosrenol Oral Powder

Reviewers: Divya Menon-Andersen PhD and Melanie Blank, MD

Date of Review: 9/13/2014

Covered Clinical Study (Name and/or Number): SPD405-127;"A Phase 1 Pharmacodynamic Equivalence Study Comparing Urinary Phosphate Excretion and Plasma Lanthanum Pharmacokinetics for a Lanthanum Carbonate Granule Formulation and Chewable Tablets Administered to Healthy Adult Subjects"

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 6		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (NOT APPLICABLE)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (NOT APPLICABLE)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ (NOT APPLICABLE)

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/s/

MELANIE J BLANK
09/18/2014

Division Director Review

Date	24 December 2013
From	Norman Stockbridge
Subject	Division Director memo
NDA/BLA # **Supplement#**	204734 000
Applicant	Shire Development LLC
Date of Submission	28 February 2013
PDUFA Goal Date	28 December 2013
Proprietary Name / **Established (USAN) names**	Fosrenol Lanthanum carbonate
Dosage forms / Strength	750, 1000 mg oral powder
Proposed Indication(s)	1. Control of serum phosphorus in patients with end stage renal disease.
Recommended:	Complete Response

I refer to reviews of CMC (Soldatova; 10 October 2013, 23 December 2013), Biopharmaceutics (Eradiri; 25 October 2013, 21 December 2013), and clinical pharmacology and clinical (Menon Andersen and Blank; 28 October 2013). There is also a CDTL memo (Menon Andersen; 21 December 2013), with which I am in complete agreement.

CMC site inspections are complete. There are no unresolved CMC issues (other than biopharmaceutics, described separately below).

The only clinical study was a two-period crossover study conducted in 72 normal volunteers, 4 days per period, comparing approved lanthanum carbonate tablets and equimolar lanthanum carbonate powder for effects on lanthanum absorption and phosphate excretion (indirectly assessed by effect on urinary phosphate). Results showed similar effects on lanthanum exposure and urinary phosphate. Adverse effects were similar in nature on the two treatments, but gastrointestinal adverse effects were more common (18% vs. 7%) on the powder.

The initial review of the biopharmaceutics package resulted in essentially a complete resubmission on 18 November 2013. Dr. Eradiri did well to complete a review of this material in time for an action by the User Fee Goal Date. Unfortunately, the resubmitted package does not support approval. The sponsor developed its dissolution testing procedure in a setting of (b) (4)% Tween 80 (surfactant to keep the powder from floating) and a paddle speed of (b) (4)RPM, but neither of these rather extreme conditions has been adequately justified by the applicant's data. Indeed, it rather appears that (b) (4)% Tween 80 and (b) (4)RPM might suffice. Once the method has been established and discriminatory criteria are set, the revised method has to be applied to stability batches.

Draft labeling has been prepared. The sole issue preventing approval is the dissolution testing.

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NORMAN L STOCKBRIDGE
12/24/2013

Cross-discipline team leader review

Date	December 21, 2013
From	Divya Menon-Andersen
Subject	Cross-discipline team leader review
NDA #	204734
Applicant	Shire Development LLC
Date of submission	02/28/2013
PDUFA goal date	12/28/2013
Propriety name/ Established (USAN) name	Fosrenol oral powder / lanthanum carbonate powder
Dosage form / strength	(b) (4) / 750 and 1000 mg
Proposed indication	To reduce serum phosphate in patients with end stage renal disease (ESRD)
Recommended	Complete response

Materials consulted

Review discipline, date	Primary reviewer
CMC, 10/10/2013	Lyudmila Soldatova
Biopharmaceutics, 10/25/2013, 12/20/2013	Okpo Eradiri
Joint clinical pharmacology - Clinical, 10/28/2013	Divya Menon-Andersen (clinical pharmacology) Melanie Blank (safety)
OSE/OMEPRM, 10/07/2013	Kimberley DeFronzo

CMC= Chemistry Manufacturing and Controls, OSE= Office of Surveillance and Epidemiology, OMEPRM = Office of Medication Error Prevention and Risk Management

Introduction

In this submission Shire Development LLC is seeking authorization to market a (b) (4) formulation of Fosrenol (lanthanum carbonate), a phosphate binder formulated as a chewable tablet, for the indication to reduce serum phosphate in patients with end stage renal disease (ESRD). Post-marketing cases of tooth damage and gastrointestinal occlusion associated with the use of Fosrenol chewable tablet were reported (dated 01/04/2011, 10/22/2010). The applicant developed a (b) (4) formulation with a view to improving compliance.

Background

Fosrenol chewable tablet was approved under NDA 21468 in 2004 for the indication to reduce serum phosphate in patients with end stage renal disease (ESRD). The current application is submitted under the provisions of 505(b)(1) of the FD&C Act and 21 CFR 314.54, and relies on the Agency's previous findings of safety and effectiveness for Fosrenol chewable tablet (lanthanum carbonate, NDA 21-468). The recommended starting total daily dose is 1500 mg, given in three divided doses with meals. The dose can be up-titrated based on serum phosphate levels at two to three week intervals. The same dosage and dosing regimen is proposed for Fosrenol oral powder.

The submission contains original data to support the chemistry, manufacturing and controls, biopharmaceutics and the clinical sections of the NDA. A single pharmacokinetic / pharmacodynamic study (study SPD045-127) was submitted to demonstrate pharmacodynamic equivalence between Fosrenol chewable tablet and Fosrenol oral powder.

CMC

The CMC reviewer recommended a Complete Response because the dissolution method and acceptance criteria were found to be unacceptable by the ONDQA biopharmaceutics discipline reviewer. The reviewer noted that an overall acceptable Office of Compliance recommendation for manufacturing facilities was issued. Also, in reference to the established name, a mismatch exception was granted for this label (see point 4 below). The key findings are listed below.

1. The two dosage strengths of Fosrenol ® (lanthanum carbonate) Oral Powder contain 1431 and 1908 mg lanthanum carbonate hydrate equivalent to 750 mg and 1000 mg lanthanum, respectively.
2. The composition of the two strengths of the drug product, 750 mg and 1000 mg, (b) (4) filled at different fill weights to achieve the required dose. Except for addition of the (b) (4) in the chewable tablet formulation, the components of lanthanum carbonate oral powder (b) (4) in the marketed Fosrenol® chewable tablet and are of compendial quality, USP/NF.
3. Drug substance used to manufacture the clinical batch, the primary registration stability batches and the validation batches for lanthanum carbonate oral powder drug product meet the approved drug substance specifications.
4. The established name, lanthanum carbonate, does not match the dosage strength expressed as the amount of elemental lanthanum, 750 mg or 1000 mg (prohibited mismatch in labeling). CDER Drug Nomenclature Policy Group, USP liaison for

FDA, DMEPA, and the clinical reviewer were consulted on this issue, and the ONDQA Precedence Committee granted the mismatch exception for this drug label on 20-Aug-2013. The applicant was advised to revise the labels by addition of the equivalence statement reflecting the quantity of lanthanum carbonate equals to the dosage strengths of 750 mg and 1000 mg.

Biopharmaceutics

The biopharmaceutics reviewer recommended a Complete Response because the dissolution method and acceptance criteria for batch release and stability testing were unacceptable. The key findings are listed below.

1. The proposed method incorporating (b) (4)% Tween 80 in the dissolution medium lacks discriminatory power. Lower concentrations of the surfactant are likely to achieve this.
2. The choice of agitation speed ((b) (4)rpm) was not adequately substantiated.
3. The process (b) (4) used to evaluate the discriminatory power of the proposed dissolution method was not considered relevant and therefore unacceptable.

Comment: Dissolution testing is part of a battery of tests that together characterize product quality and ensure product performance. Therefore, the unavailability of an adequate dissolution test has implications for product quality.

Nonclinical pharmacology and toxicology

The applicant references the Fosrenol chewable tablet in support of the nonclinical pharmacology and toxicology sections in this submission.

Clinical pharmacology

The clinical pharmacology reviewer[1] concluded that Fosrenol oral powder is similar to Fosrenol chewable tablet. There are no outstanding clinical pharmacology issues that preclude approval. An agreement has not been reached with the applicant about final labeling. The key findings are listed below.

1. Daily average urinary phosphate excretion following administration of Fosrenol oral powder was similar to that following administration of Fosrenol chewable tablet.
2. While lanthanum absorption was increased in the subjects when they received the (b) (4) by 30%, the absolute increase in absorption is very low (increase from ~ 0.002% absorption to ~0.003%).

Clinical microbiology

There are no specific clinical microbiology topics in the current submissions.

Clinical/statistical – efficacy

The clinical reviewer concluded that Fosrenol oral powder appears to be similar to Fosrenol chewable tablet in its effect of urinary phosphate excretion and systemic exposure to lanthanum. The submission does not contain additional efficacy data.

[1] CDTL and Clinical Pharmacology reviewer are the same

Safety

The clinical reviewer concluded that the incidence of gastrointestinal adverse events for Fosrenol oral powder is higher than for Fosrenol chewable tablet and that this should be reflected in the label. There are no outstanding safety issues that preclude approval. An agreement has not been reached with the applicant about final labeling. The key findings and conclusions are listed below.

1. The incidence of gastrointestinal adverse events was higher for Fosrenol oral powder (18.3%) than for Fosrenol chewable tablets (6.6%). These events occurred mostly during the first period suggesting that tolerability to both formulations improves upon repeat administration.
2. All adverse events were nonserious, the majority were mild, representing known gastrointestinal system organ class (SOC) acute drug reactions for lanthanum carbonate chewable tablets (e.g. nausea, abdominal pain upper, abdominal pain, abdominal discomfort, diarrhea, dyspepsia, epigastric discomfort, and constipation).
3. The increase in gastrointestinal adverse events for subjects on the oral (b) (4) formulation should be included in the new Fosrenol label.

Advisory committee meeting

This submission was not a subject of an advisory committee meeting.

Pediatrics

A waiver of pediatric studies was requested by the applicant and granted based on the observations that (1) lanthanum deposits in bone (2) no nonclinical assessment would be adequately reassuring of the long-term consequences for developing bone.

Other relevant regulatory issues

There are no other relevant regulatory issues.

Labeling

Relevant sections of the existing label for Fosrenol chewable tablets were updated to include information pertaining to Fosrenol oral powder and found to be acceptable by the primary reviewers.

Recommendations / risk-benefit assessment

Recommendation

The recommended regulatory action is Complete Response based on the findings and recommendations of the biopharmaceutics and CMC discipline reviews.

Risk-benefit assessment

The application does not contain data to evaluate risk/benefit of Fosrenol oral powder. However, because it was shown to be similar to the chewable tablet in its effect on urinary phosphate excretion and systemic exposure to lanthanum, the risk/benefit profile of Fosrenol oral powder is not expected to be significantly different from that of Fosrenol

chewable tablet. Additionally, because of the nature of the dosage form, lower probability of tooth damage and gastrointestinal occlusion can be expected.

There are no recommendations for post-marketing risk evaluation and mitigation strategies.

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DIVYA MENON ANDERSEN
12/21/2013

JOINT CLINICAL PHARMACOLOGY AND CLINICAL REVIEW

NDA Number	204734
Submission Type and date	Original
Applicant Name	Shire Development Inc
Submission Dates	02/28/2013, 04/10/2013
Brand Name	Fosrenol oral powder
Generic Name	Lanthanum carbonate oral powder
Therapeutic class	Phosphate binder
Dosage Form	(b) (4)
Dosage Strengths	750 mg, 1000 mg
Proposed Indication and dosing regimen	To reduce serum phosphate in patients with end stage renal disease
OCP and OND Divisions	Division of Clinical Pharmacology 1 Division of Cardiovascular and Renal Products
Primary Reviewers	Divya Menon-Andersen PhD (Clinical Pharmacology), Melanie Blank MD (Safety)
Team Leaders	Raj Madabushi PhD, Aliza Thompson MD

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1 EXECUTIVE SUMMARY

In this 505(b)(1) submission Shire Development LLC is seeking approval of Fosrenol oral powder (lanthanum carbonate) for the indication to reduce serum phosphate in patients with end stage renal disease (ESRD). The application relies on the Agency's previous findings of safety and effectiveness for Fosrenol chewable tablet (lanthanum carbonate, NDA 21-468). Fosrenol chewable tablets are indicated to reduce serum phosphate in patients with ESRD. The recommended starting total daily dose is 1500 mg, given in three divided doses with meals. The dose can be up-titrated based on serum phosphate levels at two to three week intervals. The same dosage and dosing regimen is proposed for Fosrenol oral powder. Doses up to 4500 mg have been evaluated in clinical studies conducted with Fosrenol chewable tablets, but most patients required a total daily dose between 1500 mg and 3000 mg to reduce plasma phosphate levels to 6 mg/dL. Doses were generally titrated in increments of 750 mg/day.

A single pharmacokinetic/pharmacodynamic (PK/PD) study conducted in healthy subjects was submitted to demonstrate pharmacodynamic equivalence between the two dosage forms and to establish a bridge between Fosrenol oral powder and Fosrenol chewable tablet.

1.1 Recommendations

The results of the PK/PD study demonstrate pharmacodynamic equivalence between Fosrenol oral powder and Fosrenol chewable tablet, thereby establishing a bridge between the new formulation and Fosrenol chewable tablet approved under NDA 21-468. These data support approval of Fosrenol oral powder for the indication to reduce serum phosphate in patients with ESRD.

1.2 Phase 4 Commitments

A waiver of pediatric studies was requested by the applicant and granted. There are no phase 4 commitments.

> *REVIEWER'S COMMENT(S): On October 9, 2013, the applicant's request for a waiver for pediatric studies was presented to the PeRC committee. The committee noted that no calcium-free phosphate binder is currently approved for use in children with ESRD and was not inclined to agree with the waiver.*
>
> *When Fosrenol was originally approved on October 26th, 2004, a pediatric waiver was granted because of concern for potential bone toxicity since lanthanum is incorporated into developing bone. The results of subsequent animal toxicity studies and human studies were inconclusive in characterizing the overall hazard, if any, for developing bone.*
>
> *After considering the absence of convincing evidence of bone safety, the committee decided that it is unsafe to study Fosrenol in children .*
>
> *The PeRC committee originally recommended deferring the pediatric studies while the applicant completed more animal studies to reassure us of the safety of studying Fosrenol in children.*

However, upon further discussion between the chair of PeRC and DCRP, it was decided that no non-clinical assessment would be adequately reassuring of the long-term consequences of even relatively short (months to a few years) exposure in children. For this reason, the decision was made to grant the pediatric study waiver.

1.3 Summary of Important Review Findings

The key findings are listed below.

- Daily average urinary phosphate excretion following administration of Fosrenol oral powder was similar to that following administration of Fosrenol chewable tablet.
- While lanthanum absorption was increased in the subjects when they received the (b) (4) by 30%, the absolute increase in absorption is very low (increase from ~ 0.002% absorption to ~0.003%). This minimal absolute increase in lanthanum absorption with Fosrenol oral powder is not likely to result in any concerning clinical consequences.
- The incidence of gastrointestinal adverse events was higher for Fosrenol oral powder (18.3%) than for Fosrenol chewable tablets (6.6%). These events occurred mostly during the first period suggesting that tolerability to both formulations improves upon repeat administration. All adverse events were non-serious, the majority were mild, representing known gastrointestinal system organ class (SOC) acute drug reactions for lanthanum carbonate chewable tablets (e.g. nausea, abdominal pain upper, abdominal pain, abdominal discomfort, diarrhea, dyspepsia, epigastric discomfort, and constipation). The increase in gastrointestinal adverse events for subjects on the oral (b) (4) formulation should be included in the new Fosrenol label.

2 INTRODUCTION AND REGULATORY BACKGROUND

Fosrenol oral powder (lanthanum carbonate) is a (b) (4) formulation of Fosrenol chewable tablet, formulated with a view to increasing compliance amongst patients who have difficulty chewing. The chewable tablet was approved in 2004 for use in treatment of hyperphosphatemia in patients with end stage renal disease. The applicant Shire Development LLC is seeking approval of this new formulation via the 505(b)(1) pathway, and the application relies on the Agency's previous findings of safety and effectiveness for Fosrenol chewable tablet (NDA 21-468).

The submission contains original data to support the chemistry, manufacturing and controls, and the clinical sections of the NDA. A single pharmacokinetic / pharmacodynamic study (study SPD045-127) was submitted to demonstrate pharmacodynamic equivalence between Fosrenol chewable tablet and Fosrenol oral powder.

2.1 Product information

Fosrenol oral powder will be available in strengths of 750 and 1000 mg (elemental lanthanum) packaged in 'stick-packs'. The product is intended to be mixed with a small quantity of soft food (such as a tablespoon of applesauce) before administration.

2.2 Summary of pre-submission regulatory activity related to submission

The Division accepted the applicant's proposal to cross-reference Fosrenol chewable tablet (NDA 21-468) in support of safety and efficacy for the oral (b) (4) formulation and was in agreement with the applicant on the content of the proposed submission (DARRTS date 11/06/2012).

3 REVIEW OF PK/PD

Study protocol number SPD405-127

Study dates 01/28/2009 to 06/22/2009

Study site West Coast Clinical Trials, LLC, 5630 Cerritos Avenue, Cypress, CA 90630

Title A Phase 1 pharmacodynamic equivalence study comparing urinary phosphate excretion and plasma lanthanum pharmacokinetics for a lanthanum carbonate (b) (4) formulation and chewable tablets administered to healthy adult subjects.

3.1 Objective

To establish pharmacodynamic bioequivalence between lanthanum carbonate (b) (4) and lanthanum carbonate chewable tablets using average daily urinary phosphate excretion over three days as the pharmacodynamic endpoint.

3.2 Study design

This was an open-label, randomized, two period crossover study, with a washout of at least 14 days between treatments, conducted in healthy individuals.

Eligibility criteria were reviewed and confirmed during the screening period (within 28 days prior to receiving first dose). Screening procedures included a complete physical examination, 12-lead ECGs, vital signs, blood and urine chemistry, and review of concomitant medication. Study subjects remained in the study center 3 days prior to receiving the first dose of the study medication until day 6 of the study. A follow-up contact (by phone/in clinic) was scheduled for approximately seven days after receiving the final dose of the study medication.

During period 1 of the study subjects received 1000 mg tid of Fosrenol chewable tablet or (b) (4) for three days. A single dose of 1000 mg was administered on day 4 (see **Figure 1** below). Treatments were crossed over during period 2 of the study.

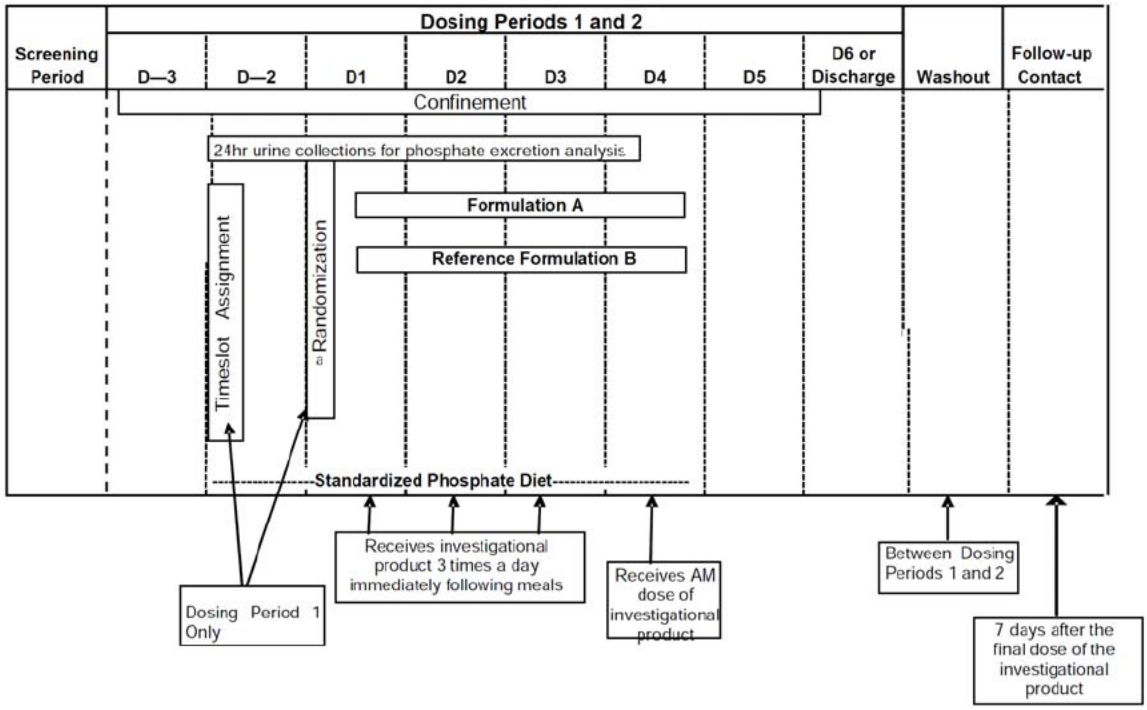

Figure 1 Schematic of the study design.

All subjects received a standardized phosphate controlled diet[1] starting with the morning meal two days prior to receiving the first dose of the study medication until day 4 of the study.

3.2.1 Study medication

Dosage Form	Lanthanum carbonate (b) (4)	Fosrenol® chewable tablet
Dosage Strength	1000 mg	1000 mg
Batch #	807012	A38683B
Administration	Oral	Oral

All study medication was administered *tid* immediately following consumption of a meal. Following this the subjects drank 240 mL distilled water. (b) (4) (test study medication) were sprinkled over one tablespoon of apple sauce and administered within 30 seconds. Subjects receiving the chewable tablet (reference study medication) were instructed to completely chew the tablet before swallowing. They received one tablespoon of applesauce immediately afterwards.

Reviewer's comment: The drug product is intended to be taken with meals sprinkled over a small portion of food. ESRD patients are not required to drink 240 mL of water immediately afterwards. Because the same quantity of water was administered in both treatment arms in this study in healthy individuals, the comparison is valid. Clinical pharmacology studies in the Fosrenol chewable tablet development program were conducted in this manner.

[1] Daily PO_4^{3-} intake of ~ 1300 mg divided over three meals.

3.2.2 PK/PD assessments

Pharmacodynamic assessments Urine was collected starting two days prior to dosing until 30 minutes after the morning meal on day 4 in 24 h collection periods.

Pharmacokinetic assessments Blood samples were collected at pre-dose on study days 1, 2, 3 and 4. Additional samples were collected on day 4 at 3, 4, 5, 6, 8, 12, 18, 24, 36 and 48 hours post dose.

3.3 Data analysis methods

The primary pharmacodynamic variable was the average daily urinary phosphate excretion over three days. The difference between the test and reference formulation in average daily urinary phosphate excretion (LS means and 90% CI) was estimated and compared with a reference interval representing ±20% of the reference formulation (LS means). Pharmacodynamic equivalence was to be claimed if the 90% CI was completely contained within the reference interval.

In the pharmacodynamic analysis set, urinary phosphate levels below the LOQ were set to half LOQ and only subjects who had consumed ≥95 % of their meals were included.

3.4 Results

3.4.1 Study Population

Of the 72 subjects randomized, 56 completed the study. Amongst the non-completers, one subject discontinued because of an adverse event (vomiting following administration of first dose), two were lost to follow up and 13 subjects discontinued the study for reasons listed under 'other'. These reasons were - withdrawal of consent (6 subjects), difficulty collecting urine (5 subjects), meal non-compliance (1 subject), and use of prohibited medication (1 subject). Summary demographics of the study subjects are presented in **Table 1**.

Table 1 Study population demographics

Randomized/Completed/ Discontinued because of AE	72/56/1*
Age (range) years	31.4 (19-54)
Male/Female	52/20
Race	
Caucasian	42
Black	26
Asian	3
Other	1

* Please see section 4.2.1 for information on dropouts because of AEs.

Pharmacokinetic results

Peak plasma concentrations of lanthanum were observed at about 4 hour following oral administration for both formulations. The plasma time course of lanthanum on day 4 following administration of (b) (4) or chewable tablet appeared similar (see **Figure 2** below**)**.

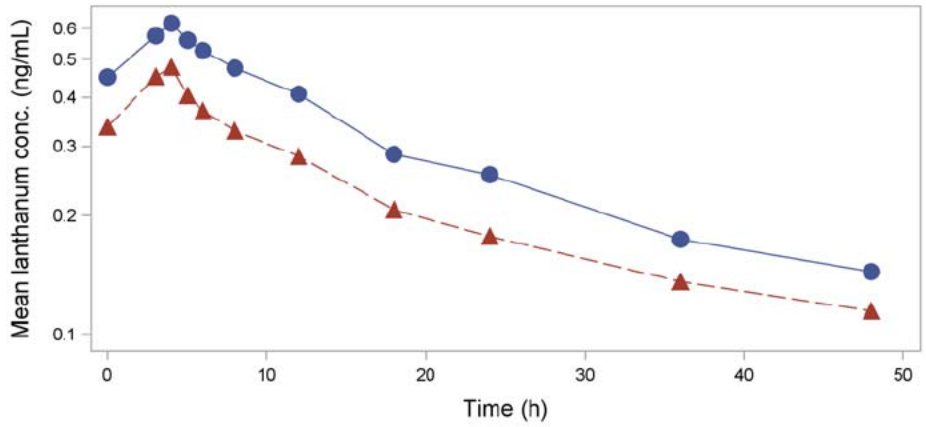

Figure 2 Mean plasma lanthanum concentration time course following oral administration of lanthanum carbonate [(b) (4)] (●) or chewable tablets (▲) 1000 mg *tid* for 3 days

Also, as presented in **Figure 3** systemic exposure (AUC and C_{max}) to lanthanum was higher following administration of [(b) (4)] as compared to chewable tablets.

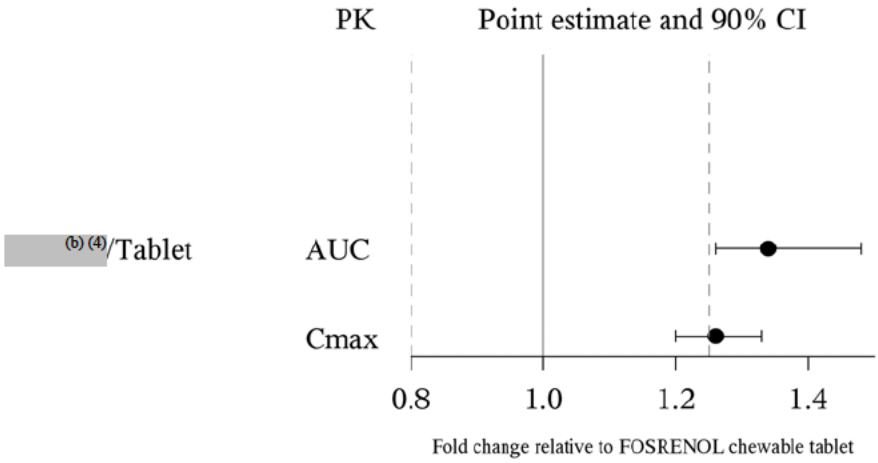

Figure 3 Total and peak systemic exposure to lanthanum following administration of lanthanum carbonate [(b) (4)] is 34 and 26%, respectively, higher than that following administration of Fosrenol chewable tablet.

Reviewer's comment: The significance of the above observation should be interpreted in the following context.

(1) Absolute bioavailability of lanthanum following administration of the chewable tablet is ~ 0.00127. Further, as is typical of drugs that are poorly absorbed, the pharmacokinetics of lanthanum exhibit high between subject variability (%CV ~ 60).

*(2) A comparison of lanthanum exposure observed in study 127 to that observed in a previously conducted study (study 131, which was submitted to IND 55054 in 2010, reviewed and judged acceptable) is presented in **Figure 4**. Study 131 was conducted using the same dose, formulation, study design and procedures. As*

seen in Figure 4, AUC_{0-48} for lanthanum observed following administration of the (b) (4) *formulation while higher than AUC_{0-48} for the chewable tablet in study 127, is in the range of exposures seen following administration of the chewable tablet in study 131.*

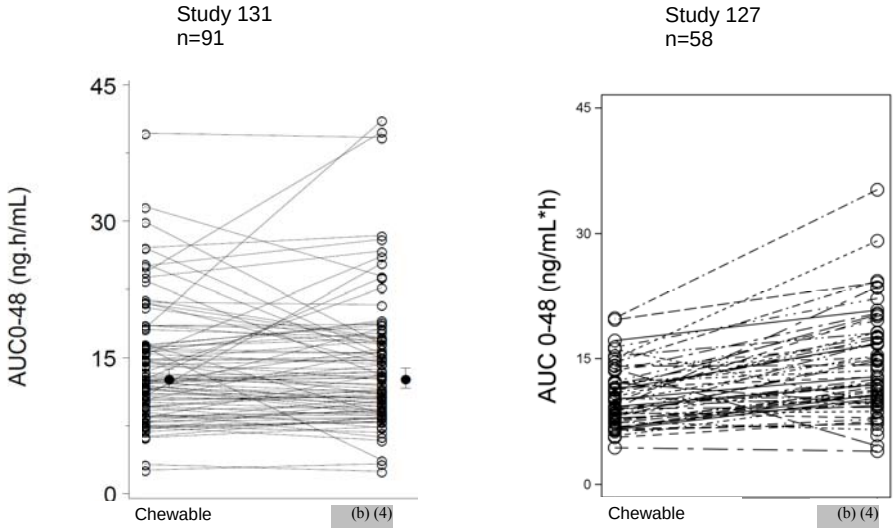

Figure 4 *The range of total systemic exposure to lanthanum observed following administration of lanthanum carbonate* (b) (4) *is within range of exposures seen with the chewable tablet.*

*(3) Plasma exposure to lanthanum observed in study 127 is within the range observed in the Fosrenol chewable tablet development program (see **Figure 5** below). These studies were conducted at the same dose but with different formulations of lanthanum carbonate.*

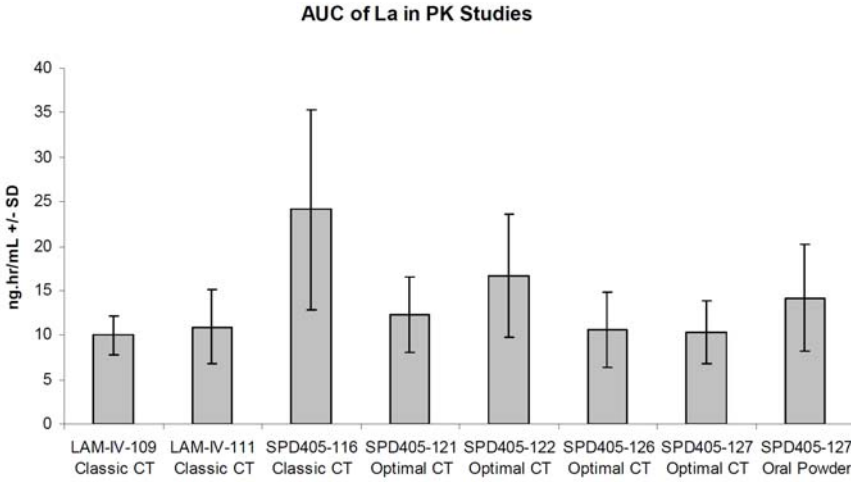

Figure 5 *A cross-study comparison of total lanthanum systemic exposure. Observations from study 127 are the last two bars on the right (ref: Summary of biopharmaceutics studies). CT=chewable tablet.*

The above factors taken together with the available safety data (discussed in section 4) for the current tablet formulation indicate that the 30% increase in lanthanum exposure is likely to be of no clinical significance.

Pharmacodynamic results

A total of 53 subjects were valid for pharmacodynamic analysis. Average change from pre-dose levels in urinary phosphate excretion observed during the study is presented in **Figure 6**. As seen in the figure, close to maximal reduction in urinary phosphate was observed on day 1 following administration of both the formulations, and the time course for urinary phosphate reduction was similar.

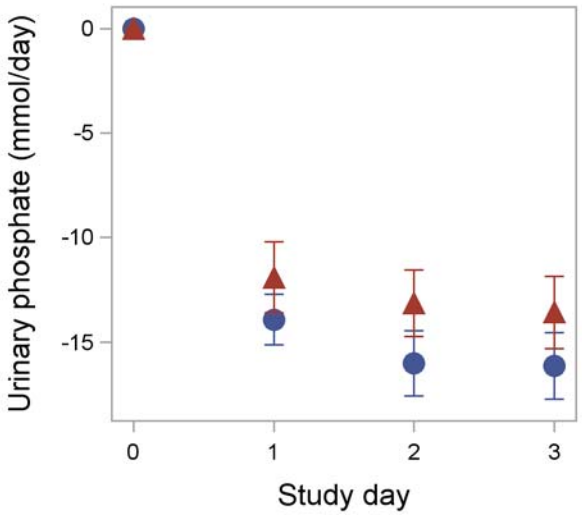

Figure 6 Mean (± 2*SE) change from baseline in daily urinary phosphate excretion following administration of 1000 mg *tid* of [redacted] (●) or chewable tablets (▲) (n=53).

Results of the pre-specified pharmacodynamic analysis are presented in **Table 2**. The mean and associated 90% CI of the difference in average daily urinary phosphate excretion (LSMEANS difference) between the chewable tablet and [redacted] formulation is contained in the reference interval, indicating that the two formulations have a similar effect on urinary phosphate excretion.

Table 2 Results of the statistical analysis.

	[redacted] **n=53**	**Chewable tablet n=53**
Baseline (mmol/day)	30.6 (0.9)	29.4 (0.9)
Averaged over three days (mmol/day)	15.3 (0.6)	16.6 (0.6)
LSMEANS difference (90% CI)	-1.6 (-2.38, -0.82)	
Reference interval	(-3.35, 3.35)	

1 mmol = 0.0323 g of P

Assay Methods

Urinary phosphate

Inorganic phosphorous in urine was measured using a validated colorimetric assay following derivatization to an ammonium phosphomolybdate complex. This is a standard clinical chemistry kit based test. Details of the method are presented in **Table 3**.

Table 3 Assay validation results for inorganic phosphorous (Ref A01206M-SPD405).

Standard curve range	3 to 50 mmol/L ($r > 0.998$)
Precision (%CV)	Intra-day ≤ 3.6 % Inter-day: ≤ 2.8 %
Accuracy (% Bias)	Intra-day: ± 7 % Inter-day: ± 5.7 %
Specificity	No interference
Matrix	Urine
Stability	Benchtop: 23 days at RT Long term stability: 23 days at 20°C Freeze-thaw: 3 cycles
Absorbance wavelength	340 nm using a Roche/Hitachi 917 Clinical Chemistry Multichannel Analyzer

Precision and accuracy of the method as applied in study 127 were within ± 15% and therefore acceptable (nominal QC sample concentrations were 8.42, 14.4, and 41.9 mmol/L).

Plasma lanthanum

Lanthanum was measured using a validated inductively coupled plasma mass spectrometry. The LLOQ was 0.03 ng/mL. The method was reviewed and judged acceptable in earlier submissions and will not be reviewed here.

Precision and accuracy of the method as applied in study 127 were within ± 15% and therefore acceptable (nominal QC sample concentrations were 0.113, 0.8, and 1.8 ng/mL).

4 REVIEW OF SAFETY

4.1 Methods

For the safety review, I reviewed the following documents:

1. Sponsor's package for new formulation, study SPD405-127 data sets, post-marketing reports for new formulation (submitted February 28, 2013)
2. 4-month safety update report (submitted June 10, 2013)
3. Original NDA 21468 clinical reviews (December 24, 2002 NDA clinical review by Dr. Juan Carlos Pelayo and July 19, 2004 NDA clinical review by Dr. Akinwole O Williams) and current label
4. Literature on lanthanum deposition (see footnotes in Section 4)

4.1.1 Studies/Clinical Trials Used to Evaluate Safety

This is a 505b1 application in which the applicant is relying on previous findings of safety for the Fosrenol chewable tablet. Because the dose and excipients are the same between the two formulations, (b) (4) and tablets, one can reasonably rely on the well-known safety findings of the tablets when assessing the safety of the (b) (4) formulation.

Safety data on the (b) (4) were collected to provide reassurance that its safety was similar enough to the safety of the tablet formulation during short-term exposure.

4.1.2 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Study SPD405-127 was conducted in a healthy adult population. Most subjects were young adults and thus, quite different from the patient population that might be expected to receive the new formulation of lanthanum carbonate, an older population with advanced renal disease and multiple comorbidities.

The demographics of the groups were equally matched by age, gender, ethnicity, weight, height, and body mass index. There was a difference between the groups in racial distribution. The group that received the powder formulation first was predominantly Caucasian (69.2% Caucasian, 28.2% Black and 2.6% Asian) while the group that received the tablets first was 45.5% Caucasian, 45.5% Black, 6.1% Asian and 3% other.

The dose tested in study SPD405-127, 1000 mg TID is an approved dose and is the maximum dose that was given in the pivotal clinical trials for the tablet formulation.

4.1.3 Explorations for Dose Response

Explorations of dose response were not done in this NDA as only one dose was studied (1000 mg TID).

4.2 Major Safety Results

There were no deaths or other serious adverse events (SAEs) in Study SPD405-127. One subject developed 2 treatment-emergent adverse events (TEAEs)* leading to discontinuation (abdominal distension and vomiting) in the first phase of the study when administered the powder formulation.

The incidence of TEAEs was higher after the administration of the (b) (4) formulation (23 subjects, 32.4%) than after the chewable tablets (14 subjects, 23.0%). The difference between the groups with regard to the incidence of TEAEs was largely attributable to gastrointestinal disorders (13 subjects, 18.3% powder formulation and 4 subjects, 6.6% chewable tablets), which was the system organ class most commonly associated with TEAEs. Most TEAEs were mild and transient, and no subjects experienced a severe TEAE.

There were no clinically relevant findings in the clinical laboratory tests, vital signs, 12-lead ECG results, or on physical examinations.

* AEs were considered treatment-emergent if they occurred (or worsened in severity) at or after the first dose of study medication and up to and including Day 6 or discharge day for each period.

Systemic exposure to lanthanum was discussed in section 3.4.1. Despite the somewhat increased exposure to lanthanum with the (b) (4) formulation, there is little concern for safety from this minimal increase in exposure. When Fosrenol was originally reviewed,

there were concerns about the potential for adverse effects of lanthanum on the liver because of animal findings. In clinical studies which included some patients treated for up to 6 years, there has been no association between lanthanum carbonate treatment and increased serum liver enzyme activities or hepatobiliary AEs.[2]

Animal studies also raised concerns about bone toxicity because of deposition of lanthanum in bone. The biological fate and bone load of lanthanum were modeled with the aid of a kinetic model[3] using plasma concentration data from healthy volunteers and bone concentration data collected from dialysis patients during 3 long-term trials. The initial deposition rate of lanthanum in bone is 1μg/g/year and after 10 years of lanthanum carbonate treatment, the model predicts a 7-fold increase in total bone lanthanum (from 10-70 mg), with lanthanum subsequently cleared on cessation of treatment at a rate of 13% per year. This rate of deposition is still very low, reflecting the very low level of absorption of lanthanum (0.00127%[4]). In 2 published 1-year studies that enrolled 98 and 63 dialysis patients, respectively, the incidence of adynamic bone disease and osteomalacia was reported to be lower and bone cell function was reported to be improved in patients treated with lanthanum carbonate, compared to those treated with calcium carbonate. [5,6] An AERS search and a 5-year post-marketing study (albeit grossly underpowered to detect a difference between treatment groups) also revealed no obvious signals for bone toxicity.

4.3 Deaths

There were no deaths in Study SPD405-127.

4.3.1 Nonfatal Serious Adverse Events

There were no nonfatal serious adverse events.

4.3.2 Dropouts and/or Discontinuations

There were 16 exclusions/discontinuations in Study SPD405-127. Of these, only one subject was reported as discontinuing as a result of TEAEs. This subject was a 28 year-old healthy white female and was randomized to receive the powder formulation during the first treatment period. During the first treatment period after administration of the powder formulation, the subject developed a feeling of fullness of the stomach (preferred term; abdominal distension) followed by vomiting. Both events were assessed by the investigator to be moderate in intensity. The subject was withdrawn as a result of these events. The events resolved quickly.

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[2] Laville M, 2011, Efficacy and safety of lanthanum carbonate in chronic kidney disease patients with hyperphosphataemia. *Nephrol Ther*;7(3): 154-61.

[3] Bronner F 1973. Kinetic and cybernetic analysis of calcium metabolism. In Irving JT (ed). Calcium and phosphorus. Academic Press, New York and London.149-86.

[4] Pennick M, Dennis K and Damment SJ 2006. Absolute bioavailability and disposition of lanthanum in healthy human subjects administered lanthanum carbonate. *J Clin Pharmacol*; 46(7):738-46.

[5] D'Haese PC, Spasovski GB, Sikole A, Hutchison A, Freemont TJ, Su kova S et al 2003. A multicenter study on the effects of lanthanum carbonate (Fosrenol) and calcium carbonate on renal bone disease in dialysis patients. *Kidney Int Suppl*; 85:S73-78.

[6] Freemont AJ, Hoyland JA, Denton J 2005. The effects of lanthanum carbonate and calcium carbonate on bone abnormalities in patients with end-stage renal disease. *Clin Nephrol*; 64(6): 428-37.

There were three times as many discontinuations when subjects were being administered or had just completed the period when they were being administered the (b) (4) formulation (12/16) compared to when subjects were being administered the chewable tablet formulation (4/16). 50% of the subjects who discontinued had AEs prior to discontinuation compared to a general rate of AEs of approximately 20-30%. This suggests that tolerability issues may have played a role in the discordant discontinuation rate. Of note, all the AEs that preceded discontinuation were mild to moderate.

Of the ten subjects who were discontinued during the first period or before the second period, nine of them were on the (b) (4) formulation whereas only one was on the chewable table formulation. Of the six of subjects who discontinued in the second period, four were randomized to receive the (b) (4) formulation and two were randomized to receive the chewable tablet formulation first. One might conclude that being randomized to receive the (b) (4) formulation first increased the chances of discontinuation. It is possible that the reason for this increase in risk for discontinuation rate on the powder formulation was from poor tolerability or it could represent a chance finding considering the small size of the trial.

None of the discontinuations and reasons for discontinuations represents a major safety issue.

4.3.3 Significant Adverse Events

There were no significant adverse events in Study SPD405-127.

4.3.4 Common Adverse Events

As shown in **Table** 4**4**, the most common AEs were gastrointestinal adverse events and differences were observed between the two treatments. When subjects were administered the (b) (4) formulation, the incidence of nausea was approximately double compared to when administered the chewable tablet [6(8.5%) vs. 3 (4.9%)]. Other observed differences between treatments were the incidence of upper abdominal pain [3(4.2%) vs. 1(1.6%)], dyspepsia [2(2.8%) vs. 0] and gastroenteritis [2(2.8%) vs. 0]. The small numbers of events, however, limit the interpretability of these findings. In **Table** 5**5** one can see that the incidence of total gastrointestinal system organ class adverse events was 13 (18.3%) when subjects were administered the (b) (4) vs. 4 (6.6%) when they were administered the chewable tablets, making the differences seen in the common gastrointestinal AEs more likely to be representative of a true vs. a chance finding. The etiology of this difference is unclear.

Although there was a difference in the racial distribution of the groups, there did not appear to be racial difference in adverse events.

Table 4: Common Treatment Emergent Adverse Events* observed in ≥2 patients (Safety set)

	A ([(b) (4)]) N=71		B (Chewable Tablet) N=61		Overall N=72	
	n (%)	events	n (%)	events	n (%)	event
Adverse Event	**23 (32.4)**	**38**	**14 (23.0)**	**18**	**30 (41.7)**	**56**
Nausea	6 (8.5)	7	3 (4.9)	3	8 (11.1)	10
Headache	4 (5.6)	5	3 (4.9)	3	7 (9.7)	8
Abdominal pain upper	3 (4.2)	3	1 (1.6)	1	3 (4.2)	4
Dizziness	2 (2.8)	2	1 (1.6)	1	3 (4.2)	3
Dyspepsia	2 (2.8)	2	0	0	2 (2.8)	2
Fatigue	2 (2.8)	2	1 (1.6)	1	2 (2.8)	3
Gastroenteritis	2 (2.8)	2	0	0	2 (2.8)	2
Muscle spasms	1 (1.4)	1	1 (1.6)	1	2 (2.8)	2

MedDRA AE coding dictionary used: version 12.0
Treatment Emergent Adverse Event: AEs were considered treatment-emergent if they occurred at or after the first dose of study medication; or were present prior to the first dose but worsened in severity; and up to and including Day 6 or discharge day for each period.
Source: clinical study report, p. 49.

Table 5: Gastrointestinal system organ class treatment emergent adverse events* observed in patients (Safety set)

	A ([(b) (4)]) N=71		B (Chewable Tablet) N=61		Overall N=72	
	n (%)	events	n (%)	events	n (%)	events
Gastrointestinal disorders	**13 (18.3)**	**19**	**4 (6.6)**	**5**	**15 (20.8)**	**24**
Nausea	6 (8.5)	7	3 (4.9)	3	8 (11.1)	10
Abdominal pain upper	3 (4.2)	3	1 (1.6)	1	3 (4.2)	4
Dyspepsia	2 (2.8)	2	0	0	2 (2.8)	2
Abdominal discomfort	1 (1.4)	1	0	0	1 (1.4)	1
Abdominal distension	1 (1.4)	1	0	0	1 (1.4)	1
Abdominal pain	1 (1.4)	1	0	0	1 (1.4)	1
Constipation	1 (1.4)	1	0	0	1 (1.4)	1
Diarrhea	1 (1.4)	1	0	0	1 (1.4)	1
Dry mouth	0	0	1 (1.6)	1	1 (1.4)	1
Epigastric discomfort	1 (1.4)	1	0	0	1 (1.4)	1
Vomiting	1 (1.4)	1	0	0	1 (1.4)	1

MedDRA AE coding dictionary used: version 12.0
* Treatment Emergent Adverse Event: AEs were considered treatment-emergent if they occurred at or after the first dose of study medication; or were present prior to the first dose but worsened in severity; and up to and including Day 6 or discharge day for each period.
Source: clinical study report, p. 50.

Most of the AEs were mild. However, there were more moderate AEs among subjects who were being administered the powder formulation. 7 subjects experienced a total of 8 moderate AE events when being administered the (b) (4) formulation: 1 abdominal distention AE, 2 gastroenteritis AEs (in two subjects), 1 dyspepsia AE, 1 nausea AE, 1 vomiting AE, 1 moderate eye irritation AE and 1 moderate headache AE. Two subjects experienced a total of 2 moderate AE events when being administered the Fosrenol chewable tablets: 1 moderate nausea AE and 1 moderate headache AE.

Chronic toxicity studies with lanthanum carbonate were reviewed during the original NDA review from 2004. The studies showed dose-related increased incidences of stomach lesions (epithelial hyperplasia of the limiting ridge and non-glandular region, sub-mucosal inflammation and inflammation of glandular epithelium) in rats and mice, but not in dogs. (The 52-week dog study did not reveal any significant toxicity.) It was shown that lanthanum carbonate is better tolerated if administered to dogs and humans with food. Nocturnal feeding habits result in rodents receiving the drug (during the day) on an empty or partially-empty stomach. It is believed that the longer duration of direct contact of lanthanum with the stomach wall, together with the inability to vomit an irritant material is likely to make rodents more susceptible than dogs to stomach lesions. There have been no post-marketing signals for serious gastrointestinal toxicity for Fosrenol.

Further inspection of all AEs in the study did not reveal any concerning or unexpected findings.

REVIEWER'S COMMENT(S): The greater incidence of gastrointestinal adverse events for subjects while being administered the oral powder formulation should be included in the label for the Fosrenol powder formulation.

4.3.5 Laboratory Findings

The majority of subjects' biochemistry, hematology and urinalysis values were within the normal range at baseline and remained within the normal range at the end of the treatment period. While some subjects had minor shifts in laboratory values from normal to high (cholesterol, glucose, and percent lymphocytes) and a shift from low to normal hematocrit values in some subjects, there was no difference between arms.
REVIEWER'S COMMENT(S): There is no reason to think that the findings were drug-related.

4.3.6 Vital Signs

There were no clinically relevant changes in mean pulse rate or blood pressure over the treatment period.

4.3.7 Electrocardiograms (ECGs)

There were no clinically relevant differences between the groups with regard to ECG findings. No clinically significant abnormal ECG findings were reported during the study.

4.3.8 Dose Dependency for Adverse Events

Dose dependency for AEs could not be evaluated because all subjects were on the same dose.

4.3.9 Time Dependency for Adverse Events

Most of the gastrointestinal AEs occurred during the first period in both treatment groups. Few gastrointestinal AEs occurred during the second period in both groups. In the pivotal trials of the tablet formulation, gastrointestinal adverse reactions typically occurred soon after initiating treatment and then lessened over time on treatment, suggesting the development of gastrointestinal tolerance over time.

4.4 Additional Safety Evaluations

Reports of Postmarketing Experience with Powder Formulation:
Fosrenol oral powder was first approved in Japan in January 2012 and was approved in the EU in March 2012. The oral (b) (4) formulation has been launched in 4 countries: United Kingdom (July 2012), Germany (October 2012), Spain and the Netherlands (January 2013). Based on the available marketing data, the estimated patient exposure for oral powder is 28,700 patient-years of treatment in Japan and the EU as of March 2013. As of January 15, 2013, there have been 19 adverse event reports (15 Japan, 14 EU) received by Shire Pharmacovigilance and Risk Management (PVRM) for the oral (b) (4) formulation. Of the 19 case reports, 3 were serious and 16 were non-serious. Of the 3 serious cases, one occurred prior to taking drug. The 2 serious cases following receipt of the drug are summarized below:

SPV1-2010-001685 Japanese case from post-marketing surveillance study reporting death, cardiac arrest, gastrointestinal necrosis, acute cholangitis, and acute pancreatitis. The patient was a 68-year-old female, treated with lanthanum chewable tablet 750 mg QD for hyperphosphatemia. Relevant medical history included nephrosclerosis, end-stage renal disease on hemodialysis, alcoholic liver disease, anemia, chronic gastritis, secondary hyperparathyroidism and cholelithiasis. The subject had experienced acute cholangitis and acute pancreatitis, most likely related to underlying cholelithiasis and alcoholic liver disease. The events resolved with treatment and Fosrenol therapy was continued. In June 2012, Fosrenol was changed from chewable tablets to (b) (4) (1500 mg/day). Approximately (b) (6) months later, the patient was found not breathing three hours after a routine dialysis procedure. Cardio-pulmonary resuscitation was ineffective and the patient was later pronounced dead at a hospital. Based on blood tests and postmortem CT, the diagnosis of small intestinal necrosis was made. Mesenteric occlusion could not be confirmed.

ALL1-2012-03664 Spontaneous case report of low back pain, defecation urgency and nausea. This is a male patient in his 70s who was previously treated with Fosrenol chewable tablets 125mg TID for unknown duration who was switched was switched to Fosrenol (b) (4) 750mg (in three divided doses) for hyperphosphatemia. The patient was taking Rocaltrol (calcitriol), Nu-Lotan (losartan potassium) and Glufast (mitiglinide calcium) concomitantly. After (b) (6) dose) of Fosrenol (b) (4) the patient experienced squeezing pain in the lower right back and dorsal region. Defecation

occurred in the morning, then the urge to defecate developed every 1 hour, but no defecation occurred. Fosrenol therapy was interrupted and resumed 2 days later with reoccurrence of the same symptoms. The patient visited the hospital for dialysis. Due to more severe pain, nausea and continued urge to defecate, he was hospitalized and monitored. The symptoms resolved upon Fosrenol discontinuation and the patient was discharged from the hospital.

REVIEWER'S COMMENT(S): The first case was likely unrelated to Fosrenol. The second case may have been caused by Fosrenol, but the patient recovered without apparent sequelae.

The 16 non-serious case reports were mostly related to the gastrointestinal system organ class and included the following adverse events: nausea, abdominal discomfort, constipation, nausea, vomiting, and abdominal distention. These AEs are not surprising and all are listed in the Fosrenol label except for abdominal distention. Other non-serious case reports included blood phosphorus increased, blood pressure increased, anemia, hypoaesthesia, eczema and choking on food after taking lanthanum with food. It is unlikely that these non-gastrointestinal case reports were related to the drug.

5 CONCLUSIONS

Fosrenol oral powder appears to be similar to Fosrenol chewable tablet in its effect on urinary phosphate excretion and systemic exposure to lanthanum. The incidence of gastrointestinal adverse events was higher for the oral (b) (4) formulation (18.3%) than for the chewable tablets (6.6%) and occurred mostly during the first period suggesting that tolerability to both formulations of the drug improves in days to a couple of weeks. All adverse events were non-serious, the majority were mild representing known gastrointestinal system organ class (SOC) acute drug reactions for lanthanum (e.g. nausea, abdominal pain upper, abdominal pain, abdominal discomfort, diarrhea, dyspepsia, epigastric discomfort, and constipation). The increase in gastrointestinal adverse events for subjects on the oral powder formulation should be included in the new Fosrenol label. There were no concerning changes in laboratory, ECG or vital sign change during the course of the study. The minimal absolute increase in lanthanum absorption with the powder formulation is not likely to result in any concerning clinical consequences.

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/s/

DIVYA MENON ANDERSEN
10/25/2013

RAJANIKANTH MADABUSHI
10/25/2013

MELANIE J BLANK
10/28/2013

ALIZA M THOMPSON
10/28/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Division of Cardiovascular and Renal Products

Memo: Fileability Assessment (Clinical Reviewer Perspective)
NDA: 204734
Applicant: Shire Development, LLC
Trade name: FOSRENOL
Established name: Lanthanum Carbonate
Dosage Form: Oral Powder, 750 mg and 1000 mg
Route of Administration: Oral
Indication: Reduction of serum phosphate in patients with end stage renal disease
Letter Date: February 28, 2013
Stamp Date: February 28, 2013
PDUFA Date: December 28, 2013
Reviewer: Melanie Blank, MD
Date of Completion: April 10, 2013

Background:
Lanthanum carbonate (FOSRENOL) is a phosphate binder indicated to reduce serum phosphate in patients with end stage renal disease (ESRD) and was approved in the U.S. in 2004. The original formulation of Fosrenol is a chewable tablet which must be chewed thoroughly because it does not contain dispersing excipients. Lanthanum carbonate (b) (4) formulation was developed for patients who experience difficulty with chewing or who develop chewing fatigue.

Fosrenol oral powder was first approved in Japan in January 2012 and launched in Japan in May 2012. Following European approval in March 2012, the oral powder formulation has been available to patients in 4 countries: United Kingdom (July 2012), Germany (October 2012), Spain and the Netherlands (January 2013). Based on the available marketing data, the estimated patient exposure for oral powder is 9,366 patient-years of treatment (Japan) and 13 patient-years of treatment (EU) as of September 30, 2012.

Brief Description of Study, Endpoints and Results according to applicant:
A phase 1 clinical study that enrolled 72 subjects was conducted to assess any potential differences in the pharmacodynamics and pharmacokinetics between the 2 lanthanum carbonate formulations; lanthanum carbonate (b) (4) formulation and lanthanum carbonate chewable tablets. The primary endpoint was the comparison of average daily urinary phosphate excretion over 3 days following dosing with a lanthanum carbonate (b) (4) formulation sprinkled over applesauce followed by 250 cc water and with lanthanum carbonate chewable tablets, each dose administered as 1000mg 3 times per day given with apple sauce immediately following meals. The subjects were studied on a standardized phosphate diet. The secondary endpoint was the assessment of urinary phosphate excretion on Day 4 of dosing. According to the applicant, the study was successful in meeting both primary and secondary endpoints, thereby showing bioequivalence.

Safety Assessments and Safety Review Plan:

Important safety assessments were made, including the extent of absorption of lanthanum. According to the applicant's summary, there was a higher rate of absorption of lanthanum in the powder formulation than the chewable table with increased overall exposure (by ~30%). Because lanthanum absorption raises concerns of hepatic and bone toxicity, this will be a review issue.

According to the applicant, there were also more gastrointestinal adverse events in the powder formula, but there were no deaths or SAEs. There were several discontinuations for a variety of reasons but according to the applicant, only one subject was discontinued because of AEs. The AEs and the other safety variables will be the main subject of the clinical review. The postmarketing experience in Europe and Japan will also be considered.

Labeling:
The study was conducted with subjects drinking 250 cc of water after consuming the powder sprinkled on applesauce. Consideration needs to be given to recommending that patients ingest 250 cc of water after taking each dose. Further assessments of safety data will inform the need for changes in the proposed labeling.

Comments and Recommendations:
This application is fileable from the perspective of the clinical reviewer who will be conducting a review of safety only. The efficacy in this 505(b)(2) application will be assessed by the clinical pharmacology and statistics reviewers. See further comments in the filing document attached.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204734 **Applicant: Shire** **Stamp Date: 2/28/13**

Drug Name: FOSRENOL **NDA/BLA Type: 505 (b)(2)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	√			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	√			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	√			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	√			
5.	Are all documents submitted in English or are English translations provided when necessary?	√			
6.	Is the clinical section legible so that substantive review can begin?	√			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	√			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	√			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			√	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			√	
11.	Has the applicant submitted a benefit-risk analysis for the product?	√			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2), reference drug is Lanthanum carbonate (Fosrenol) chewable tablets
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			√	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	√			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1: A phase 1 pharmacodynamic equivalence study comparing urinary phosphate excretion and plasma lanthanum pharmacokinetics for a lanthanum carbonate granule formulation and chewable tablets administered to healthy adult subjects Indication: phosphate binding in dialysis patients Pivotal Study #2: N/A Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	√			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	√			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			√	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	√			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			√	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	√			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			√	This is a Bioequivalence study. No changes have been made to the lanthanum carbonate drug substance and all information regarding the drug substance (including site of manufacture, method of synthesis, control of materials, process controls, specifications, analytical methods, and container closure) for

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					Fosrenol (lanthanum carbonate) Oral Powder [redacted] (b) (4) to that registered and approved in NDA 021468 for Fosrenol (lanthanum carbonate) Chewable Tablets. The efficacy and safety of Fosrenol (lanthanum carbonate) Chewable Tablets was established in NDA 021468 and it was approved by the FDA on October 26, 2004.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			√	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		√		MedDRA 12.0 used but not included in submission. This is acceptable.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	√			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			√	
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			√	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			√	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	√			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			√	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			√	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	√			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	√			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	√			
34.	Are all datasets to support the critical safety analyses available and complete?	√			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	√			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?		√		CRF of patient who discontinued due to an AE was requested from applicant.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	√			Submitted the above requested CRF on April 10, 2013
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	√			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	√			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes.

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant. **N/A**

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. **None presently.**

Reviewing Medical Officer Date

Clinical Team Leader Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MELANIE J BLANK
04/10/2013