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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-468

Administrative/Correspondence

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13.0 PATENT INFORMATION

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US005968976A

United States Patent [19]

Murrer et al.

[11] Patent Number: 5,968,976

[45] Date of Patent: Oct. 19, 1999

[54] **PHARMACEUTICAL COMPOSITION CONTAINING SELECTED LANTHANUM CARBONATE HYDRATES**

[75] Inventors: **Barry A Murrer; Nigel A Powell**, both of Berkshire, United Kingdom

[73] Assignee: **AnorMed Inc.**, Langley, Canada

[21] Appl. No.: **08/913,960**

[22] PCT Filed: **Mar. 19, 1996**

[86] PCT No.: **PCT/GB96/00575**

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§ 102(e) Date: **Jan. 2, 1998**

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PCT Pub. Date: **Oct. 3, 1996**

[30] **Foreign Application Priority Data**

Mar. 25, 1995 [GB] United Kingdom 9506126

[51] **Int. Cl.**[6] **A01N 55/02**

[52] **U.S. Cl.** 514/492; 514/512; 424/715; 534/16

[58] **Field of Search** 534/16; 514/492, 514/512; 424/715

[56] **References Cited**

PUBLICATIONS

Yanagihara et al., "Synthesis of Lanthanide Carbonates", Journal of the Less–Common Metals, 167(2) pp. 223–232, 1991.

Patent Abstract of vol. 11, No. 371, (C–462), Dec. 3, 1987 & JP, A, 62 145024 (Asahi Chem Ind Co Ltd), Jun 29, 1987.

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Chemical Abstracts, vol. 104, No. 26, Jun. 30, 1986, abstract No. 236218, Mzareulisvili et al., "Study of interaction of lanthanum nitrate with alkali metal and ammonium carbonates", XP002010789, Soobshch. Akad. Nauk Gruz. 121(1), pp. 81–84, (1986).

Chemical Abstracts, vol. 87, No. 20, Nov. 14, 1977, abstract No. 161013, Oda et al., "Studies on the crystal water of lanthanum carbonates", XP002010790, Oita Daigaku Kyoikygakubu Kenku Kiyo, Shizen Kagaku, 4(5), pp. 1–6, 1975.

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Attorney, Agent, or Firm—Morrison & Foerster, LLP

[57] **ABSTRACT**

Selected lanthanum carbonate hydrates may be administered into the gastrointestinal tract, to treat hyperphosphataemia in patients with renal failure.

10 Claims, 4 Drawing Sheets

Fig. 1

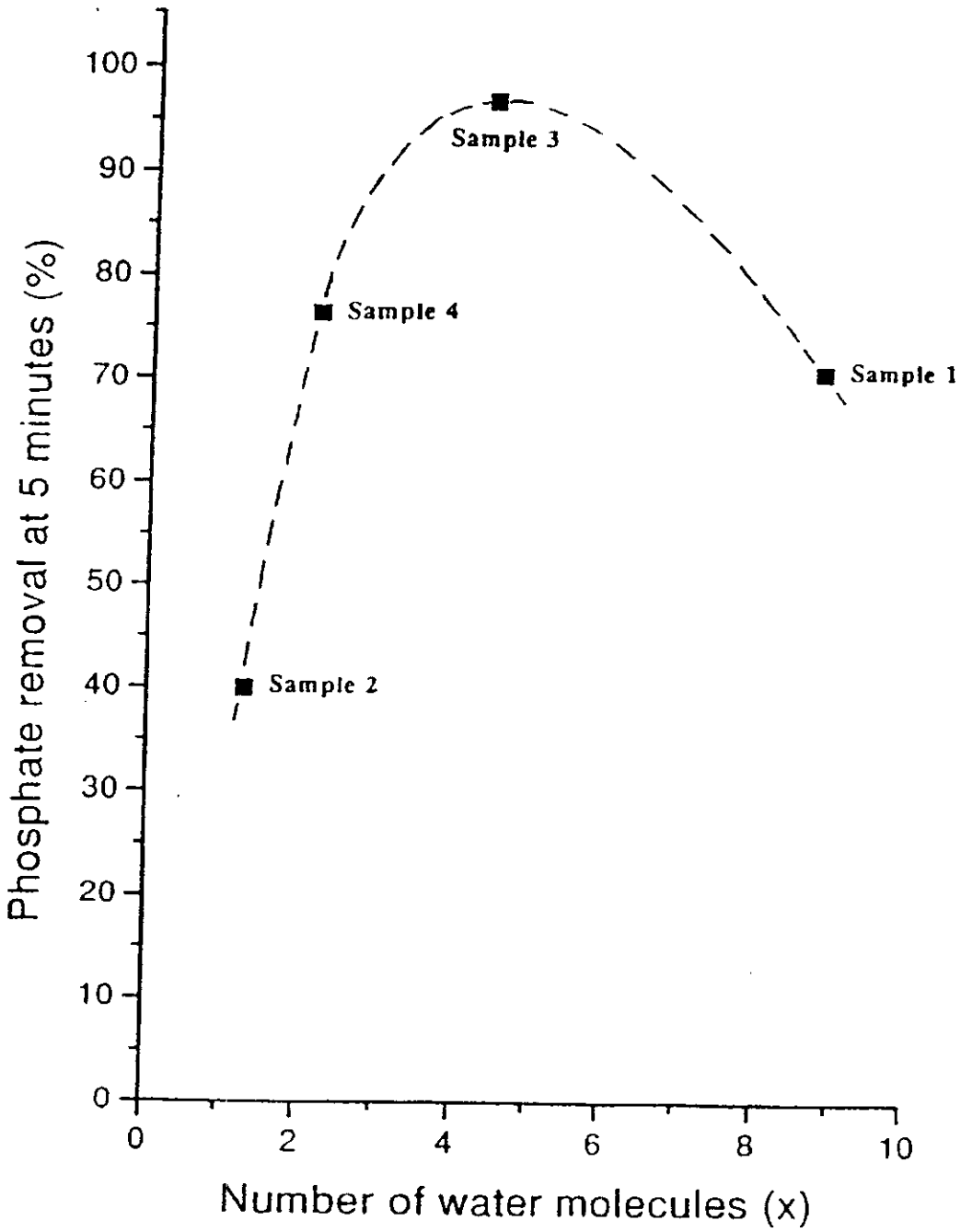

Phosphate removal at 5 minutes (%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
Number of water molecules (x)
Sample 1
Sample 2
Sample 3
Sample 4

Fig. 2

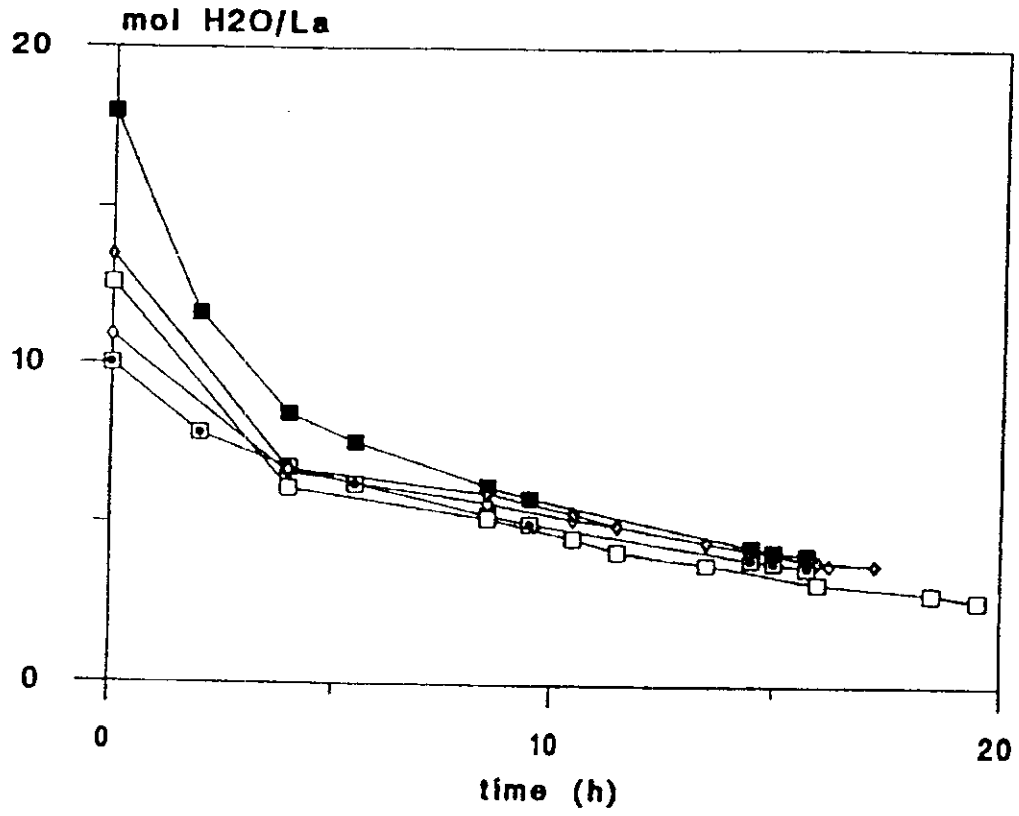


Fig. 3

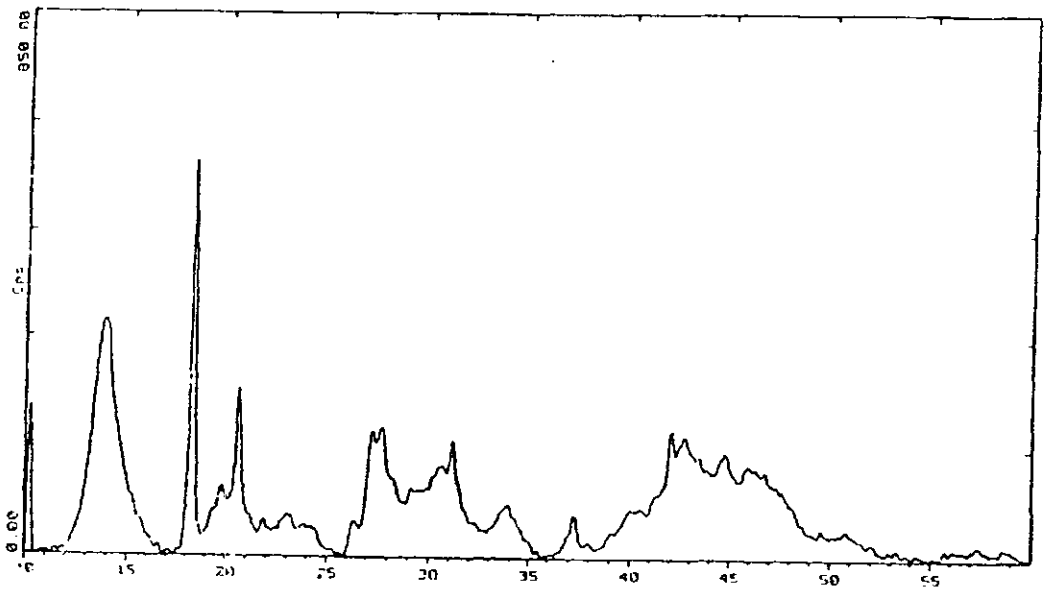
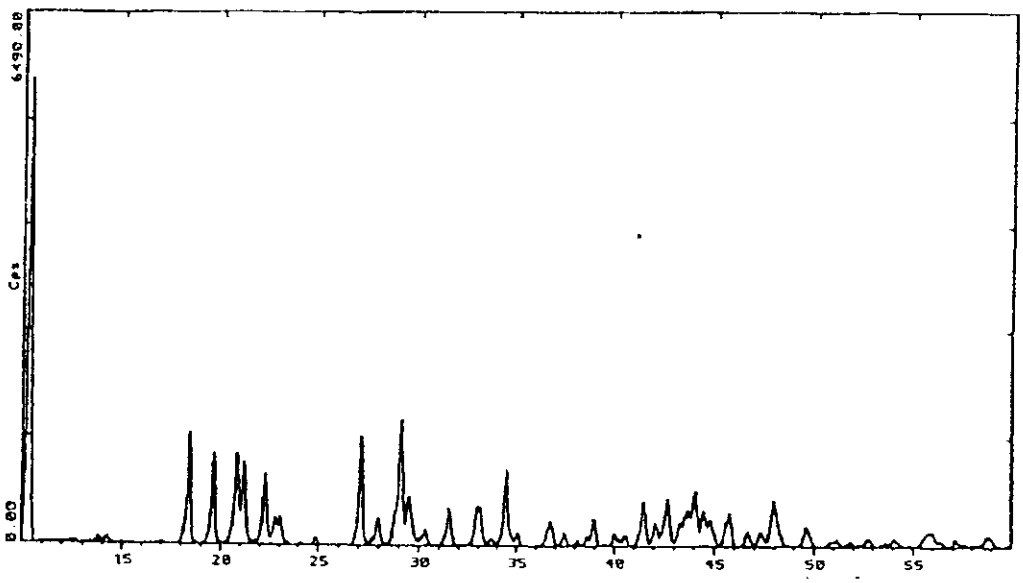


Fig.4



PHARMACEUTICAL COMPOSITION CONTAINING SELECTED LANTHANUM CARBONATE HYDRATES

This application is a 371 of PCT/GB96/00575 filed on Mar. 19, 1996.

This invention concerns a novel and inventive pharmaceutical composition and method, more particularly it concerns a composition for the treatment of hyperphosphataemia.

Hyperphosphataemia is a particular problem of patients with renal failure, using dialysis equipment. Conventional dialysis fails to reduce levels of phosphate in the blood, so that the levels rise in time. It is known to control phosphate levels by the oral administration of aluminium salts, or calcium salts. With the known toxic effects of aluminium, aluminium-based therapy tends to be avoided. In the case of calcium salts, calcium is absorbed rather readily from the gut, and in turn causes hypercalcaemia.

It has been suggested (Nakagawa et al, Trans Am Soc Intern Organs, 31, (1985) 155–9) that hydrous cerium oxide could be used as a bead in an ion-exchange column, to bind phosphate during dialysis. Japanese published patent application 61 004 529 appears to cover the same idea, suggesting that the hydrous oxides of La, Ce and Y may be used in the column. However, although the rare earths are generally considered of low toxicity according to the Hodge-Sterner classification system (Am Ind Hyg Assoc Quart, 10, (1943), 93), their toxicity when given iv, which corresponds to use in a blood dialysis system, is significant and we are not aware that the suggested ion exchange system or any development thereof has met with widespread acceptance or has been tested clinically for hyperphosphataemia.

It appears that cerium oxide or oxalate was administered many years ago for different medical indications, but that this has fallen into complete disuse.

Japanese published patent application number 62-145024 (Asahi Chemical Ind KK) discloses that rare earth carbonates, bicarbonates or organic acid compounds may be used as phosphate binding agents. One example of said published application relates to the use of lanthanum carbonate, although in the tests described, cerium organic acid salts and carbonate gave better phosphate ion extraction than lanthanum carbonate. Example 11 of said published application prepares $La_2(CO_3)_3.H_2O$, ie the monohydrate; all the other Examples are directed to rare earth carbonates other than lanthanum carbonate.

We have now discovered that certain forms of lanthanum carbonate exhibit improved performance in a variety of tests, over standard commercial lanthanum carbonate, which is believed to be the octahydrate form, and over $La_2(CO_3)_3.H_2O$ or similar compounds.

According to one aspect therefore, the present invention is the use of lanthanum carbonate of formula $La_2(CO_3)_3.xH_2O$ where x has a value from 3 to 6, preferably from 3.5 to 5, more especially from 3.8 to 4.5, for the preparation of a medicament for the treatment of hyperphosphataemia by administration into the gastrointestinal tract.

The invention further provides a pharmaceutical composition comprising said lanthanum carbonate, in admixture or association with a pharmaceutically acceptable diluent or carrier, in a form for administration into the gastrointestinal tract for the treatment of hyperphosphataemia.

The invention may also be expressed as a method of treatment of hyperphosphataemia in a patient with renal failure, comprising the administration of an effective dose of said lanthanum carbonate into the gastrointestinal tract.

According to another aspect, the present invention is a process for the preparation of lanthanum carbonate which comprises the steps of:

(i) reacting lanthanum oxide with an acid which gives a soluble salt of lanthanum;

(ii) reacting a solution of the thus obtained lanthanum salt with an alkali metal carbonate to produce a wet cake of lanthanum carbonate octahydrate; and

(iii) controlled drying of the wet cake of lanthanum carbonate octahydrate so as to obtain a lanthanum carbonate with 3 to 6 molecules of water of crystallisation.

According to yet another aspect, the present invention is lanthanum carbonate when obtained by the above-mentioned process.

According to a further aspect, the present invention is lanthanum carbonate of the formula $La_2(CO_3)_3.xH_2O$ where x has a value from 3 to 6.

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments of the present invention are described below, by way of example only, with reference to the accompanying drawings in which:

FIG. 1 illustrates the phosphate-binding capability of lanthanum carbonates having different degrees of water of crystallisation;

FIG. 2 illustrates the drying curves for five batches of lanthanum carbonate prepared by the method indicated in Example 1;

FIG. 3 illustrates the XRD analysis of lanthanum carbonate $4H_2O$ prepared by the method indicated in Example 2; and

FIG. 4 illustrates the XRD analysis of lanthanum carbonate $8.8H_2O$ of Sample 1 above.

For the tests described hereinafter, samples of lanthanum carbonate were obtained as follows:

Sample 1. Commercial lanthanum carbonate obtained from a chemical company.

This was characterised by elemental analysis (La, C, H), TGA, X-ray powder diffraction and ir spectroscopy, to have the formula $La_2(CO_3)_3.8.8H_2O$.

Samples 2–4 were prepared by heating portions of Sample 1 at varying temperatures for varying lengths of time, either under vacuum or at atmospheric pressure to obtain materials of formula $La_2(CO_3)_3.xH_2O$ where $0<x<8$.

Sample	Initial wt (g)	Temp (° C.)	Time (min)	Vacuum (Y/N)	Wt loss (g)	x
2	5.00	175	240	Y	1.09	1.3
3	20.0	80	180	N	2.6	4.4
4	5.01	100	720*	N	0.96	2.2

*Dried to constant weight

Sample 5 is a sample of lanthanum carbonate which when analysed indicated a formula of $La(CO_3)_3.4H_2O$.

Sample 6 is a sample of lanthanum carbonate prepared according to Example 1 below and having the formula $La_2(CO_3)_3.3.8H_2O$.

In order to show that certain lanthanum carbonate hydrates are significantly different in phosphate binding activity from both lanthanum carbonate octahydrate and from $La_2(CO_3)_3.H_2O$, samples were tested as follows:

i) a stock solution was prepared by dissolving 13.75 g of anhydrous Na_2HPO_4, 8.5 g of NaCl in 1 litre deionised water.

ii) 100 ml of the stock solution was adjusted to pH3 by the addition of concentrated HCl.

iii) A 5 ml sample was taken and filtered through a 0.02 μm filter to give a Time 0 sample. This was analysed for phosphate using a Sigma Diagnostics Colorimetric Phosphorus test kit.

iv) 5 ml fresh stock solution was added to reestablish 100 ml, and the pH was re-adjusted to approximately 3.

v) $La_2(CO_3)3.xH_2O$ as a dry powder was added in an amount according to the molecular weight of the particular hydrate, to give a two-fold molar excess of lanthanum over phosphate and stirred at room temperature.

vi) Sampling was carried out at time intervals from 0.5 to 10 minutes, and the percentage of phosphate was determined as in iii) above. The results are shown in the Table 1 below.

TABLE 1

TIME	% PHOSPHATE REMOVED Sample					
(Minutes)	1	2	3	4	5	6
0						
0 5		13.4	18.8	15.1	22.9	31.4
1	29	18.4	31.5	26.8	40.4	55.5
1.5		25 4	43.1	36	55 2	74 8
2		28 1	50.6	45 3	69 5	88.1
2.5		30.8	60.5	51 8	79.9	95.3
3		34.4	69	57.6	90 3	99.6
4						100
5	70 5	39.9	96.5	76 3	100	100
10	100	ND	99.1	ND	100	100

It can readily be seen from Table 1 that Sample 3 ($La_2(CO_3)_3.4.4H_2O$); Sample 5 ($La_2(CO_3)_3.4H_2O$) and Sample 6 ($La_2(CO_3)_3.3.8H_2O$ appreciably quicker than the $8.8H_2O$, $.1.3H_2O$ or $2.2H_2O$ forms. We believe that the results for $La_2(CO_3)_3.1.3H_2O$ are in agreement with the results shown in the above mentioned Japanese published patent application number 62-145024 where for $La_2(CO_3)_3.H_2O$, only 90% removal is shown after 120 minutes.

It can also be readily seen from FIG. 1 of the accompanying drawings that the highest phosphate removal is obtained with lanthanum carbonates having 3 to 6 molecules of water.

The present invention offers the possibility of binding phosphate without any incursion of lanthanum into the blood stream, where toxic effects can cause problems. The specified lanthanum carbonate has negligible absorption from the gut, as shown by the in vivo tests described below.

Throughout this document, the term "treatment" is intended to include preventative treatment.

Processes for preparing lanthanum carbonates according to the present invention are described by way of illustration in the following Examples 1 and 2.

EXAMPLE 1

Lanthanum oxide (1.5 kg, 4.58 mol) was suspended in water (5.5 litres) in a 20 litre flask. Nitric acid (Analar grade, 69%, SG 1.42, 1.88 litres, 29.23 mol) was added to the stirred solution over 1.5 hours at such a rate as to keep the temperature between 60–80° C. The resulting lanthanum nitrate solution was left to cool to room temperature and filtered. A solution of sodium carbonate (1.65 kg, 15.57 mol) in water (7.75 litres) was added to the stirred lanthanum nitrate solution over 45 minutes. At the end of the addition the pH of the suspension w as 9.74. The suspension was left overnight, filtered (Buchner funnel, 540 paper) and dried on the filter in a current of air for 30 minutes. The solid was then re-suspended in water, stirred for 40 minutes and filtered. This procedure was repeated to give a total of six washes, when the nitrate concentration in the filtrate was <500 ppm. The final material (4.604 kg) was divided between three Pyrex dishes and a sample from each analysed for water content. (By decomposition of weighed sample of ($La_2(CO_3)_3.xH_2O$ at 1050° C., 2 hours to La_2O_3). The dishes were then placed in a fan oven at 80° C. and the weight loss of each dish monitored until the material of the required degree hydration was obtained. The progress of the drying is shown below

Time	mol H_2O/La		
(hours)	Dish 1	Dish 2	Dish 3
3.50	10.9	13.5	12.6
12	5.7	6.0	5.2
14	5.3	5.4	4.6
16	4.9	5.1	4.3
17	4.4	4.6	3.8
19.5	3.8	4.0	3.2

Drying curves for five batches produced by this route are shown in FIG. 2.

$La_2(CO_3)_3.3.8H_2O$ from dish 1 was selected as Sample 6 for the phosphate binding tests set forth in Table 1.

EXAMPLE 2

The process of Example 1 was repeated but using hydrochloric acid (12.28M, 2.48 litres) in place of nitric acid to dissolve lanthanum oxide (1.5 kg). The yield of crude product after six washes was 4.378 kg. The product was divided in three approximately equal portions in Pyrex dishes and dried in a fan oven at 80° C. After 2 hours a sample was taken from each tray and water analysed by decomposition to lanthanum oxide as described above. These figures were used to calculate the weight loss needed to give material of the required composition. The time course of the drying process is shown below.

Time	mol H_2O/La		
(hours)	Dish 1	Dish 2	Dish 3
2	21.3	22.1	20.4
5.5	12.3	13.2	12.2
9	7.9	8.0	7.6
11.5	6.9	7.0	6.6
17	4.9	5.1	4.6
18.5	4.6	4.8	4.2
19.5	4.4	4.6	4.1
20	4.3	4.6	4.0

Samples were taken from each dish, combined and analysed. The following results were obtained:

	Found	Calculation for $La_2(CO_3)_3.4H_2O$
% La (gravimetric)	52.38%	52.4%
carbonate (titration)	5.76 mol/g	5.66 mol/g
H_2O (NMR)	13.06%	13.59%

The XRD analysis for lanthanum carbonate $4H_2O$ prepared by the method of Example 2 is illustrated in FIG. 3.

FIG. 4 illustrates the XRD of lanthanum carbonate $8.8H_2O$ and it is evident that it has a different crystalline structure from lanthanum carbonate $4H_2O$ prepared by the method of Example 2. The XRD analysis of lanthanum carbonate $4H_2O$ prepared by the method of Example 1 was similar to the XRD analysis of lanthanum carbonate $4H_2O$ prepared by the method of Example 2.

Pharmaceutical compositions for oral administration according to the invention may be formulated and manufactured using methods well known in the art. Suitable diluents or carriers are also well known. The compositions may desirably be in a dosage form, to provide a single daily dose, or a number of sub-daily dosages. Conventional pharmacological methods may be used to ascertain suitable dose levels. The level of phosphate in the food that an individual ingests is important. Daily dosages are indicated to be in the range 0.1 to 50 g, preferably about 0.5 to 15 g. Suitable forms for oral administration include solid forms such as tablets, capsules and dragees and liquid forms such as suspensions or syrups. In addition to diluents and carriers, it is conventional in the formulation of oral preparations to include non-active ingredients such as thickeners, taste-improving components and colouring agents. The said carbonate may also be coated or treated to provide delayed-release forms. Preferably, the required daily dosage is given in tablet form, eg chewable tablet form, to be taken with meals. A suitable daily dosage of about 2 g for 70 kg man, should be compared with a daily dosage of 20 g for a commercial calcium-based phosphate binding composition.

To demonstrate that the lanthanum carbonate of the invention (or lanthanum phosphate formed after binding to phosphate in the gut) is fully excreted and does not pass out of the gut into the circulation system when given orally, three rats were dosed with 20 mg/kg of $La_2(CO_3)_3.4H_2O$ (Sample 5) and kept in metabolic cages where faeces and urine could be collected. The results are shown in Table 2 below.

Animal No	Time (hours)	% La Recovered
1	24	103.2
1	48	0.1
1	72	<0.2
1	Total	103.3
2	24	75.3
2	48	23
2	72	1.2
2	Total	99.5
3	24	93.8
3	48	10
3	72	0.1
3	Total	103.8

It can be seen that after 72 hours, all of the lanthanum has been excreted. In the urine samples, the amount of lanthanum was below detection limits. After the test, the rats were sacrificed, and kidney, liver and femur were analysed for lanthanum. In all cases, the amount of lanthanum was below 0.1 ppm.

We claim:

1. A pharmaceutical composition for the treatment of hyperphosphataemia comprising lanthanum carbonate of the formula

$$La_2(CO_3)_3.xH_2O$$

where x has a value from 3 to 6, in admixture with a pharmaceutically acceptable diluent or carrier in a form for administration to the gastrointestinal tract.

2. A composition according to claim 1, wherein x has a value from 3.5 to 5.

3. A composition according to claim 2, wherein x has a value from 3.8 to 4.5.

4. A composition according to any one of claims 1 to 3 in unit dosage form to provide from 0.1 to 20 g/day.

5. A process for the preparation of lanthanum carbonate as defined in any one of claims 1 to 3 which comprises the steps of:

(i) reacting lanthanum oxide with hydrochloric acid to obtain lanthanum chloride;

(ii) reacting a solution of the thus obtained lanthanum chloride with an alkali metal carbonate to produce a wet cake of lanthanum carbonate octahydrate; and

(iii) drying the wet cake of lanthanum carbonate octahydrate so as to obtain a lanthanum carbonate with 3 to 6 molecules of water of crystallisation.

6. A process as claimed in claim 5 wherein the alkali metal carbonate is sodium carbonate.

7. A method to treat hyperphosphataemia in a subject which method comprises administering to said subject an amount of lanthanum carbonate of the formula

$$La_2(CO_3)_3.xH_2O$$

wherein x has a value from 3 to 6 effective to treat said hyperphosphataemia.

8. The method of claim 7 wherein x has a value from 3.5 to 5.

9. The method of claim 8 wherein x has a value from 3.8 to 4.5.

10. The method of any of claims 7–9 wherein said administering is by an oral route.

* * * * *

13.1 Patent Exclusivity Information

US patent 5,968,976 entitled "Pharmaceutical Composition Containing Selected Lanthanum Carbonate Hydrates" was issued on October 19, 1999, to AnorMed Inc., Langley, Canada.

The undersigned declares that Patent No. 5,968,976 covers the formulation, composition, and/or method of use of lanthanum carbonate. This product is the subject of this application for which approval is being sought.

Time Sensitive Patent Information pursuant to 21 CFR 314.53 for NDA #21-468.

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: FOSRENOL
Active Ingredient(s): Lanthanum Carbonate Hydrate
Strength(s): 250 mg and 500 mg
Dosage Form: Chewable tablets
Approval Date: _____

A. Information for each individual patent submitted:

US Patent Number: 5 968 976

Expiration Date: March 19, 2016

Type of Patent: Drug Substance (Active Ingredient)

Drug Product (Composition/Formulation)

Method of Use
If patent claims method of use, please specify approved method of use or method of use for which approval is being sought that are covered by patent: phosphate binding

Name of Patent Owner: AnorMED Inc, Langly, Canada

US Agent (if patent owner or applicant does not reside or have place of business in the US): Shire Pharmaceutical Development Inc, Rockville, Maryland

B. The following declaration statement is required by 21 CFR 314.53. If any of the submitted patents have Composition/Formulation or Method of Use claims, it should be submitted for each patent that contains composition/formulation or method of use claims.

The undersigned declares that the above stated United States Patent Number 5 968 976 covers the composition, formulation and/or method of use of lanthanum carbonate hydrate. This product is the subject of this application for which approval is being sought.

Sumakrishn
Suma Krishnan
Senior Manager
Regulatory Affairs

April 19th 2002
Date

13.2 Market Exclusivity

Shire is claiming exclusivity of Lanthanum Carbonate, a new chemical entity that has never been approved by FDA in any other application submitted under section 505(b) of the act.

14.0 PATENT CERTIFICATION

Lanthanum Carbonate Hydrate is being submitted as a 505(b)(1) application. The active ingredient in Lanthanum Carbonate Chewable Tablets is Lanthanum Carbonate and is protected by US Patent Number 5 968 976, expiration dating March 19, 2016. Furthermore, Shire Pharmaceutical Inc is the sponsor of the Lanthanum Carbonate New Drug Application 21-468. Therefore, no patent certification information is required for this submission.

EXCLUSIVITY SUMMARY FOR NDA # 21-468

Trade Name Fosrenol Generic Name (lanthanum carbonate)

Applicant Name Shire Pharmaceutical Development Inc.

HFD# 110

Approval Date: October 26, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /___/ NO /X/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8 /NA/

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

NA

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

NA

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

NA

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

NA

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other

than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of

the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical

investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new"

investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ ! NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

(See appended electronic signature page)
Denise M. Hinton
Regulatory Health Project Manager, HFD-110
October 14, 2004

(See appended electronic signature page)
Robert Temple, MD
Director, Office of Drug Evaluation I
October 26, 2004

Form OGD-011347 Revised 05/10/2004

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # : 21-468 Supplement Type (e.g. SE5): N/A Supplement Number:

Stamp Date: January 26, 2004 Action Date: October 26, 2004

HFD 110 Trade name/dosage form: FOSRENOL (lanthanum carbonate) 250 and 500 mg Chewable Tablets

Applicant: Shire Pharmaceutical Development Inc. Therapeutic Class: Standard

Indication(s) previously approved: NA

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: [redacted]

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
X There are safety concerns
☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other:_____

studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

ction D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: **NDA 21-468**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

REQUEST FOR WAIVER OF PEDIATRIC STUDIES

NDA Number: 21-468

Drug Name: Fosrenol (lanthanum carbonate)

Sponsor: Shire Pharmaceutical Development Inc.

Indication: Fosrenol is indicated for [illegible]

Age ranges included in waiver request: 0 – 18 years

Reasons for waiving pediatric studies:

a) No meaningful therapeutic benefit over existing treatments and is unlikely to be used in a substantial number of pediatric patients.

b) Studies are impossible or highly impractical because the number of patients is so small or geographically dispersed.

Justification for waiver:

The reasons for the request for a full waiver are as follows:

a) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

   The standard treatment for pediatric patients with end-stage renal failure is transplantation. Because pediatric patients are given a high priority as candidates for rapid organ transplant, there is a very low available ESRF pediatric patient population to study.

b) Any necessary clinical studies of lanthanum carbonate in pediatric patients that would be conducted to secure a pediatric indication would be highly impractical, if not impossible, given the very low numbers of potentially available patients.

   When the protocol of one of the studies submitted in this NDA (LAM-IV-307) was amended to include patients from age 12 – 18, no such patients were identified to enroll in this study. It is estimated that only 1200 – 1300 pediatric patients of all age groups constitute the target patient population for this drug. Because these patients have the highest priority for renal transplants, there are even fewer than this who could potentially be candidates for investigational studies, thus making such studies highly impractical to conduct as enrollment rates would be prohibitively slow for any meaningful size study.

20.0 Pediatric Use Information

In accordance with 21 CFR 314.55(c)(2)(i) and 21 CFR 314.55(c)(2)(ii), Shire requests a full waiver of the requirements of 21CFR 314.55(a) for a pediatric assessment of lanthanum carbonate for all pediatric age groups.

The reasons for the request for a full waiver are as follows:

1) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

   The standard treatment for pediatric patients with end-stage renal failure is transplantation. Because pediatric patients are given a high priority as candidates for rapid organ transplant, there is a very low available ESRF pediatric patient population to study.

2) Any necessary clinical studies of lanthanum carbonate in pediatric patients that would be conducted to secure a pediatric indication would be highly impractical, if not impossible, given the very low numbers of potentially available patients.

   When the protocol of one of the studies submitted in this NDA (LAM-IV-307) was amended to include patients from age 12 – 18, no such patients were identified to enroll in this study. It is estimated that only 1200 – 1300 pediatric patients of all age groups constitute the target patient population for this drug. Because these patients have the highest priority for renal transplants, there are even fewer than this who could potentially be candidates for investigational studies, thus making such studies highly impractical to conduct as enrollment rates would be prohibitively slow for any meaningful size study.

16.0 DEBARMENT CERTIFICATION

On behalf of Shire Pharmaceutical Development Inc. (Shire), I hereby certify that Shire did not and will not use in any capacity the services of any individual, partnership, corporation, or association debarred under Subsection (a) or (b) of §306 of the Federal Food, Drug, and Cosmetic Act in connection with this NDA application for Lanthanum Carbonate.

R. J. Lilley

Rick Lilley, Ph.D.
Senior Vice President
Regulatory Affairs

19 Apr 02

Date

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: October 5, 2004

FROM: Abraham Karkowsky, M.D., Ph.D. Team-Leader, Division of Cardio-Renal Drug, Products HFD-110

THROUGH: Norman Stockbridge, Acting Director, Division of Cardio-Renal Drug Products, HFD-110

TO: Dr. Robert Temple, Office Director, ODE-1

SUBJECT: Approvable recommendation for lanthanum carbonate

This memo outlines the rationale for issuing [redacted] for lanthanum carbonate. The approvable recommendation covers only the dose strengths of 250 and 500 mg of the "current" formulation. [redacted]

[redacted]

Approval for lanthanum carbonate should await the submission for review, and

[redacted]

[redacted]. Furthermore, since the events of concern (mortality, gastrointestinal effects and fractures) are relatively common in a dialysis population, a control population to be agreed upon would appear necessary to interpret any of the results. If lanthanum carbonate is approved, labeling should incorporate the level of current uncertainty, particularly, with respect to lanthanum's effect on mortality, gastrointestinal events and bone-related events.

The current submission of 26 January 2004 with its subsequent amendments attempts to respond to the deficiencies as outlined in the Approvable letter of 27 February 2003. My memo relies on previous supervisory review and primary reviews. Current reviews in response to this amendment were also included in the construction of this memo. An outside consultant, Dr. Capen on Ohio State University, was consulted with respect to the animal bone pathology slides.

Sources

Initial reviews:

Clinical Pharmacology (Dr. Dorantes) dated 10 January 2003.
Chemistry (Dr. Raman) dated 31 December 2002 and 16 January 2003.
Medical Review (Dr. Pelayo) dated 31 December 2002.
Canine Toxicology (Dr. Koerner) dated 4 December 2002.
Primary Statistical Reviews (Dr. Freidlin) dated 5 November 2002 and 6 January 2003.
Pharmacology and Toxicology (Dr. Joseph) 14 January 2003.
Supervisory Medical Review (Dr. Stockbridge) 3 February 2003.
Supervisory Medical Review (Dr. Throckmorton) 25 February 2003.

Current reviews:

Clinical Pharmacology (Dr. Dorantes) dated 19 August 2004.
Chemistry (Dr Raman) dated 14 September 2004.
Medical Review (Dr. Williams) dated 14 July 2004.
Primary statistical Review (Dr. Freidlin) dated 18 May 2004.
Clinical Pharmacology (Dr Joseph) dated 8 June 2004.
DMETS review (Ms Holquist, RPh) dated 1 July 2004.
DSI Review (Dr. Skelly) dated 6 July 2004.
Outside Animal Pathologist report (Dr. Capen; D.V.M, Ph.D; Ohio State University), was undated.

Background:

Lanthanum carbonate, when administered with meals, binds dietary phosphate and lowers the serum phosphate levels in patients with end-stage renal disease who are treated either with peritoneal or hemo- dialysis. Although the incidence of isolated hypercalcemia appears less on Fosrenol compared to the control therapies, there is no evidence these events lead to meaningful changes in therapy or required interventions. As such, there does not appear to be a demonstrable benefit of lanthanum when compared to other phosphate binding treatments either approved (Renalgel®), calcium acetate (Phoslo®) or frequently utilized but unapproved such as calcium carbonate (e.g., TUMS).

The lanthanum ion is minimally (<< a fraction of a percent) but demonstrably absorbed and accumulates to a substantial degree in certain tissues. Based on intravenous studies in humans, only 7.25% of an intravenous dose (120 pg of elemental lanthanum) could be accounted for as excreted either in urine (1.75 %) or feces (5.6%) after a 7 day collection; the rest of the dose appears to be distributed in human tissues.

So what is the fate of lanthanum? Animal study strongly suggests that lanthanum is concentrated in specific tissues. The residence time in these tissues is extremely long since the half-life for washout once treatment is discontinued is on the order of years. In chronic studies of mouse (80 weeks), rat (78 weeks) and dog (52 weeks), high concentrations are bound throughout the gastrointestinal tract (> 10ug/g tissue wet weight), with lesser but substantial amounts (between 1 to 10 ug/g tissue wet weight) in bone (weight bearing bones, flat bones as well as the growth plate of femur) . Lanthanum is also concentrated in liver. In rats, after 4 weeks of treatment, followed by a 26-week washout period there was substantial clearance of lanthanum

from the lower GI tract, however, > 50% of the measured lanthanum concentrations remained in the glandular stomach, duodenum, mesenteric lymph nodes jejunum, femur sternum and trachea. In dogs, after 4 weeks of treatment followed by a 26-week washout period there was persistent lanthanum and slowly decreased levels in liver, femur and fundic stomach.

Not surprisingly, there is less available data for tissue concentrations in humans. There are three databases for which chronic levels of lanthanum from bone biopsy were available (see page 11-19 of Dr. Dorantes review). These studies are LAM-IV-301, LAM-IV-303 and LAM-IV-307. Considering all data, both paired and unpaired bone lanthanum measurements, there is a slow but progressive accumulation of this ion in bone and this accumulation is related to the duration of treatment. The duration of exposure to lanthanum carbonate in these studies ranged from approximately 1 year to approximately 60 months. Paired, on-therapy measurements of bone lanthanum concentrations were available for 12 subjects. Paired bone-lanthanum concentrations one on-treatment and one approximately 24-months off-therapy were also available for a separate cohort of 12 treated patients. Based on the on-therapy samples, the half-life for accumulation was 1.9 years; the half-life for washout was calculated as 3.94 years. Neither estimate appears to be sufficiently accurate to establish and assess the duration of treatment appropriate to assess the steady state effects of lanthanum. Both estimates of the half-life would suggest that it would take approximately a decade or longer of treatment for the steady state effect of lanthanum to manifest.

As each of the clinical reviewers makes clear, the issue of most concern is the consequence of the long-term accumulation of lanthanum. There are two distinct concerns related to lanthanum's long half-life in tissues. The first is that the available database is unlikely to capture the full consequence of the use of lanthanum as it accumulates over time. The second is that once an adverse event occurs, the persistence of the lanthanum ion in patients could translate into the persistence or slow resolution of these events.

Long-term safety:

The long-term, open-label, safety of lanthanum carbonate is best described by those enrolled into study LAM-307. This study included 1,354 patients with end-stage renal disease, who were treated with hemodialysis at least three times weekly, and had elevated serum phosphate levels. Phosphate levels were controlled in one group with lanthanum carbonate. In the comparative group (control group), phosphate levels were controlled by one of several commonly used treatments i.e., sevelamer hydrochloride (Renagel®), calcium acetate (Phoslo®) or calcium carbonate (Tums). Adverse events of sufficient severity among those treated with lanthanum resulted in discontinuation. For those treated with other phosphate binders, a choice of an alternate phosphate binder could be made and did not therefore, require the patient's discontinuation. Dropouts, though much greater with lanthanum carbonate may at least partly be explained by the control treatments made available to the control group. The mean duration of treatment in the lanthanum treated group was 0.91 years and 1.25 years in the control therapy group.

Mortality:

The last available mortality update for study LAM-307, the positive controlled study reflects the information through May 30, 2003. As of that date, 680 patients were treated with lanthanum and 674 with the alternate phosphate binders. As per the agency's request, the sponsor ascertained the vital status of 97% of those enrolled was available. Although there did not appear to be differences in early mortality rates (6.6%/year for both lanthanum and control groups),

confidence intervals for this estimate are difficult to construct, primarily because patients were crossed-over from control therapies to lanthanum and visa versa. Longer term data, considering the long half-life of lanthanum in certain tissues, makes the extrapolation of the available mortality data to longer durations of treatment, far from certain.

Gastrointestinal:

More patients treated with lanthanum than those treated with the control phosphate binding regimens, discontinued for GI adverse events in study LAM-307. As noted above, the difference in dropout rate reflects other treatments allowed for those in the control phosphate binding group. Overall adverse events for gastrointestinal adverse events when corrected for the duration of available exposure, as tabulated from Dr. Freidlin's review favor the control therapy.

Table 1: Rates of specific gastrointestinal-related adverse events in the 15-month safety update (% patients normalized to exposure)*.

Specific GI AE	Lanthanum	Control
Abdominal pain	13.3	11.5
Constipation	10.3	9.6
Diarrhea	18.1	16.2
Nausea	26.7	20.1
Vomiting	22.4	15.9

*The numbers reflect the % of patients during the study with the event, with the rate in the control-group corrected by the average difference in the duration of exposure.

The difference in adverse events between the two treatments groups does not appear to be of major clinical significance. The unresolved issue is the time to resolution of the adverse events once lanthanum is discontinued. Chronic unresolved adverse events in a dialysis population may be of particular significance since this population has minimal nutritional reserve. In response to our concern, the sponsor submitted the following data describing the resolution of gastrointestinal events. The table below suggests that the vast majority of adverse events are resolved and the number of unresolved or resolved with sequelae events do not appear to be related to the nature of the treatment or with the duration of exposure. Although the specific time to resolution of the gastrointestinal adverse events is not entirely clear, there does not appear to be a signal suggesting a difference compared to the control therapy. The number of events and number of patients with GI events are shown in the shaded area in the table below.

Table 2: Consequence of gastrointestinal adverse events comparing lanthanum to control-treated patients.

		Lanthanum carbonate			Control Therapy		
Outcome↓	Time on-Tx at onset of event	# events/#pts with event	# pt at risk	Events or /(pts) per # pt at risk	# events/#pts with event	# pt at risk	Events or /(pts) per # pt at risk
Resolved	1-4 wks	277/178	680	0.41/(0.26)	201/137	674	0.30/(0.20)
	5-26 wks	544/233	618	0.88/(0.38)	644/281	651	0.99/(0.43)
	27-52 wks	328/161	414	0.79/(0.39)	513/231	535	0.96/(0.43)
	> 1 yr	375/115	269	1.39/(0.43)	825/222	396	2.08/(0.56)
Resolved with Sequelae	1-4 wks	0/0	680	0/(0)	0/0	674	0/(0)
	5-26 wks	7/6	618	0.01/(0.01)	1/1	651	0/(0)
	27-52 wks	5/5	414	0.01/(0.01)	2/2	535	0/(0)
	> 1 yr	1/1	269	0/(0)	2/2	396	0.01/(0.01)
Unresolved	1-4 wks	39/33	680	0.06/(0.05)	29/26	674	0.04/(0.04)
	5-26 wks	68/54	618	0.11/(0.09)	77/55	651	0.12/(0.08)
	27-52 wks	56/37	414	0.14/(0.09)	61/50	535	0.11/(0.09)
	> 1 yr	52/42	269	0.19/(0.16)	122/76	396	0.31/(0.19)

Bones:

Much of the concern about the effects of lanthanum on bone is attributable to the previous use of aluminum, also a trivalent cation, as a phosphate binder and the associated consequences of aluminum toxicity, particularly on bone. The concern is further compounded by the large lanthanum levels measured in tissues of humans, dogs, rats and mouse. There are several lines of evidence either implicating or absolving lanthanum as potentially altering bone homeostasis. These studies include *in vitro* models of bone metabolism as well as long-term animal as well as a small amount of human biopsy data. Although there are clearly signals that lanthanum could alter bone metabolism, there is insufficient evidence that it does.

In vitro assays indicate that at bath concentrations > 100 ng/ml, certainly within the concentrations or levels measured in bone during short term human use, lanthanum alters osteoblastic, osteoclastic and bone formation, although it did not show activity in a bone resorption assay (see pages 24-25 of Dr. Joseph's review of January 13, 2003). There was an increase in osteoblastic differentiation at a dose of 100 ng/ml but inhibition at concentrations of 5,000-15,000 ng/ml. Bone formation was activated at doses of 5,000-15,000 ng/ml; with the NOAEL dose of < 100 ng/ml. With respect to placing these concentrations into perspective, in humans after 1-year of treatment with lanthanum carbonate, lanthanum levels accumulated in the flat bone as measured in biopsy samples. Median concentrations (as per Dr. Pelayo's review) were approximately 2, 000 ng/gram tissue.

Bone histology was examined in a 13-week and 26-week study in mice, 52-week oral studies in dogs as well as part of the long-term carcinogenicity study in mice (99 weeks) and rats (104 weeks). The sponsor did not indicate any histological alterations of either weight-bearing bones (femur) or flat bone (sternum).

Dr. Williams, however, reviewed a small number of slides (seven) of non-uremic lanthanum treated mice (no concomitant controls were submitted for his review). He concluded that there was evidence of increased osteoclastic activity and bone loss with periosteal thickening. In some portion of the slide, severe cortical bone loss resulted in architectural disruption and replacement with fibrocollagenous tissue.

I cannot tell whether these changes reflect a direct bone toxicity of lanthanum or are secondary to the induction of a hypophosphatemic state by excessive phosphate binding by lanthanum exposure. A chronic low-dose intravenous study, with concentrations of lanthanum inadequate to substantially alter phosphate metabolism but adequate to mimic plasma concentrations could easily answer whether lanthanum accumulation results in direct bone toxicity.

With respect to the effects on human bone, there were paired baseline and on-treatment bone-biopsy samples which were analyzed for histomorphometry for lanthanum-treated and control subjects in study LAM-IV-307. Subjects had biopsies at baseline and some had paired samples at 1 year and others at 2 years of treatment. Relatively few subjects had biopsies after longer durations of treatment. There were 36 and 39 lanthanum and control therapy subjects, respectively that had paired biopsies at baseline and year 1. There were 25 and 19 subjects in the lanthanum and control group respectively, that had paired biopsy samples at baseline and year 2.

The tables below contain the histomorphometric-based diagnosis at baseline and at the 1 and 2 year paired measurement for both lanthanum and control-treated patients. There were

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substantial shifts in comparing the diagnosis at baseline and year 1 or year 2. Nevertheless, there was little shift in the net diagnosis. The number of subjects without bone pathology (i.e. none) was 8 % at baseline and 14% at the one year biopsy for lanthanum and 13% and 18% for the respective points in the alternate therapy group. For year 2 the results the percent of subjects with no pathology (none) increased from 12% to 16% for lanthanum and decreased from 16% to 11% for the alternate therapy group. None of these differences reflect a convincing change.

? 17

Table 3: Histomorphometric paired results for Lanthanum and Alternate therapy patients study LAM-IV-307, year 1 (% patients).

	Lanthanum					Control				
	Baseline (n=36)	Adynamic bone disease	Mixed uremic osteodystrophy	Hyperparathyroid bone disease	None	**Baseline (n=39)**	Adynamic bone disease	Mixed uremic osteodystrophy	Hyperparathyroid bone disease	None
Adynamic bone disease	44	14	8	19	3	31	13	2	11	5
Mixed uremic osteodystrophy	22	8	0	8	3	26	3	8	13	2
Hyperparathyroid bone disease	25	3	6	17	3	31	8	6	13	5
None	8	3	0	0	6	13	5	0	2	5
Total	100	27	14	44	14	100	28	15	38	18

Table 4: Histomorphometric paired results for Lanthanum and Alternate therapy patients study LAM-IV-307, year 2 (% patients).

	Lanthanum					Control				
	Baseline (n=25)	Adynamic bone disease	Mixed uremic osteodystrophy	Hyperparathyroid bone disease	None	**Baseline (N=19)**	Adynamic bone disease	Mixed uremic osteodystrophy	Hyperparathyroid bone disease	None
Adynamic bone disease	32	8	12	12	0	26	0	0	11	11
Mixed uremic osteodystrophy	24	4	4	8	8	26	0	5	13	0
Hyperparathyroid bone disease	32	0	4	20	8	32	16	5	13	0
None	12	4	4	0	0	16	16	0	2	0
Total	100	16	24	40	16	100	32	11	38	11

In study LAM-IV-307 osteocalcin, parathyroid hormone and bone-related alkaline phosphatase, plasma markers reflective of bone turnover were increased in the lanthanum-treated when compared to control treated patients. Since nearly all of those in the control therapy group were treated with calcium salts to bind phosphate, the changes may equally reflect the consequences of an increase in calcium as opposed to the direct effects of lanthanum.

Fracture data were not prospectively defined as an adverse outcome of interest. Consequently, the collection of supporting information related to each event is of uncertain completeness. In addition, the duration of follow-up was short relative to the time for attaining steady state lanthanum levels. It is therefore, unclear if the collected data reflect the full consequence of chronic lanthanum treatment. When corrected for number of patients who discontinued, there did not appear to be convincing signals that lanthanum either increases or has

no effect on the risk of fractures. There was no increase in the rate of events comparing lanthanum to control treatment nor did the rate of events per unit time increase with increased exposure to lanthanum.

Table 5: Fracture rates by treatment and per unit time comparing lanthanum to control-treated patients.

	Lanthanum			Control Therapy		
Interval (months) of exposure	Fractures	Adjusted rate	Adjusted for duration of interval Events/subject/month	Fractures	Adjusted rate	Adjusted for duration of interval
0-2	14	0.9	0.3	12	1.3	0.43
3-5	9	0.8	0.26	7	0.9	0.3
6-11	22	2.4	0.4	11	1.6	0.25
12-23	15	2.7	0.2	19	4.3	0.36
24-35	5	2.2	0.19	3	1.3	0.11
≥ 36	1	2.2	?	0	?	?

Summary:

So where do we go from here? The sum of the data does not indicate a specific safety signal. The unknowns and potential consequences of these unknowns are the vexing problems and it is unlikely that additional analyses of the existing data will be useful in sorting out these risks. Based on the long time to achieve steady state and the added uncertainty as to when steady state will occur, the sum of the information currently available may be not totally reflect the consequence of chronic lanthanum carbonate treatment. Lanthanum, therefore, appears to be approvable with the uncertainties clearly outlined in labeling [redacted]

Since the nature of the events that will be [redacted] reflects common adverse events, i.e., mortality, fractures and GI adverse events, in this population, [redacted] requires the comparison to an appropriate control group. The duration of follow-up as well as the sizing of the study is currently unclear. The specifics [redacted] should be submitted by the sponsor and reviewed and agreed upon by this Division prior to issuing an approval.

Other issues:

Pediatric Waiver:

Since lanthanum accumulates in growth plate of animals, since alternate therapies to bind phosphate are available and since the half-life of lanthanum in bone is very long, it does not seem possible to assess the unique consequences related to growth and development of this drug in children. It does not appear that the risk of exposing this group of vulnerable patients can be balanced against any known or proposed benefit of lanthanum treatment. A waiver of the pediatric studies is appropriate and labeling should discourage Fosrenol's use in pediatric patients.

Formulation issues:

The formulation and dose strength of lanthanum carbonate utilized in the clinical studies was limited to the 250 mg dose of the "current" formulation. Dr. Dorantes, the biopharmaceutic

reviewer recommends a biowaver for the 500 mg dose strength of the "current" formulation based on the compositional proportionality of the 250 and 500 mg doses. In addition, the 500 mg dose is within the tested clinical range and the 500 mg dose strength dissolution profile was acceptable when performed under FDA-accepted conditions. The biowaver appears appropriate.

With respect to the dissolution specifications for both the 250 and 500 mg "current" formulation, the biopharmaceutic reviewer recommends that a the currently validated whole tablet method (USP Apparatus 2, and rpm) with a Q at 45 minutes serve as the appropriate method for lot release testing and stability testing.

Division of Medication Errors and Technical Support (DMETS):

DMETS had no problem with the trade name Fosrenol. DMETS' comments concerning packaging and labeling in their review of 26 July 2004 should be transmitted to the sponsor. As noted by DMETS, the dose strength refers to mg of lanthanum equivalents. Both the package insert as well as the packaging should clarify to what the dose-strength refers.

Chemistry:

The remaining chemistry issues have been resolved for the 250 and 500 mg "current" formulation. In particular, the specifications for potential metal impurities were agreed upon by the Division and the sponsor.

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/s/

Abraham Karkowsky
10/12/04 09:42:26 AM
MEDICAL OFFICER

Norman Stockbridge
10/13/04 04:50:46 PM
MEDICAL OFFICER

10/21/04

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page(s) of trade secret and/or confidential commercial information (b4)

1/15/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-468

Shire Pharmaceutical Development Inc.
Attention: Lisa Wittmer, Ph.D.
1801 Research Boulevard, Suite 600
Rockville, MD 20850

Dear Dr. Wittmer:

Please refer to your new drug application (NDA) originally submitted on April 30, 2002 and resubmitted on January 26, 2004, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosrenol (lanthanum carbonate) 250, 500, [redacted], Chewable Tablets.

We acknowledge receipt of your July 8, 2004 CMC/Clinical Pharmacology amendment to this application. We consider this a major amendment, as the receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is October 26, 2004.

If you have any questions, please call Ms. Denise Hinton, Regulatory Health Project Manager, at (301) 594-5333.

Sincerely,

/S/

{See appended electronic signature page}

Edward Fromm
Acting Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
7/15/04 04:42:07 PM

7/2/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-468
Shire Pharmaceutical Development Inc.
Attention: Lisa Wittmer, Ph.D.
Associate Director, Regulatory Affairs
1801 Research Boulevard, Suite 600
Rockville, MD 20850

Dear Dr. Wittmer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosrenol (lanthanum carbonate) 250, 500 — mg Chewable Tablets.

Reference is made to the meeting held on June 17, 2004 to discuss outstanding clinical issues from the February 28, 2003 approvable letter. Enclosed are photomicrographs with legends to support the Agency's observation that the bones of rats with normal renal function show abnormalities after exposure to lanthanum carbonate. A brief summary of the descriptive pathology of bones in rats and humans exposed to lanthanum, pathology reports of slides from bones in the rat pilot study (as per your letter dated October 12, 1999), and bone biopsies from humans (as per your letter dated May 5, 2004) are also enclosed.

The materials reviewed are as follows:

1. Slides from 3 groups of rats were received and reviewed. Treatment groups A and G were animals with chronic renal failure receiving vehicle, slides from animals with chronic renal failure receiving lanthanum carbonate were labeled B,G, and H and slides from animals with normal renal function treated with lanthanum were labeled C, F and I.

2. Microscopic slides from only 3 patients exposed to lanthanum for 4 to 5 years were received and reviewed. In addition, slides from 7 patients on lanthanum and 6 patients on standard therapy followed for periods of 6 months to 2 years were also received and reviewed. Slides received from 3 patients on "Calcium" were not reviewed as calcium is not approved for the treatment of hyperphosphatemia. Furthermore, there is no controversy about the toxicity of calcium on bones as a safety concern.

Each micrograph has a brief legend and has been labeled according to the group of the animal. For human bone slides, the alphabet "H" has been used before the slide number as provided by the sponsor. We note that the special stain, [ ] for routine examination of undecalcified bone that was requested by the Agency was not made available for this review.

If you have any questions, call Ms. Denise M. Hinton, Regulatory Health Project Manager, at (301) 594-5333.

Sincerely,

{See appended electronic signature page}

Akinwole Olufemi Williams, M.D.
Medical Officer
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Description of Rat bone histopathology slides and lanthanum effects

Bone pathology and bone toxicity
Disease manifestations in bones can be regarded as a function of time, place and quantity and they are more readily comprehended when correlated with the evolving and changing cellularity of bone development, structure and function. However, the evaluation of drug induced toxicity can best be detected by a careful examination of structural defects affecting both the osseous and myeloid components of bone. The selective vulnerability of the metaphysis is well recognized particularly in inflammation. It is, therefore, not surprising that the metaphysis is affected most frequently in lanthanum toxicity in the rats. The architectural disruption of metaphyseal cortical bone and the accompanying reparative fibrosis and periosteal thickening characterize the lanthanum injury to long bones of rats with normal renal function given lanthanum carbonate. A brief descriptive pathology of these observed lesions, not previously reported, is as follows:

The abnormal histological lesions found in slides from 7 rats with normal renal function were predominantly in the metaphyseal and metadiaphyseal areas of the long bones. The lesions are consistent with areas of bone loss that are usually characterized by multiple defects with irregular edges in the cortices of long bones. Periosteal thickening overlying the areas of bone loss was common and the extent of the periosteal abnormality varied with the size of the cortical bone defects. These bone defects may have inflammatory cells in their vicinity or may have large cells that may be osteoclasts. In some areas of severe cortical bone loss resulting in architectural disruption, the defect may be completely replaced by fibrocollagenous tissue (Figure 9). The cortical bone defects may be surrounded by collagenized desmoplastic fibroblastic cells, and may be relatively vascular suggesting an inflammatory type of granulation tissue. Xanthoma cells were not seen in this vascular granulation tissue.

There are a few host osteoclasts resorbing the outer cortical surface of the metaphysis. Similar lesions seen in rats with normal renal function are also seen in uremic rats given lanthanum, but the lesions in the uremic rats were more severe. Since the rat with normal renal function differs from the uremic rats in that there is no hypophosphatemia, it is conceivable that the observed changes in the normal rat represent lanthanum toxicity to bone. No immunohistochemistry was done on these bones. These observed changes are subtle in places and could be easily missed.

Description of pathology of human bones exposed to Lanthanum Carbonate

All the bone biopsies from patients exposed to lanthanum carbonate showed abnormalities at baseline and at follow up regardless of follow up. These abnormalities represent renal osteodystrophy and its variants. Of relevance is the fact that the cortical bone defects seen in rats with normal renal function given lanthanum are also seen in ESRD humans given lanthanum. The 3 unpaired slides from patients given lanthanum for four to five years are too few to make any meaningful comments particularly with the poor technical preparation of the slides submitted for review (See Figures 17-19). Some of the slides submitted had no cortical bone for microscopic examination. However, the temporal differences among the paired biopsies have been captured by histomorphometry and reported in the NDA, but the possible confounding effect of lanthanum cannot be dissected from the histomorphometric evaluation even with comparators. There is no compelling evidence that lanthanum does not affect bones in humans. There is evidence that lanthanum accumulates in bones in humans and in animals. For comparative data among treatment groups to be compelling, the severity and extent of bone changes in patients with ESRD at baseline should be equal. Since this was not ascertained prior to randomization, the only empirical clinical parameter left is the evaluation of fractures in both treatment groups.

However, with rapid advances in molecular biology, identification of systemic and local biomolecules that are known to regulate bone metabolism can now be achieved. For example, the study of localization and levels of

expression and synthesis of these factors in bone and its microenvironment is now feasible through applications of in situ hybridization histochemistry (ISHH) and immunohistochemistry (IHC). Application of ISHH allows study of specific mRNA expression. Combining histomorphometric techniques with ISHH and IHC elevates the study of bone metabolism and pathology to greater heights. In effect, cellular and molecular issues can now be studied to evaluate subclinical and clinical outcomes ***(Langub MC, Faugere MC, Malluche HH. Pediatric Nephrol 14: 629-635, 2000)***. This technique was available and in use at the time Shire had a meeting with the Agency. This should have been considered and applied to elucidate the role of lanthanum in bone toxicity.

Microscopic Slides from Rats -
Rats with Normal renal function given lanthanum -- C14, C13, CO4, FO1, FO2, C16, C15,
Uremic rats receiving vehicle --G12,
Uremic rats given lanthanum carbonate --- H13, HO2, XO6 and BO4

Rat with normal renal function administered lanthanum

Figure 1 shows irregular cortical bone surface with periosteal thickening in the metaphyseal area of rat tibia- left of photograph (** Enlarged in Figures 3 and 4)
Note the relatively normal cortical surface-right side of photo (Enlarged in Figure 2).

Rat with normal renal function administered lanthanum

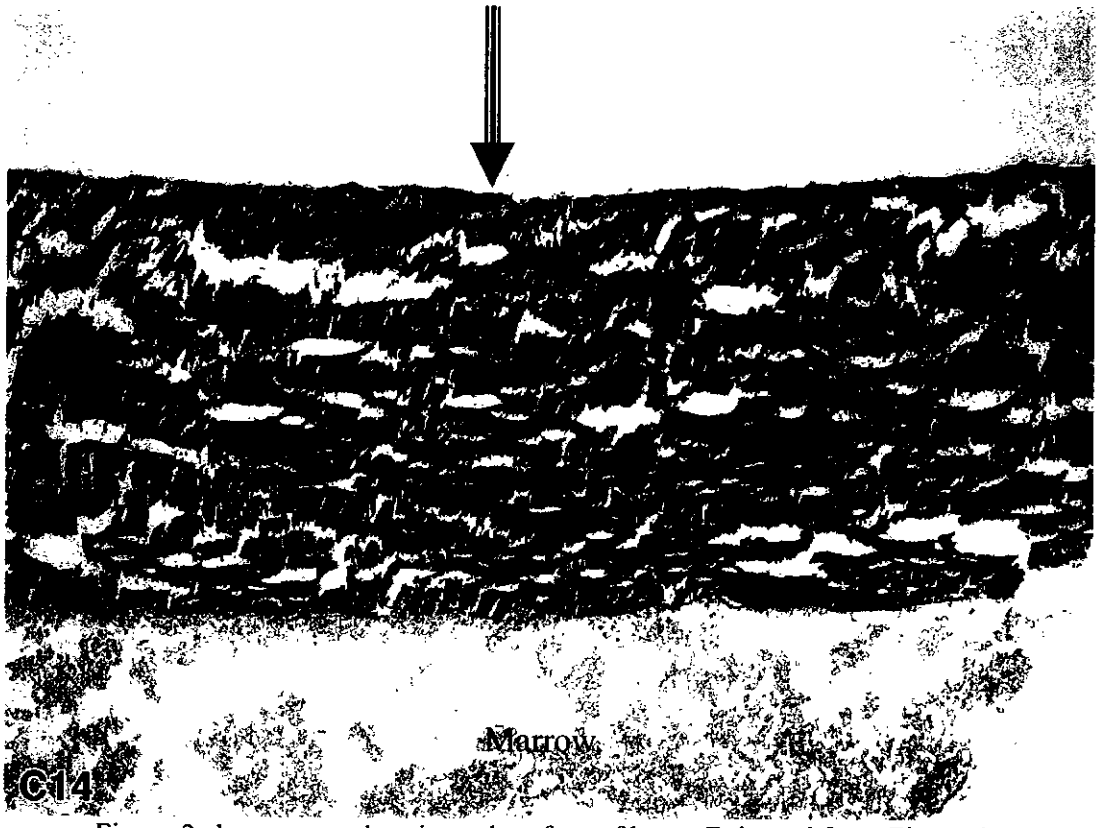

Figure 2 shows normal periosteal surface of bone. Enlarged from Figure 1.

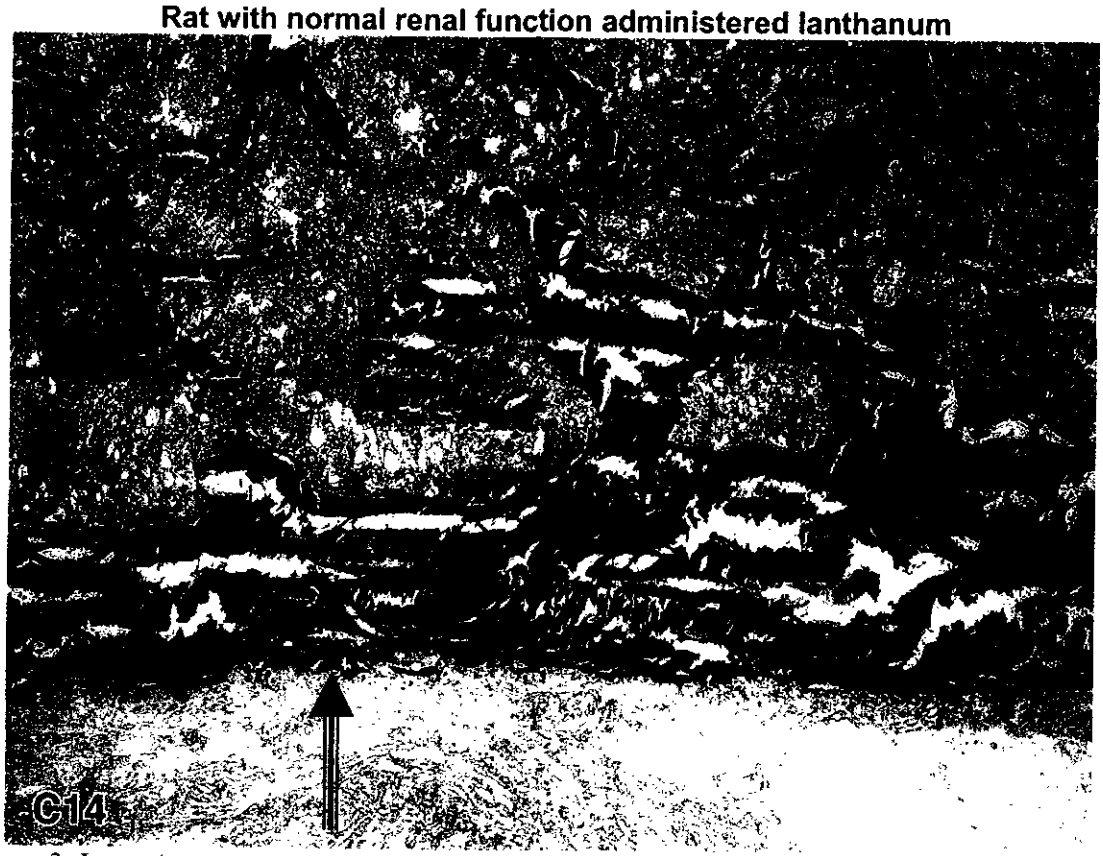

Figure 3: Long Arrow traverses periosteal thickening overlying irregular surface of cortical bone of rat with normal renal function given lanthanum ((See ** in Figure 1) Short arrow points to a focal demineralized area of bone.

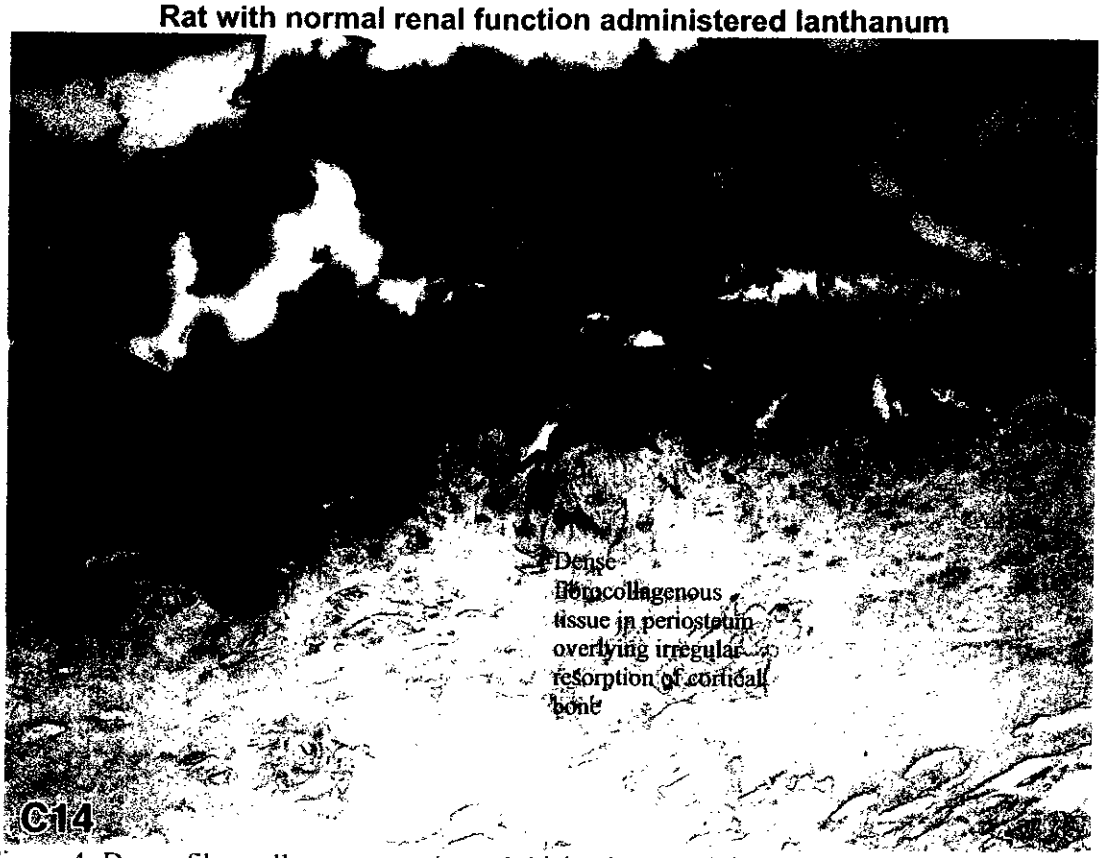

Figure 4: Dense fibrocollagenous periosteal thickening overlying irregular surface of cortical bone of rat with normal renal function given lanthanum ((See ** in Figure 1). Note some large cells that may be osteoclasts, adjacent to the irregular cortical surface.

Rat with chronic renal failure administered lanthanum carbonate

HO2

Figure 5: Micrograph of long bone from rat with chronic renal failure administered lanthanum carbonate showing periosteal thickening and irregular cortical bone surface (short arrow). Note similarity with figures 3 and 4 that show periosteal thickening and irregular cortical surface in rat with normal renal function given lanthanum.

Figure 6: Micrograph of long bone from rat with chronic renal failure administered lanthanum carbonate showing periosteal thickening and irregular cortical bone surface (short arrow and bar). Note similarity with figures 3 and 4 that show periosteal thickening and irregular cortical surface in rat with normal renal function given lanthanum carbonate.

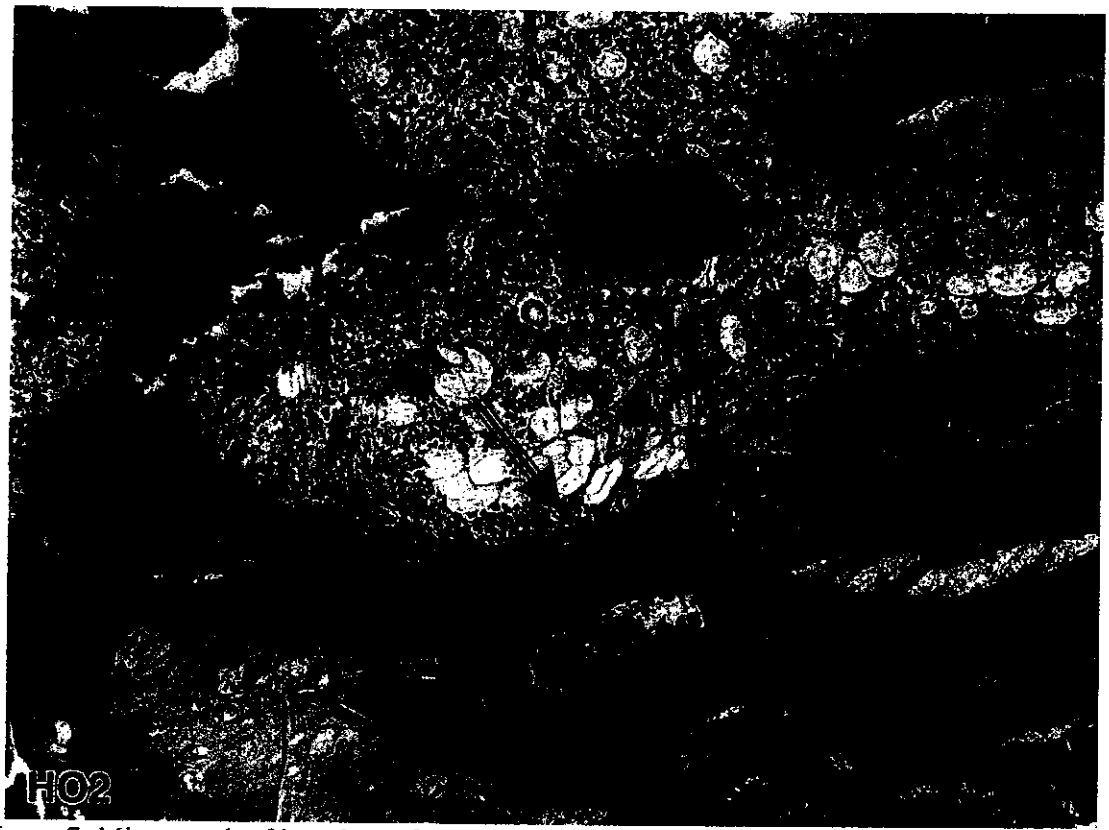

Figure 7: Micrograph of long bone from rat with chronic renal failure administered lanthanum carbonate showing evidence of collagen deposition adjacent to bone (Arrows).

Figure 8: Dense collagenous periosteal thickening overlying irregular surface of cortical bone of rat with normal renal function given lanthanum. TP= Thickened periosteum.

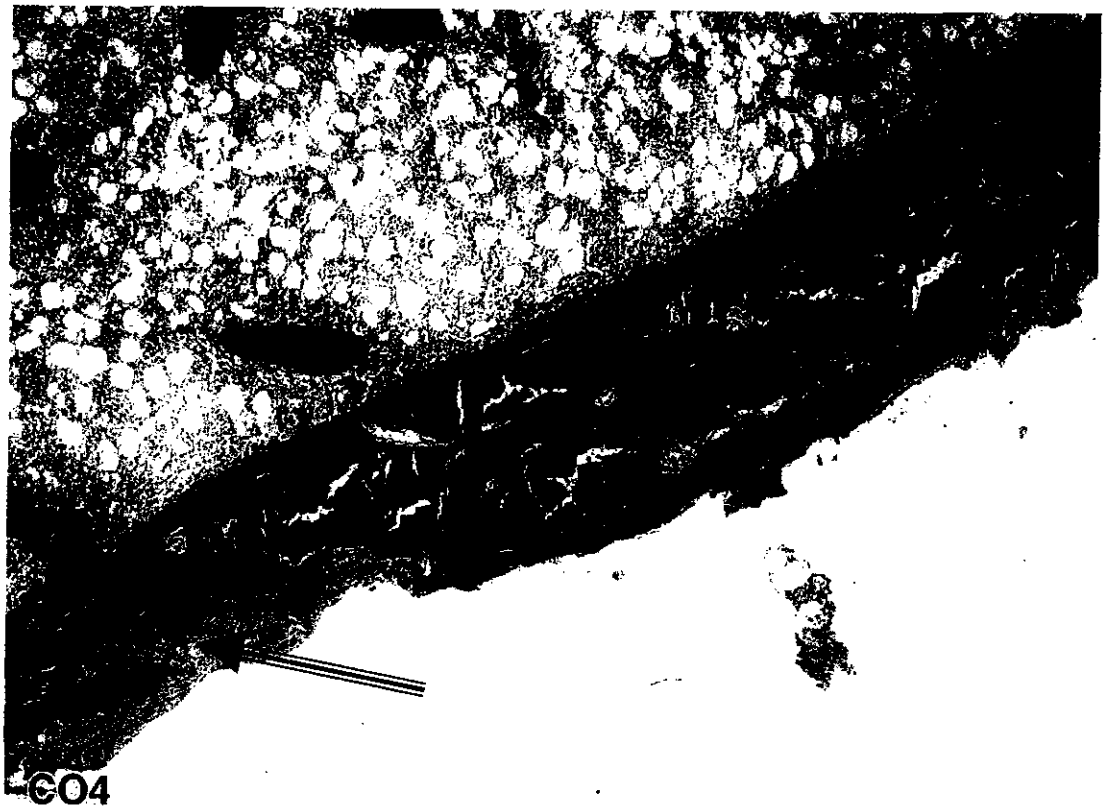

Figure 9: Dense fibrous tissue replacing areas of bone resorption (arrow) in a rat with normal renal function given lanthanum. The amount of bone resorption and the irregularity of the cortical bone surface are extensive. There is no periosteal or endosteal thickening. This suggests bone damage by lanthanum with replacement fibrosis.

Figure 10: Dense fibrocollagenous periosteal thickening overlying irregular surface of cortical bone of rat with normal renal function given lanthanum carbonate.

Figure 11: Dense fibrocollagenous periosteal thickening overlying irregular surface of cortical bone of rat with normal renal function given lanthanum carbonate. Arrows are in the bone defects resulting from bone loss. Note increased vascularization of periosteum.

Figure 12: Dense fibrocollagenous periosteal thickening overlying areas of bone loss (arrow) in rat with normal renal function given lanthanum carbonate. The thickened periosteum is highly vascular and has fat cells with granulation tissue suggesting a reparative process to tissue injury.

Figure 13: Micrograph of an exostosis (arrow) attached by a muscular pedicle to the metaphysis of a rat with normal renal function given lanthanum carbonate. The "exostosis" is composed of dense hyalinized collagenous tissue and foci of calcification consistent with dystrophic calcification. The etiology of this lesion is not clear.

Figure 14: Micrograph of rat with chronic renal failure given lanthanum carbonate showing demineralization of the cortex (Long arrow) and irregular cortical surface with bone defects (short arrow) consistent with bone loss.

Figure 15: Micrograph of rat with chronic renal failure given lanthanum carbonate showing demineralization of the cortex (long arrow) and irregular cortical surface with little pits (short arrow) consistent with bone loss.

Figure 16: Iliac bone biopsy from patient on lanthanum after 2 year follow up. Micrograph shows preparative artifact that is difficult to interpret to the left of field.

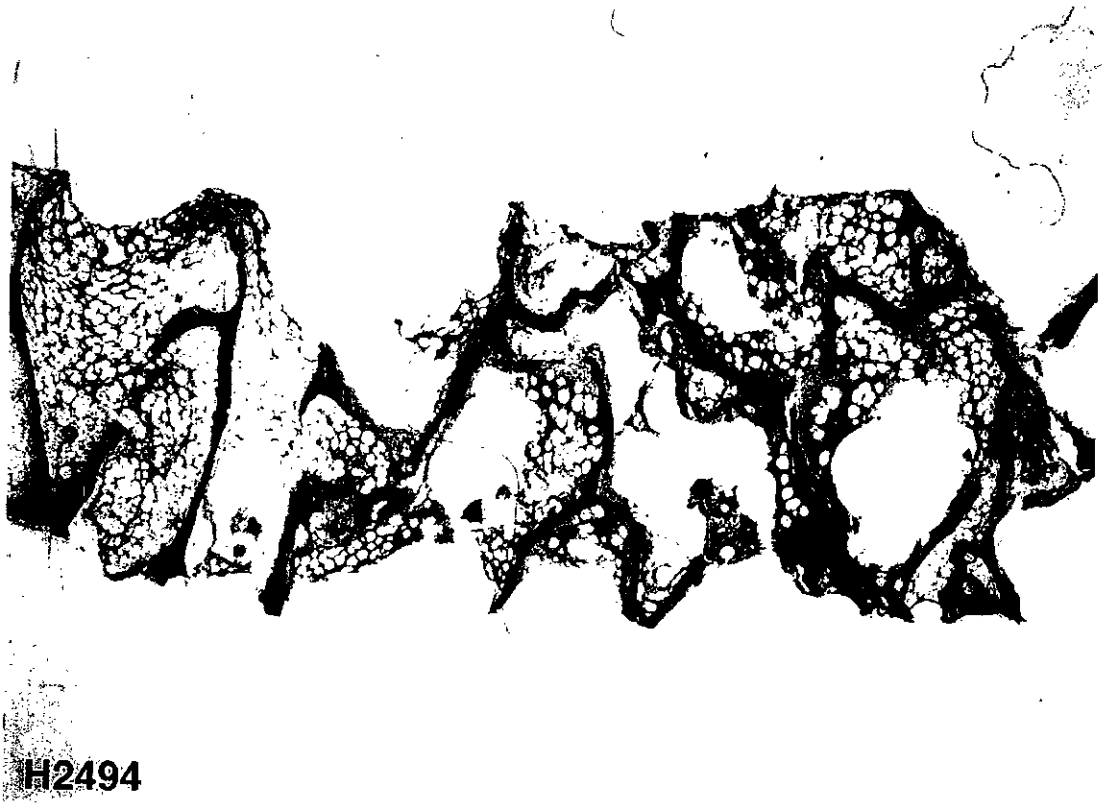

Figure 17: Iliac bone biopsy from patient on lanthanum after 4 years on drug. Micrograph shows extensive thinning of bone trabeculae with patchy bone loss. Cellular architecture of marrow is poorly preserved and uninterpretable.

Figure 18: Iliac bone biopsy from patient on calcium at baseline. Micrograph shows foci of calcification within marrow that is abnormal. There is also periosteal thickening (arrow). These changes at baseline in a patient treated with Calcium, an unapproved drug, raises the question of using these bone biopsies for comparative purposes in this clinical program. Figure 19 shows a higher power view of one of these foci of calcification in the marrow of this patient.

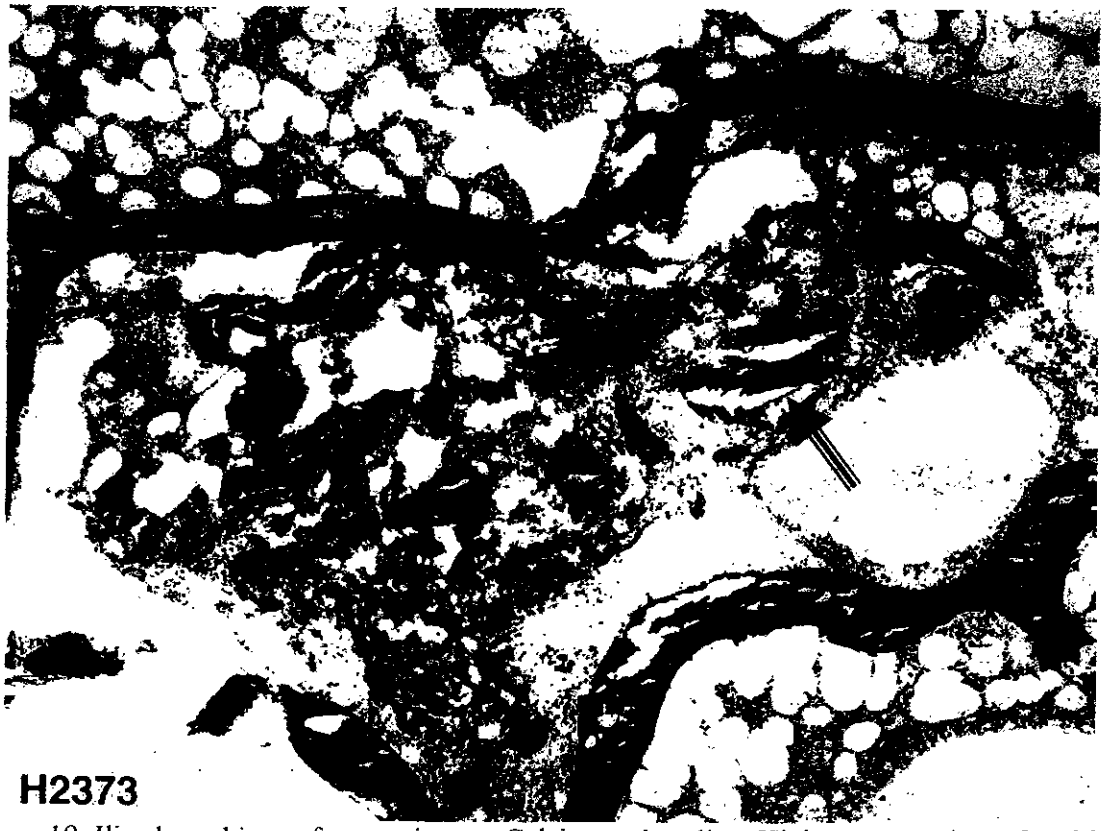

Figure 19: Iliac bone biopsy from patient on Calcium at baseline. Higher power view of multiple foci of dystrophic calcification in the marrow of patient (arrow) in Figure 18.

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/s/

Akinwole Williams
7/2/04 05:36:27 PM

7/2/04

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: June 17, 2004	**DESIRED COMPLETION DATE:** July 1, 2004 **PDUFA DATE:** July 26, 2004	**ODS CONSULT #:** 00-0287-2

TO: Norman Stockbridge, MD
Acting Director, Division of Cardio-Renal Drug Products
HFD-110

THROUGH: Denise Hinton
Project Manager
HFD-110

PRODUCT NAME: **Fosrenol®** (Lanthanum Carbonate Hydrate Tablets) Chewable 250 mg, 500 mg, **NDA #: 21-468**	**NDA SPONSOR:** Shire Pharmaceutical Incorporated

SAFETY EVALUATOR: Linda M. Wisniewski, RN

RECOMMENDATIONS:

1. DMETS has no objection to the use of the proprietary name, Fosrenol®. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name and its associated labels and labeling must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Fosrenol® acceptable from a promotional perspective.

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 1, 2004

NDA# 21-468

NAME OF DRUG: **Fosrenol** (Lanthanum Carbonate Hydrate Tablets)
250 mg, 500 mg,

NDA HOLDER: Shire Pharmaceutical Incorporated

I. INTRODUCTION:

This consult was written in response to a request from the Division of Cardio-Renal Drug Products (HFD-110), for a re-review of the proprietary name "Fosrenol®", regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Fosrenol contains the active ingredient, lanthanum carbonate hydrate. It is an orally active phosphate binder. Fosrenol is indicated for [redacted] Fosrenol binds dietary phosphorus from food and inhibits absorption of phosphorus to the blood by the formation of highly insoluble complexes that cannot easily pass through the wall of the gastrointestinal tract. The proposed initial dose for adults is 750 mg daily with meals; doses should be divided among meals with more doses for a heavy meal. Doses may be increased or decreased gradually to bring serum phosphate levels below 6 mg/dl. Most patients may require a daily dose of 1,500 mg of lanthanum and the sponsor does not recommend doses greater than 3,000 mg. Fosrenol will be available in 250 mg, 500 mg, [redacted] chewable tablets packaged in bottles of [redacted]

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Fosrenol to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, Drugs@fda.gov , and the electronic online version of the FDA Orange Book.

the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. Since this is a re-review of the proposed name, DMETS did not conduct the prescription studies.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Fosrenol. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC has no concerns regarding the proposed proprietary name from a promotional perspective.

2. The Expert Panel identified two additional proprietary names, Fer-In-Sol and Foscavir, that were thought to have potential to look-alike to Fosrenol. These products along with their dosage forms and usual dosages are listed in Table 1 (see below).

Product Name	Dosage form (s), Generic Name	Usual Adult Dose*	Other**
Fosrenol	Lanthanum Carbonate Hydrate Tablets 250 mg, 500 mg	750 mg daily with meals, increased to a max of 3,000 mg to maintain serum phosphate levels below 6 mg/dl.	
Fer-In-Sol	Ferrous Sulfate 15 mg/0.6 mL Elemental Iron Infant Drops	2 mg to 6 mg/kg/day once daily	SA/LA
Foscavir	Foscarnet Sodium 24 mg/mL Intravenous	40 mg/kg/day to 120 mg/kg/day q 12 or q 8 depending on response and renal function.	LA
*Frequently used, not all inclusive. **L/A (look-alike), S/A (sound-alike).			

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. No additional names of concern were identified in POCA that were not discussed in EPD.

[4] WWW location http://www.uspto.gov/tmdb/index.html.
[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Fosrenol, the primary concerns related to look-alike and sound-alike confusion with: Fer-In-Sol and Foscavir.

1. Fer-In-Sol may look similar to Fosrenol when scripted. Fer-In-Sol is indicated for prophylactic iron supplementation for preterm infants, established iron deficiency, and for iron supplementation with administration of Erythropoietin. Although the formal name is Fer-In-Sol, the prescription may be written without the hyphens. The names share seven of their eight letters, although with different placement, thereby enhancing the scripted similarities (see below). However, there are product characteristics that may help to differentiate the two products. They are dose (750 mg to 3,000 mg/day vs. 2 mg to 6 mg/kg/day), dosage form (tablets vs. drops), strength (250 mg, 500 mg, [ ] vs. 15 mg/0.6 mL), frequency of administration (with each meal vs. once daily), and indication of use (hyperphosphatemia vs. anemia). Despite the orthographic similarities, the product characteristics will help to differentiate the two products and minimize confusion.

Fosrenol
Fosrenol

2. Foscavir may look similar to Fosrenol when scripted. Foscavir is indicated in patients with CMV retinitis, mucocutaneous acyclovir-resistant herpes simplex virus infection, and varicella zoster infection. Both names begin with letters that look similar (fosc vs. fosr) (see below). Additionally, the rest of the letters may also look similar (avir and enol) despite the upstroke of the letter 'l'. However, the product characteristics may help to minimize confusion between these two products. They are dose (750 mg to 3,000 mg/day vs. 40 mg to 120 mg/kg/day), dosage form (tablets vs. injection), strength (250 mg, 500 mg, [ ] mg vs. 24 mg/mL), frequency of administration (with each meal vs. every 8 to 12 hours), indication of use (hyperphosphatemia vs. CMV retinitis, hsv, and varicella zoster), and storage location (oral solids vs. injection). A Fosrenol 3,000 mg daily dose may overlap with a Foscavir 3,000 mg daily dose (i.e. 50 kg patient at 60 mg/kg/day). However, the frequency of Fosrenol (TID with meals), is usually interpreted to mean three times a day while the patient is awake, whereas, every eight hours is usually scheduled around the clock to maintain a continuous therapeutic blood level of the particular drug. Thus, it would be unlikely that the frequencies would be confused. Additionally, the strengths of the Fosrenol tablets (250 mg, 500 mg, [ ] will help to differentiate this order. Despite the orthographic similarities, the route of administration and the strength will help to minimize confusion and error involving Foscair and Fosrenol.

Fosrenol
Foscavir

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Fosrenol, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL (250 mg, 500 mg, [ ]

1. The strength of this product is based on the active moiety Lanthanum and not the salt Lanthanum Carbonate. Additionally, the dosage form (tablet) should appear in conjunction with the established name. Therefore, we recommend one of the following presentations:

   a. Fosrenol
   (Lanthanum Tablets) Chewable
   XXX mg

   b. Fosrenol
   (Lanthanum Carbonate Tablets) Chewable
   equivalent to XXX mg of Lanthanum

   c. Fosrenol
   (Lanthanum Carbonate Tablets) Chewable
   XXX mg*
   *Each tablet contains Lanthanum Carbonate equivalent to XXX mg of Lanthanum.

   Note: DMETS prefers the first option because this nomenclature is consistent with USP recommendations on 'labeling of salts of drugs'.

2. We recommend relocating the statement of strength to appear in juxtaposition to the proprietary and established name. The current presentation may cause confusion because it allows the net quantity to be closer to the established name rather than the strength.

3. The corporate name appears in bolded font. It appears to be more prominent than the proprietary name. Please revise accordingly.

4. The boxing colors used for the 250 mg (blue), 500 mg (purple), [ ] blend in with the blue background of the label. We recommend revising the boxing colors with different colors or some other means so that they are clearly differentiated from the label background color.

5. [ ]

6. DMETS questions what the that appears in the upper left corner, in front of the proprietary name represents. Please elaborate.

B. PROFESSIONAL SAMPLE -500 mg)

1. See comments A1, A2, A3, and A6.

2. The boxing color used for the 500 mg (blue) blends in with the purple background of the label. We recommend revising the boxing color with a different color or some other means so that it is clearly differentiated from the label background color.

C. INSERT LABELING

DMETS notes that the Information for Patients section contains the directions "Fosrenol tablets should be chewed and taken with meals". DMETS recommends including these directions in the DOSAGE AND ADMINISTRATION Section of the package insert.

IV. RECOMMENDATIONS:

A. DMETS has no objection to the use of the proprietary name, Fosrenol®. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name and its associated labels and labeling must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. DDMAC finds the proprietary name Fosrenol acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

/S/

Linda M. Wisniewski, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur: /S/

Denise P. Toyer, PharmD.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Linda Wisniewski
7/2/04 02:29:11 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
7/2/04 02:54:37 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/2/04 02:57:57 PM
DRUG SAFETY OFFICE REVIEWER

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commercial information

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NDA Meeting Minutes

Meeting Date:	June 24, 2004
NDA Application:	21-468
Sponsor:	Shire Pharmaceutical Development Inc.
Product name:	Fosrenol (lanthanum carbonate)
Meeting Type:	B
Classification:	CMC
Meeting Request Date:	June 18, 2004 (Agency request)
Confirmation Date:	June 18, 2004
Meeting Chair:	Kasturi Srinivasachar, Ph.D.
Meeting Recorder:	Denise Hinton

FDA Attendees:

Kasturi Srinivasachar, Ph.D.	Chemist, Team Leader, HFD-810
Kris Raman, Ph.D.	Chemist, HFD-810
Denise Hinton	Regulatory Health Project Manager, HFD-110

Shire Pharmaceutical Development Inc.

Rick Lilley	Senior Vice President, Regulatory Affairs
Steve Damment	Senior Vice President, Biosciences
Jo Ferdinando	Senior Vice President, Pharmaceutical Development

BACKGROUND
The Division requested this meeting with Shire Pharmaceutical Development Inc. to discuss deficiencies identified in the Chemistry review of the resubmission.

Discussions:
C 3 supplier
Dr. Raman asked Shire if they have C 7 supplier. Shire confirmed that they have C supplier

3

C

1

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page(s) of trade secret and/or confidential commercial information (b4)

The specification limits proposed in the 4/1/2004 submission for the following impurities should be revised as recommended in the table below.

Meeting recorder: *{See appended electronic signature page}*
Denise M. Hinton

Meeting concurrence: *{See appended electronic signature page}*
Kasturi Srinivasachar, Ph.D.

Draft: 30Jun04
Final: 5Aug04

RD: 1Jul04
Raman 4Aug04
Srinivasachar 5Aug04

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/s/

Denise Hinton
8/6/04 02:13:44 PM

RHPM Overview of NDA 21-468

NDA:	**21-468**
Drug:	**Fosrenol (Lanthanum Carbonate Hydrate) 250mg and 500 mg Chewable Tablets**
Sponsor:	**Shire Pharmaceutical Development Inc.**
Date of original submission:	**April 30, 2004**
Date of resubmission:	**January 26, 2004**
Related IND:	**55,054**

Background

Lanthanum carbonate is a phosphate binder that acts in the lumen of the gut to bind dietary phosphorus released from food during digestion. Fosrenol inhibits the absorption of phosphorous by the formation of highly insoluble lanthanum phosphate complexes that cannot easily pass through the wall of the GI tract, and are excreted in feces.

On April 30, 2002 Shire Pharmaceutical Development Incorporated filed an NDA for Fosrenol (lanthanum carbonate) 250 and 500 mg Chewable Tablets with the proposed indication "

On February 28, 2003 Shire was issued an Approvable letter because of issues related to its safety in the dialysis population. The three areas of concern were related to Chemistry, Manufacturing and Controls, Clinical Pharmacology, and Clinical deficiencies.

On January 26, 2004, Shire resubmitted their NDA for Fosrenol (lanthanum carbonate) and addressed the deficiencies cited in the Approvable letter. The original goal date on the resubmission was July 26, 2004, however was extended to October 26, 2004 as a major amendment was submitted within three months of the July 26, 2004 goal date.

Key meetings in regard to the resubmission of Fosrenol (lanthanum carbonate) are as follows:

1. March 27, 2003/Clinical-Biopharmaceutics deficiencies
2. April 2, 2003/CMC
3. June 26, 2003/CMC/Stability
4. July 3, 2003/Bioequivalence discussion regarding the 3b study (312)
5. August 7, 2003/CMC
6. October 21, 2003/Pharmacodynamic-equivalence
7. December 3, 2003/Pre-resubmission meeting (pre-clinical/clinical data)
8. March 2, 2004/Clinical (mortality data)
9. March 10, 2004/Chemistry and Biopharmaceutics
10. June 17, 2004/Outstanding clinical issues
11. June 24, 2004/CMC deficiencies

Division Director's Memo
In his memorandum dated October 13, 2004, Dr. Stockbridge recommended "Approval" of Fosrenol for [ ]. He is in agreement with the conclusions conveyed by Dr. Karkowsky in his October 12, 2004 review; however [ ] phase 4 commitment will be required to track long-term concerns of gastrointestinal symptoms and bone effects, as they are theoretically based and data from the Sponsor's proposed long-term studies would be difficult to interpret.

Primary Medical Review
In his review dated July 19, 2004, Dr. Williams concluded that there needs to be further evaluation of the potential toxicity of lanthanum carbonate in bone and the gastrointestinal tract after it has reached steady state. The Sponsor provided 2- year follow-up data in which Dr. Williams perceives to be inadequate since the mean half life is greater than 2 years and it will take more than 10 years to reach steady state in bone and the time to resolution of GI adverse events in patients receiving lanthanum is not known.

In regard to efficacy, Dr. Williams concluded that although lanthanum carbonate is inferior to the currently approved phosphate binders, it is an effective phosphate binder that reduces phosphorous levels and maintains the level at a pre-specified level of < 5.9 mg/dL.

Financial disclosure is addressed on page 77 of the medical review.

The safety update review is incorporated into the medical review. The deaths are included in the discussion of treatment emergent adverse events and the safety data are incorporated into the integrated review of safety.

Secondary Medical Review
In his review dated October 12, 2004, Dr. Karkowsky conveyed that approval for lanthanum carbonate should be dependent upon t [ ] to assess the effect on mortality, gastrointestinal, and bone-related events. He stated that the issue of most concern is the consequence of the long-term accumulation of lanthanum, although the sum of the data does not indicate a specific safety signal. If approved, he recommended that the uncertainties be clearly stated in the label.

[

Dr. Skelly concluded that the lanthanum pharmacokinetic data was acceptable with the exception of the patients in the study mentioned above. A biowaiver was granted for the 500 mg current formulation.

Statistical Review
In her review dated, May 17, 2004, Dr. Freidlin concluded that based on the 15-month safety update, lanthanum carbonate was not as well tolerated as the alternative therapy. Compared to the alternative therapy, there were a significant statistical number of lanthanum patients that discontinued from the studies due to adverse events.

In regard to mortality, there was no significant statistical difference between lanthanum and the alternative therapy patients. Due to the high discontinuation rates and statistically significantly shorter drug exposure among lanthanum patient, Dr. Freidlin recommended that the mortality assessment incorporate mortality follow up of discontinued patients instead of mortality while on treatment.

The evaluation of efficacy and safety are incorporated in her review.

Clinical Pharmacology and Biopharmaceutics Review
In her review dated August 19, 2004, Dr. Dorantes concluded that the long-term safety profile of lanthanum is uncertain, as there is limited data on the concentrations of lanthanum in bone after long term exposure.

A biowaiver was granted for the 250 and 500 mg current formulation.

Pharmacology review
In his review dated, June 8, 2004, Dr. Joseph stated that there were no approvability issues for lanthanum carbonate based on the non-clinical toxicity-testing program.

Chemistry
In his reviews dated September 14, 2004, Dr. Raman recommended approval of the 250 and 500 mg current formulation from a CMC perspective with an expiration date of 24 months.

Environmental Assessment
The Sponsor's claim for categorical exclusion from filing an environmental assessment under 21 CFR 25.31 (c) is acceptable.

Trade Name Review
In their trade name review dated July 2, 2004, DMETS found the proprietary trade name, FOSRENOL®, acceptable.

The Sponsor complied with DMETS recommendation to apply to the United States Adopted Name (USAN) Council for a different established name, as the current established name, lanthanum carbonate, might potentially cause confusion with lithium carbonate; however, USAN approved lanthanum carbonate as the established name.

The package insert and carton and container labels were updated and discussed during the Preapproval Safety Conference on October 12, 2004. A new consult was not needed as the recommendations did not change from the July 1, 2004 review of the carton and container label. Office of Drug Safety recommended a request for a postmarketing commitment to address safety concerns mentioned in the clinical reviews.

EER
The overall EER recommendation dated February 18, 2004 is acceptable.

Methods Validation
Methods validation packages for district laboratories have been provided.

Pediatric Rule
The Sponsor was granted a full waiver for pediatric studies based on safety concerns. As stated in Dr. Karkowsky's October 12, 2004 review, lanthanum accumulates in the growth plate of animals, the half-life of lanthanum in bone is very long, and it would not be prudent to risk assessing the consequences related to growth and development of Fosrenol in children. The labeling discourages the use of Fosrenol in pediatric patients.

Labeling
The Sponsor electronically submitted labeling in WORD format on January 26, August 11 and October 12, 2004. Labeling meetings were held on September 9, 16, 22 and 29, and October 7, 2004. Final revision requests for labeling were communicated to the Sponsor via email and telephone. Final draft labeling was submitted to the EDR on October 20, 2004 in accordance with the Agency's recommendations and was added to the approval letter.

The carton and container label comments/recommendations were communicated to the Sponsor by Dr. Raman during the review process and final recommendations were communicated to the Sponsor via email on October 13, 2004. Dr. Raman communicated DMETS' recommendations in regard to the carton and container label to the Sponsor and the changes were made accordingly with the exception of the colors used for the net quantity and strength and the Shire logo as stated in the July 1, 2004 review.

Advisory Committee
No meeting held.

RHPM Summary
To my knowledge, there are no issues that might prevent action on this NDA.

Denise M. Hinton
Regulatory Health Project Manager, HFD-110

RHPM Overview of NDA 21-468
Fosrenol (Lanthanum Carbonate Hydrate)
250mg and 500 mg Chewable Tablets

Sponsor: Shire Pharmaceutical Development Inc.
Date of submission: April 30, 2002
Related IND: 55,054

Background
Lanthanum carbonate is a phosphate binder that acts in the lumen of the gut to bind dietary phosphorus released from food during digestion. The sponsor claims that Fosrenol inhibits the absorption of phosphorous by the formation of highly insoluble lanthanum phosphate complexes that cannot easily pass through the wall of the GI tract, and are excreted in feces.

On April 30, 2002 Shire Pharmaceutical Development Incorporated filed an NDA for Fosrenol (lanthanum carbonate) 250 and 500 mg Chewable Tablets with the proposed indication '

Meetings
EOP-2 CMC Meeting: May 26, 1999
EOP-2: May 27, 1999
Toxicology: April 10, 2000
Pre-NDA: September 18, 2001
Deficiency discussions: September 5, 2002
Deficiency discussions: December 3, 2002

Division Director's Memo
In his memo dated February 25, 2003, Dr. Throckmorton recommended an **"approvable"** action; however, there are substantial issues related to its safety in the dialysis population that need to be resolved prior to approval. The three areas of concern are in the following areas:
1. Chemistry, Manufacturing and Controls
2. Clinical Pharmacology
3. Clinical

Primary Medical Review
In his review dated December 24, 2002, Dr. Pelayo recommended a **"not approvable"** action for Fosrenol® based on the lack of an adequate safety margin. The current safety evaluation showed that long-term exposure to lanthanum carbonate may be unacceptably toxic and its ability to bind phosphate is inferior to the currently approved phosphate binder.

Secondary Medical Review
In his review dated February 3, 2003, Dr. Stockbridge recommended an "**approvable**" action for Fosrenol® based on the listed biopharmaceutics deficiencies, safety issues of a higher mortality and slightly increased QT interval. He states that Fosrenol® is effective in controlling hyperphosphatemia associated with chronic renal failure, however, the low power of the safety program, the progressive deposition of lanthanum and lack of long-term safety data due to the drug not being well tolerated failed to provide adequate assurance. Available data support safe and effective use of lanthanum carbonate for the indicated treatment for a few weeks. Dr. Stockbridge recommended that use in children be actively discouraged and longer term use also be discouraged because the risk of accumulating lanthanum is not well characterized.

DSI
No DSI inspections requested.

Statistical Review
In her review dated January 6, 2003, Dr. Freidlin stated that the Four-Month Safety Update of Study LAM-IV-307, showed that lanthanum seemed to prolong the QT interval to a greater extent than the standard therapy. In addition, the study data was not adequate for mortality comparisons.

In her November 5, 2002 review, Dr. Freidlin found that lanthanum is statistically worse than the standard therapy with more lanthanum patients terminated compared to patients on standard therapy.

Clinical Pharmacology and Biopharmaceutics Review

In her review dated January 10, 2003, Dr. Dorantes stated that the clinical pharmacology information provided in the NDA is incomplete and that additional data needs to be provided to address the following:

Dissolution
Method: The newly proposed method using ——— s and a specification of Q= — at — minutes does not provide useful dissolution information. The originally proposed method for the crushed tablets can be accepted on an interim basis. The sponsor should continue with the development of an adequate dissolution methodology for the whole tablets.

Specification: The originally proposed dissolution specification is not acceptable. A specification of — at — minutes would be appropriate for the 250 and 500 mg Fosrenol® chewable tablets.

Commitment: The sponsor should continue pursuing the development of an appropriate dissolution methodology for the whole tablets. They should also make the commitment to submit a final report with the development and validation of a revised and more

suitable dissolution method for the whole tablets and complete dissolution data for at least [ ] lots of the 250 and 500 mg tablets using the revised method within the first year of approval.

Bio-waiver/Bio-Study
The sponsor is seeking approval for the 250 and 500 mg strengths, however; only the 250 mg strength was used in the Phase 2 and 3 clinical studies. The sponsor needs to provide appropriate information to support a bio-waiver and data from a bio-study.

Mass Balance
Dr. Dorantes recommended that the sponsor provide information regarding the mass balance of lanthanum in humans after IV and/or oral administration.

Pharmacology review
In his review dated January 13, 2003, Dr. Joseph recommended an "**approvable**" action from the pharmacology with proposed changes to the package insert.

Chemistry
In his review dated December 31, 2002, Dr. Raman recommended a "**not approvable**" action based on numerous deficiencies in the chemistry, manufacturing and controls section of the NDA. The list was faxed to the sponsor on December 6, 2002 (see pages 101-104) and January 16, 2003.

Environmental Assessment
The sponsor's claim for categorical exclusion is accepted.

Trade Name Review
In their trade name review dated December 18, 2002, DMETS found the proprietary trade name, Fosrenol®, acceptable.

DMETS recommended that we request that the sponsor apply to the United States Adopted Name (USAN) Council for a different established name. They stated that the current established name, lanthanum carbonate, might potentially cause confusion with lithium carbonate.

EER
The overall EER recommendation dated February 25, 2003 is acceptable.

Methods Validation
Methods validation packages for district laboratories have been provided.

Advisory Committee
No meeting held.

CSO Summary
To my knowledge, there are no issues that might prevent action on this NDA.

Denise M. Hinton
Regulatory Health Project Manager, HFD-110

84 pages redacted from this section of the approval package consisted of draft labeling

4/23/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-468

INFORMATION REQUEST LETTER

Shire Pharmaceutical Development Inc.
Attention: Lisa L. Wittmer, Ph.D.
1801 Research Boulevard, Suite 600
Rockville, MD 20850

Dear Dr. Wittmer:

Please refer to your January 26, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosrenol (lanthanum carbonate) 250, 500, [ ] Chewable Tablets.

We also refer to your submissions dated February 2, March 11, 22, and April 1, 2004.

We are reviewing the Clinical, Statistical, Biopharmaceutics, Chemistry, Manufacturing and Controls sections of your resubmission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

CLINICAL

1. As discussed in the March 10, 2004 teleconference with Dr. Akinwole Williams, we request a complete description of the histological findings from bone biopsies as a complement to the histomorphometry and categorical assessments you previously provided. In addition, we request the 2 representative histological slides marked with double asterisks from the table below, Overview of Bone Biopsy Data. Provide the ID of each patient from which the slides have been obtained. A total of 15 slides stained with 1) H&E and 2) van Gieson should be provided.

Overview of Bone Biopsy Data			
Total number of biopsies	Biopsies per treatment group	Study	Submissions
140	Lac: 34 baseline/one year pairs **2 one year Cac: 35 baseline/one year pairs	LAM-IV-303	Original NDA (4/30/2004) LAM-IV-303 Study report
Approvable letter			
142	Lac:** 28 baseline/one year pairs	LAM-IV-307	Resubmission LAM-IV-307

	ST: **6 baseline/two year pairs		
21	Lac: 11 off-treatment Cac: 10 off-treatment	LAM-IV-303	Resubmission
166	Lac: 91 63 baseline, **5 one year, **19 two year 1 three year, 3 off-treatment ST: 75 58 baseline, 1 one year **12 @ 2 year, 4 off-treatment	LAM-IV-307	Resubmission
13	La: 13 *1 four year, **11 five yr and one off- treatment	LAM-IV-301	Resubmission
497 = Total number of biopsies with end stage renal disease in lanthanum studies			

2. We request any additional information you may have on the resolution of mortality, bone adverse events, and major GI adverse events, in patients receiving lanthanum and standard treatment. Include subjects who discontinued from the study and those whose follow-up extended beyond the last closing date.

CHEMISTRY

Drug Product

1. [redacted]. You need to update the stability data, to support the expiration dating.

2. The dissolution data provided consisted of only [redacted] data for most of the stability lots. Provide initial and intermediate time point results.

3. Provide chemical names for [redacted] in the Description section of the package insert and remove the word **talc** from the list of inactive ingredients on the draft label for the containers.

BIOPHARMACEUTICS

1. The newly proposed [redacted] dissolution test, whole tablets in [redacted] at [redacted] using Apparatus paddles at 2 and [redacted] rpm, appears to be appropriate with the exception that the test is referred to as [redacted] dissolution test," and this is not acceptable. If a lot fails [redacted] the testing should be continued to [redacted] if needed. Only a lot that fails [redacted] called a "Failed" lot. In regard to the proposed speicification of Q = [redacted] in 45 minutes, FDA's final recommendation will be given after the review of the overall dissolution data from the bio-lots, stability, and commercial batches is completed.

2. Your proposal [ ] is not acceptable.

3. We note that the resubmission includes the current 250- and 500-mg chewable tablets [ ] You need to provide complete dissolution data (i.e., individual results, means, and profiles [ ] for the bio-lots, stability, and commercial batches. These data need to be provided for — current — formulations using the whole tablets test. Complete dissolution data are needed for the setting of appropriate specifications.

4. We remind you that the approval of the requested biowaivers for the 500-mg current formulation and for the 250-, 500 [ ] is based on having an acceptable dissolution test for the whole tablets.

If you have any questions, please call:

Ms. Denise M. Hinton
Regulatory Health Project Manager
(301) 594-5333

Sincerely,

{See appended electronic signature page}

/S/

Ms. Zelda McDonald
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Zelda McDonald
4/23/04 02:59:26 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-468

INFORMATION REQUEST LETTER

Shire Pharmaceutical Development Inc.
Attention: Lisa Wittmer, Ph.D.
1801 Research Boulevard, Suite 600
Rockville, MD 20850

Dear Dr. Wittmer:

Please refer to your January 26, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosrenol (lanthanum carbonate) 250 and 500 mg Chewable Tablets.

We also refer to your submissions dated February 2, March 11 and 22, 2004.

We are reviewing the Clinical, Statistical, Biopharmaceutical, Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Please provide the following information:

CLINICAL

1. Information on bone histology from patients receiving lanthanum and standard treatment.

2. Information on the relative duration of resolution of major GI adverse events from patients receiving lanthanum and standard treatment including those who discontinued and those followed up after the approvable letter.

3. Definite information as to the additional number of patients and length of time that you have followed the patients up for bone changes and for resolution of GI adverse events.

STATISTICS

1. Mortality data for all patients (including dropouts) exposed to lanthanum in Phase 2-3 long-term studies should be updated to a current date, as the submitted mortality data includes follow-up contact information only through December 2002.

2. For each table comparing adverse event rates in the lanthanum and standard therapy patients, a supplementary table adjusting for the drug exposure should be submitted.

APPEARS THIS WAY ON ORIGINAL

CHEMISTRY

Drug Substance

1. Please provide site-specific stability at 5°C and 25°C/60% RH for [ ] batches of the drug substance **manufactured at** [ ]

2. Reference is made to our August 7, 2003 meeting, wherein the division required that specifications should be set for [ ] metal impurities. You have proposed in the resubmission to specify only [ ] potential metal impurities. In addition, the justification provided (Volume 2, Page 4-213) for not specifying the remainder [ ] metal impurities is not acceptable.

Drug Product

1. [ ]

2. [ ]

3. The dissolution data provided consisted of only [ ] data point for most of the stability lots. Provide initial and intermediate time point results.

4. Labeling

   - Please provide chemical names for [ ] in the description section of package insert.
   - Please remove the word **talc** from the list of inactive ingredients on the draft label for the containers.

BIOPHARMACEUTICS

1. Dissolution method for the whole tablet is acceptable. However, the data for the whole tablet and crushed tablet and the proposed Q = [ ] in 45 minutes is not acceptable.

If you have any questions, please call:

Denise M. Hinton
Regulatory Health Project Manager
(301) 594-5333

Sincerely,

/S/

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Food and Drug Administration Meeting Minutes

Drug:	**Fosrenol (Lanthanum Carbonate)**
Sponsor:	**Shire Pharmaceutical Development Inc.**
NDA:	**21-468**
Date of meeting request:	**May 4, 2004 (Agency)**
Date meeting confirmation:	**May 18, 2004**
Briefing document received:	**June 1, 2004**
Type/Classification:	**B/NDA resubmission discussions**
Meeting Date:	**June 17, 2004 (Rescheduled from June 11, 2004)**
Meeting chair:	**Robert Temple, M.D.**
Meeting recorder:	**Denise Hinton**
FDA Attendees:	
Robert Temple, M.D.	**Director, Office of Drug Evaluation 1**
Norman Stockbridge, M.D., Ph.D.	**Acting Director, Division of Cardio-Renal Drug Products**
Abraham Karkowsky, M.D., Ph.D.	**Acting Deputy Director, Division of Cardio-Renal Drug Products**
Femi Williams M.D.	**Medical Officer**
Xavier Joseph, Ph.D.	**Pharmacologist**
Valeria Freidlin, Ph.D.	**Statistician**
Denise Hinton	**Regulatory Health Project Manager**
Shire Attendees:	
Raymond Pratt, M.D.	**Vice President, Clinical Research**
Simom Tulloch, M.D.	**Global Senior Vice President, Clinical Research**
Steve Damment, Ph.D.	**Senior Vice President, Biosciences**
Yuxin Zhang, Ph.D.	**Senior Director, Biostatistics**
Rick Lilley, Ph.D.	**Senior Vice President, Regulatory Affairs**
Lisa Wittmer, Ph.D.	**Director, Regulatory Affairs**
Iain Cockburn, M.D.	**Worldwide Director Pharmacovigilance**
[ ]	**Consultant**

Background:
Shire received an approvable letter on February 28, 2003. Before the application could be approved, Shire was asked to address clinical, clinical pharmacology, and chemistry deficiencies. The purpose of this meeting was to discuss the outstanding clinical issues in regard to adverse events, mortality, long-term safety information, and bone histology. Biopharmaceutics and Chemistry issues have been addressed separately.

Discussions:

1. **Does the Agency agree that the investigative studies provided in the NDA support the conclusion that the mineralization defect observed in uraemic rats is pharmacologically mediated and expected for a phosphate-binding agent?**

   The Agency does not agree that the investigative studies provided in the NDA settle the question and whether the mineralization defect observed in uraemic rats is pharmacologically mediated and expected for a phosphate-binding agent. Better exposure data and longer follow up is needed to see whether there are late fractures. The Agency also noted that there should be no impediment to getting follow up on those who have been in trials.

   Shire asked for clarification of the request for pre-clinical bone histomorphometry. Dr. Williams explained that bone resorption and lesions in rats with normal renal function treated with lanthanum were seen in microscopic slides and that the abnormal bone changes raise concern that lanthanum is toxic to bone. More importantly, bone changes were also seen in patients with long-term lanthanum exposure (4/5 years on treatment).

   Shire stated that their experts did not observe any bone changes in rats with normal renal function and therefore disagreed with the Agency's contradictory evaluation of the slides, especially since their investigator has already conducted a second review with the same conclusion of no bone abnormalities. No bone toxicity was seen in their long term animal studies. Dr. Williams offered to demonstrate the observed bone changes in rats with normal renal function to the Shire's representatives after the meeting. Dr. Williams also offered to provide confirmatory evidence of these histopathological changes.

2. **Does the Agency agree that the human bone biopsy data submitted with this NDA application shows no evidence of aluminum-like toxicity?**

   Dr. Temple said we needed assurance that enough information has been provided to be able to draw a definitive conclusion as to what happens to people who have been exposed to lanthanum long term. Long-term fracture outcomes are necessary to give the Agency certainty that lanthanum will not show the kinds of adverse effects long term that were eventually seen with aluminum. Additional biopsies are not needed, but information on how many people had bone fractures is necessary.

   Shire stated they believe the fracture analysis data has been adequately addressed, as they provided information in the original NDA and updates in the resubmission from the 15-month data in long-term open-label studies. Included in the information was an adverse event analysis that included fracture related adverse events (all fractures irrespective of the type). The 301 study data included patients that had 4 to 6 years of follow up.

   The Agency will reevaluate the information submitted in the March 2004 submission to be certain that a reasonable sample population was used in the Phase 2 and 3 studies. We are interested in what happened to people that were exposed for a longer period of time.

3. **Does the Agency agree that the human bone data show no consistent evidence of detrimental bone changes?**

   Data were provided on 212 people on lanthanum at 15 months and 196 people from the active therapy group with exposure over 2 years.

   The Agency expressed concern over the appearance of bone abnormalities and requested that Shire provide a description of long-term fracture data study by study, as these data are critical to the approval of the NDA. After comparing the data, the Agency will inform them as to whether the dataset is adequate. The Agency will also provide Shire with pictures and a brief summary of the bone pathologic changes from the few animal and human bone tissue slides supplied by Shire.

4. **Is the summary of bone tissue deposition and histomorphometry data in the proposed package insert adequate to ensure the prescribing information for lanthanum carbonate is informative?**

   Discussions in regard to language in the package insert will be deferred until the issues discussed above are resolved.

5. **Shire has provided data and summaries to support that gastrointestinal adverse events leading to discontinuation are similar in severity, frequency and length to those occurring in patients on standard therapy or who continued on lanthanum treatment. Does the Agency agree with these conclusions?**

   The Agency had stated that it would be important to know how long it took for GI symptoms to resolve once the patients were discontinued from lanthanum carbonate. In March 2004, Shire submitted information in regard to the duration of adverse events (Table 1b), however, the blank Table submitted by Shire on June 16 2004, when filled by Shire, will provide a complete response and be complementary to previously submitted Tables 8.2 and 8.10.

   Shire stated that they believed that information was adequately addressed in the resubmission. They used the 15-month safety database on patients with lanthanum exposure over 2 years. A full analysis was conducted in the 307 study with information on time to onset, duration, and outcome and no differences were noted. Information was also provided on the small number of patients whose symptoms did not resolve. The table with that information was provided in Table 8.2 and 10 in the April 2004 submission.

6. **Shire has provided safety data on over 1700 patients with a mean exposure of approximately 9 months and patients with greater than 2 years exposure. Does the Agency agree that these data on GI adverse events are adequate to characterize the GI safety profile?**

After a brief discussion about the similarities of GI adverse events in the standard versus lanthanum therapy groups, the Agency agreed that data from the Phase 2 and 3 programs appeared to have characterized the safety profile adequately. A definitive answer can be given after further review of the GI adverse events of those exposed to lanthanum including time to onset.

7. **Shire has presented mortality analyses from the lanthanum carbonate development program, although mortality was not considered an endpoint. Does the Agency agree that these data exclude a significant excess risk of mortality associated with long-term treatment of lanthanum carbonate compared to standard therapy?**

   Shire stated that they did get the vast majority of follow-up data from patients in the clinical studies, although HIPPA did prevent them from getting 100% of the data. There was some discussion about the amount of excess mortality in patients treated with lanthanum that could be excluded based on their current dataset.

   Shire referred to the information provided (page 9, Figure 1 in the 1Jun04 briefing document) on the estimated excess risk based on observed and hypothetical ("worst-case") mortality data. The Agency and Shire agreed that a true "worst-case" would be to assume that subjects lost to follow-up on lanthanum died and that subjects lost on control did not die at all. It was not clear how the sponsor's analyses were performed. In general, however, considering the Kaplan-Meier curves, survival did not appear to be adversely affected.

8. **The data contained in the NDA submission(s) characterize the extent of deposition of the small fraction of lanthanum that is absorbed. These data combined with the significant safety database and exposure from the lanthanum clinical development program allow for a benefit/risk assessment of the use of lanthanum carbonate to treat hyperphosphatemia in ESRD patients. If the Agency does not agree, which additional data or analyses are needed?**

   The Agency will have further internal discussions in regard to the risk/benefit assessment. After the pending issues discussed above are resolved, this issue can be discussed with the Sponsor.

   Shire agreed to provide a summary of all submissions sent in response to the approvable letter. The Agency will provide a brief summary that will accompany relevant photomicrographs of rat and human bone biopsies that demonstrate the abnormal bone findings within 2 weeks.

Meeting recorder: /S/
Denise M. Hinton

Meeting concurrence: /S/
Robert Temple, M.D.

Draft: 21Jun04
Final: 24Jun04

RD:
Freidlin 6/22/04
Joseph 6/23/04
Williams 6/23/04
Karkowsky6/23/04
Stockbridge 6/24/04
Temple 25Jun04

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/s/

Denise Hinton
6/28/04 10:28:30 AM

Robert Temple
6/29/04 04:14:16 PM

Teleconference between Shire and the FDA Division of Cardio-Renal Drug Products

Drug:	**Fosrenol (Lanthanum Carbonate)**
Sponsor:	**Shire Pharmaceutical Development Inc.**
NDA:	**21-468**
Date of meeting request:	**February 25, 2004 (Division request)**
Date of Briefing Document:	**NA**
Date Meeting Confirmation Faxed:	**NA**
Type:	**C**
Classification:	**Guidance/Information request**
Meeting Date:	**March 4, 2004**

FDA Participants:

Akinwole Williams, M.D.	**Medical Officer**
Denise Hinton	**Regulatory Health Project Manager**

Shire Participants:

Raymond Pratt, M.D.	**Vice President, Clinical Research**
Simon Tulloch, M.D.	**Senior Vice President, US R&D**
Rick Lilley, Ph.D.	**Senior Vice President, Regulatory Affairs**
Lisa Wittmer, Ph.D.	**Associate Director, Regulatory Affairs**

Background:
Shire submitted their complete response to the February 28, 2003 approvable letter on January 26, 2004.

Dr. Williams requested a teleconference with Shire to discuss the need for bone histology data and updated GI event data.

Discussion:
Dr. Williams requested that Shire provide information on the length of time actively treated and discontinued patients were followed up for gastrointestinal and bone adverse events since receipt of the February 28, 2003 approvable Letter.

Shire stated that they submitted data up to May 30, 2003 on patients who were ongoing in Study 307 and had previously discontinued treatment. The protocol

included follow up time of 30 days; adverse events were followed for 30 days and serious adverse events were followed until resolution.

Dr. Williams requested that Shire submit data on resolution of the gastrointestinal adverse events and provide clarification of when resolution took place, as their summary stated that resolution took place in about 7 days but the table submitted stated that resolution took place in 26 days or more.

Shire stated that they provided a cohort of patients that discontinued from treatment in Table 11 in the resubmission. Dr. Williams stated that the table needed to be revised to show duration in days and show a comparison of how long it took for resolution of GI adverse events with patients treated with lanthanum versus standard therapy. It is important to look at rate of distribution, not just outcome. Shire agreed to perform the analysis. In performing the analysis, Shire should qualify the duration of adverse events from time to resolution in terms of days for each event and serious versus non-serious adverse events.

Shire agreed to provide the Division with categorical information and stated that Table 1b under duration includes ongoing events over 21 days. Shire stated that out of 397 cases, 119 had duration over 28 days and stated they would conduct an analysis for all GI events in more detail and include duration of unresolved events in the submission. The ISS will also be updated to the current date and address the requested adverse events. Updated information on study 307 will also be provided.

<u>Bone Data</u>

Dr. Williams stated he would be evaluating individual information on patients with histomorphometry and bone data to better understand Shire's conclusion that there were no bone changes similar to aluminum effects. He requested a summary table for data collected prior to and after the approvable letter dated February 28, 2004.

Shire stated that they have bone biopsy data summarized in the resubmission along with the 307 study (unscheduled biopsies). Dr. Williams requested that a separate table be provided to show the additional biopsies that were taken after the approvable letter.

Shire stated that data from Studies 303 and 307 were provided in the resubmission. Unscheduled biopsy data from study 301 (long term open data) and 307 were additional and were not in original submission. The only submitted bone data was

from the original Study 303 and all other data are new and were collated after the approvable letter in the context of the ongoing 307 study.

Shire commented that the data are integrated and difficult to separate out, however they will summarize whatever data were collected after the approvable letter and send a revised table. Shire presented data such as data sets for parameters with time it took for biopsy grouped into study in the response dated January 26, 2004.

Dr. Williams clarified that he needs bone histology data, not histomorphometry data in order to evaluate bone changes such as exostosis and severe periosteal changes seen by him on bone histological slides in rats with ESRD.

Shire stated that the histomorphometry data has been developed and validated by [redacted] **and other experts in the field. Dr. Williams informed Shire that histomorphometry data are perhaps not sufficient for bone toxicity and can not be interchanged with histological changes. A concern is that the enormous amount of lanthanum deposition in bone will not be seen by a histomorphometric assessment. Histomorphometry is useful for ruling out osteomalacia, but histology is necessary to rule out other possible bone lesions such as osteitis fibrosa cystica.**

Shire agreed to provide Dr. Williams with a table of adverse events related to bone (i.e, bone fracture, bone diseases, etc.) showing updated bone changes including unscheduled biopsies. They will rerun the analysis with original data set adverse events that occurred before and after the approvable letter. They will also provide a descriptive histology report to support their complete response, in addition to an updated time table of all updates that were submitted since February 28, 2003.

Meeting recorder: /S/
Denise M. Hinton

Meeting concurrence: /S/
Akinwole Williams, M.D.

Slides Attached

Table 1b: Occurrence, Time to Onset, Duration and Extent of Resolution of Gastrointestinal Adverse Events: LAM-IV-307

	Lanthanum n=680	Standard Therapy n=674
Occurrence	1752	2480
Time to onset		
1-4 weeks	316 (18.0%)	230 (9.3%)
5-26 weeks	619 (35.3%)	723 (29.2%)
27-52 weeks	389 (22.2%)	577 (23.3%)
>1 year	428 (24.4%)	950 (38.31%)
Duration		
0 [illegible]ays	1158 (66.1%)	1776 (71.6%)
8-14 days	112 (6.4%)	138 (5.6%)
15-21 days	59 (3.37%)	54 (2.2%)
22-28 days	26 (1.5%)	33 (1.3%)
>28 days	397 (22.6%)	479 (19.3%)
Extent of resolution		
Death	-	2 (0.1%)
Resolved	1524 (87.0%)	2183 (88.0%)
Resolved with sequelae	13 (0.7%)	5 (0.2%)
Unknown	-	1 (0.04%)
Unresolved	215 (12.3%)	289 (11.6%)

Source: Tables 8.1-8.6

The SAS System
Table 8.2
Incidence Rate of GI AEs
By Preferred Term

WHOART preferred label	Lanthanum # of events in WHO-ART	Lanthanum # (%) of pts (n=680)	Standard # of events in WHO-ART	Standard # (%) of pts (n=674)
AAA: ANY EVENTS	1752	444 (65.3)	2480	486 (72.1)
ABDOMEN ENLARGED	3	3 (0.4)	13	8 (1.2)
ABDOMINAL ADHESIONS	1	1 (0.1)	2	2 (0.3)
ABDOMINAL PAIN	160	110 (16.2)	256	145 (21.5)
ANAL FISSURE	1	1 (0.1)	0	0
ANOREXIA	40	36 (5.3)	67	58 (8.6)
APPENDICITIS	2	2 (0.3)	2	1 (0.1)
APPETITE INCREASED	1	1 (0.1)	3	3 (0.4)
BOWEL MOTILITY DISORDER	1	1 (0.1)	1	1 (0.1)
CHANGE IN BOWEL HABITS	1	1 (0.1)	9	5 (0.7)
COLITIS	5	5 (0.7)	1	1 (0.1)
COLITIS PSEUDOMEMBRANOUS	0	0	1	1 (0.1)
CONSTIPATION	124	93 (13.7)	160	118 (17.5)
DIARRHOEA	248	154 (22.6)	376	205 (30.4)
DIARRHOEA, CLOSTRIDIUM DIFFICILE	4	4 (0.6)	2	2 (0.3)
DISEASES OF OESOPHAGUS	0	0	3	3 (0.4)
DIVERTICULITIS	9	7 (1.0)	11	11 (1.6)
DIVERTICULOSIS	5	5 (0.7)	6	6 (0.9)
DUODENAL ULCER	3	3 (0.4)	6	6 (0.9)
DUODENAL ULCER HAEMORRHAGIC	1	1 (0.1)	0	0
DUODENAL ULCER REACTIVATED	1	1 (0.1)	0	0
DUODENITIS	0	0	4	4 (0.6)
DYSPEPSIA	99	70 (10.3)	171	117 (17.4)

The SAS System
Table 8.2
Incidence Rate of GI AEs
By Preferred Term

WHOART preferred label	Lanthanum # of events in WHO-ART	Lanthanum # (%) of pts (n=680)	Standard # of events in WHO-ART	Standard # (%) of pts (n=674)
DYSPHAGIA	11	10 (1.5)	7	7 (1.0)
ENTERITIS	1	1 (0.1)	0	0
ERUCTATION	3	2 (0.3)	2	2 (0.3)
FAECAL INCONTINENCE	4	2 (0.3)	2	2 (0.3)
FAECES DISCOLOURED	0	0	1	1 (0.1)
FLATULENCE	31	26 (3.8)	38	30 (4.5)
GASTRIC DILATATION	9	8 (1.2)	31	19 (2.8)
GASTRIC ULCER	5	5 (0.7)	6	6 (0.9)
GASTRIC ULCER HAEMORRHAGIC	2	2 (0.3)	2	2 (0.3)
GASTRITIS	27	24 (3.5)	38	35 (5.2)
GASTRO-INTESTINAL DISORDER NOS	12	9 (1.3)	13	10 (1.5)
GASTROENTERITIS	18	17 (2.5)	15	14 (2.1)
GASTROESOPHAGEAL REFLUX	19	17 (2.5)	25	23 (3.4)
GI HAEMORRHAGE	29	18 (2.6)	33	27 (4.0)
GI MUCOSAL NECROSIS GENERAL	0	0	1	1 (0.1)
GI NEOPLASM BENIGN	4	4 (0.6)	8	8 (1.2)
GINGIVAL RECESSION	0	0	1	1 (0.1)
GINGIVITIS	3	3 (0.4)	0	0
GUM HYPERPLASIA	0	0	1	1 (0.1)
HAEMATEMESIS	2	2 (0.3)	6	6 (0.9)
HAEMORRHAGE RECTUM	4	4 (0.6)	18	15 (2.2)
HAEMORRHOIDS	11	11 (1.6)	18	17 (2.5)
HICCUP	3	3 (0.4)	4	4 (0.6)

The SAS System
Table 8.2
Incidence Rate of GI AEs
By Preferred Term

WHOART preferred label	Lanthanum # of events in WHO-ART	Lanthanum # (%) of pts (n=680)	Standard # of events in WHO-ART	Standard # (%) of pts (n=674)
ILEUS	4	3 (0.4)	2	2 (0.3)
INCREASED STOOL FREQUENCY	0	0	1	1 (0.1)
INCREASED STOOL URGENCY	0	0	1	1 (0.1)
INTESTINAL FISTULA	0	0	2	1 (0.1)
INTESTINAL ISCHAEMIA	1	1 (0.1)	4	4 (0.6)
INTESTINAL NECROSIS	0	0	1	1 (0.1)
INTESTINAL OBSTRUCTION	2	2 (0.3)	7	7 (1.0)
INTESTINAL ULCERATION	2	2 (0.3)	1	1 (0.1)
MELAENA	10	10 (1.5)	23	23 (3.4)
MOUTH DRY	3	3 (0.4)	12	12 (1.8)
MUCOSITIS NOS	0	0	1	1 (0.1)
NAUSEA	444	239 (35.1)	604	255 (37.8)
OESOPHAGEAL ULCERATION	2	2 (0.3)	2	2 (0.3)
OESOPHAGEAL VARICES	1	1 (0.1)	1	1 (0.1)
OESOPHAGITIS	11	11 (1.6)	11	10 (1.5)
OESOPHAGOSPASM	0	0	2	2 (0.3)
ORAL HAEMORRHAGE	1	1 (0.1)	1	1 (0.1)
PANCREATITIS	9	8 (1.2)	8	6 (0.9)
PEPTIC ULCER	3	3 (0.4)	2	1 (0.1)
PEPTIC ULCER AGGRAVATED	0	0	1	1 (0.1)
PERIODONTAL DESTRUCTION	1	1 (0.1)	3	3 (0.4)
PERITONITIS	1	1 (0.1)	3	3 (0.4)
PROCTITIS	0	0	1	1 (0.1)

The SAS System
Table 8.2
Incidence Rate of GI AEs
By Preferred Term

WHOART preferred label	Lanthanum # of events in WHO-ART	Lanthanum # (%) of pts (n=680)	Standard # of events in WHO-ART	Standard # (%) of pts (n=674)
RECTAL DISORDER	2	2 (0.3)	1	1 (0.1)
RECTAL PROLAPSE	1	1 (0.1)	0	0
SALIVARY GLAND ENLARGEMENT	1	1 (0.1)	2	2 (0.3)
STOMATITIS	0	0	1	1 (0.1)
STOMATITIS ULCERATIVE	2	2 (0.3)	1	1 (0.1)
TENESMUS	1	1 (0.1)	2	2 (0.3)
TONGUE OEDEMA	0	0	1	1 (0.1)
TOOTH ACHE	32	21 (3.1)	16	15 (2.2)
TOOTH CARIES	4	4 (0.6)	7	6 (0.9)
TOOTH CARIES AGGRAVATED	0	0	1	1 (0.1)
TOOTH DISORDER	10	9 (1.3)	17	16 (2.4)
VOMITING	297	172 (25.3)	373	195 (28.9)

The SAS System
Table 8.3
Frequencies of time to onset of AEs

The FREQ Procedure

Table of tweek by group			
tweek(Time to Event (weeks))	group(Treatment Received)		
Frequency Col Pct	Lanthanum	Standard	Total
1-4 wks	316 18.04	230 9.27	546
5-26 wks	619 35.33	723 29.15	1342
27-52 wks	389 22.20	577 23.27	966
>1 Year	428 24.43	950 38.31	1378
Total	1752	2480	4232

The SAS System
Table 8.4
Duration of GI AEs

The FREQ Procedure

Table of DAYS by group			
DAYS(Duration (day))	group(Treatment Received)		
Frequency Col Pct	Lanthanum	Standard	Total
0-7days	1158 66.10	1776 71.61	2934
8-14days	112 6.39	138 5.56	250
15-21days	59 3.37	54 2.18	113
22-28days	26 1.48	33 1.33	59
>28days/Unresolved	397 22.66	479 19.31	876
Total	1752	2480	4232

SAEs with unknown duration are included in the >28days/Unresolved category

The SAS System
Table 8.5
Duration of AEs
By time of onset

The FREQ Procedure

Table 1 of tweek by DAYS						
Controlling for group=Lanthanum						
tweek(Time to Event (weeks))	DAYS(Duration (day))					
Frequency Row Pct Col Pct	0-7days	8-14days	15-21days	22-28days	>28days/Unresolved	Total
0-26 wks	599 64.06 51.73	65 6.95 58.04	33 3.53 55.93	13 1.39 50.00	225 24.06 56.68	935
27-52 wks	253 65.04 21.85	26 6.68 23.21	13 3.34 22.03	6 1.54 23.08	91 23.39 22.92	389
>1 Year	306 71.50 26.42	21 4.91 18.75	13 3.04 22.03	7 1.64 26.92	81 18.93 20.40	428
Total	1158	112	59	26	397	1752

AEs with unknown duration are included in the >28days/Unresolved category

The SAS System
Table 8.5
Duration of AEs
By time of onset

The FREQ Procedure

Table 2 of tweek by DAYS						
Controlling for group=Standard						
tweek(Time to Event (weeks))	DAYS(Duration (day))					
Frequency Row Pct Col Pct	0-7days	8-14days	15-21days	22-28days	>28days/Unresolved	Total
0-26 wks	645 67.68 36.32	60 6.30 43.48	26 2.73 48.15	16 1.68 48.48	206 21.62 43.01	953
27-52 wks	431 74.70 24.27	30 5.20 21.74	13 2.25 24.07	2 0.35 6.06	101 17.50 21.09	577
>1 Year	700 73.68 39.41	48 5.05 34.78	15 1.58 27.78	15 1.58 45.45	172 18.11 35.91	950
Total	1776	138	54	33	479	2480

AEs with unknown duration are included in the >28days/Unresolved category

The SAS System
Table 8.6
Outcome of AEs : Lanthanum Treatment

Body System	resolved	resolved w/ seq	unresolved	All
	AEs #	AEs #	AEs #	AEs #
Total	1524	13	215	1752
GASTRO-INTESTINAL SYSTEM DISORDERS	1524	13	215	1752

Body System	death	resolved	resolved w/ seq	unknown	unresolved	All
	AEs #	AEs #	AEs #	AEs #	AEs #	AEs #
Total	2	2183	5	1	289	2480
GASTRO-INTESTINAL SYSTEM DISORDERS	2	2183	5	1	289	2480

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/s/

Denise Hinton
4/13/04 04:47:39 PM

Akinwole Williams
4/15/04 12:57:26 PM

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

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5600 Fishers Lane
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Transmitted to FAX Number:	(240) 453-6456
Attention:	Lisa Wittmer, Ph.D.
Company Name:	Shire Pharmaceutical Development
Phone:	(240) 453-2032
Subject:	**10Mar04 CMC/Biopharm Meeting Minutes NDA 21-468**
Date:	April 21, 2004
Pages including this sheet:	8

From: **Denise M. Hinton**
Phone: **301-594-5333**
Fax: **301-594-5494**

NDA Meeting Minutes

Meeting Date:	March 10, 2004
NDA Application:	21-468
Sponsor:	Shire Pharmaceutical Development Inc.
Meeting Type:	B
Classification:	CMC/Biopharm
Meeting Request Date:	March 2, 2004
Confirmation Date:	March 5, 2004
Meeting Chairs:	Kasturi Srinivasachar, Ph.D. Patrick Marroum, Ph.D.
Meeting Recorder:	Denise Hinton

Attendees:

Division of Cardio-Renal Drug Products

Kasturi Srinivasachar, Ph.D.	Chemist, Team Leader, HFD-810
Patrick Marroum, Ph.D.	Biopharmaceutist, Team Leader, HFD-860
Kris Raman, Ph.D.	Chemist, HFD-810
Angelica Dorantes, Ph.D.	Clinical Pharmacologist/Biopharmaceutist, HFD-860
Denise Hinton	Regulatory Health Project Manager, HFD-110

Shire Pharmaceutical Development Inc.

Iain Cockburn M.D.	Worldwide Director of Pharmacovigilance
Stephen Damment, Ph.D.	Director, Preclinical Sciences
[ ]	Shire Consultant
[ ]	Shire Consultant
Michael Pennick, Ph.D.	Manager, Preclinical Sciences
Raymond Pratt, M.D.	Vice President, Clinical Research
Wilson Totten, M.D.	Group Research and Development Director
Simmon Tulloch, M.D.	Senior Vice President, US Research and Development
Isobel Webster	Project Leader
[ ]	Shire Consultant
Lisa Wittmer, Ph.D.	Associate Director, Regulatory Affairs
Yuxin Zhang, Ph.D.	Senior Director, Biostatistics

BACKGROUND

The Division requested this meeting with Shire Pharmaceutical Development Inc. to discuss deficiencies identified in the Chemistry, Clinical Pharmacology and Biopharmaceutics review at present.

Discussions:

Mass Balance Study

Shire submitted a brief description of the approach for oral mass balance data (see attachment).

Dr. Dorantes asked Shire to provide the data on the percentage of lanthanum that is excreted after intake. Although lanthanum carbonate is mainly excreted in the feces, there is concern over how much may be absorbed and remain in the GI tract.

Shire stated that they felt that the oral mass balance approach would not be helpful and do not have all oral excretory data, however they do have systemic bioavailability and amount excreted in urine. They reiterated that the vast majority of lanthanum is excreted in feces. Dr. Dorantes commented that if they would have measured the amount of lanthanum recovered in feces in the absolute bioavailability study, this would have answered the question of whether lanthanum accumulates in the GI tract. Dr. Marroum stated that he understands Shire's concerns, though he does not agree with the assay sensitivity argument.

Dissolution

Shire explained that the dissolution test developed reflects the Drug Substance and Formulation. The — testing is the same approach used for the gelatin capsules. They have seen many occurrences that the tablets will not meet the specifications of not less than [ ] in 45 minutes due to the tablets not disintegrating. Shire moved to — after the first tested lots failed. These lots failed — as well; therefore they did not go to — due to the poor performance of these lots. The whole tablet was used with all available options to develop an test that would be consistent. Dr. Marroum stated that either the test or the production is no good. In regard to the dissolution data in the resubmission, out of – batches only - failed — Out of the – were manufactured at [ ] The methodologies of — dissolution method with whole tablets and crushed tablets are not acceptable. The Division needs to see — data for the whole tablets. If a lot does not pass — testing then it is considered a "Failed" lot.

Shire stated that the [ ] batches were tested longer than the [ ] batches. [ ] has more batches, test at different time points, and see more failures. The Division cannot interpret the data because the - different dissolution tests do not correlate with each other. Shire should focus their concern on the lots since they, not the test, could be the cause for failure. Shire was asked to resolve the difference in the behavior of the lots and submit the information to the Agency.

Shire agreed to acquire the data — but anticipates that the lots that fail — testing will also not pass — They stated [

] They have [

]

They may consider using [ ]. Shire said [

]

Dr. Srinivasachar inquired about whether Shire looked at the difference in dissolution within a batch. Shire stated [

]

Dr. Marroum asked how we would know [ ] batches do not have a different [ ] profile and how they would behave in vivo and in vitro using the first test. Shire stated that there was no data linked to in vivo and in vitro comparison and limited solubility, but inferred that the crushed tablets gave good results.

Dr. Marroum stated [

] Two different tests with two specifications and conditions are unacceptable. It would be a deviation from policy to allow the two different tests and it would be difficult to correlate the results. Shire needs to make certain that the whole tablet test is informative and meaningful; otherwise it would be futile to conduct it.

Shire stated that they provided the crushed and whole tablet tests in an effort to satisfy the FDA. They proposed to base the data on scientific rationale and present the crushed tablet method as a single process and conduct a crushed tablet test on the chewable tablets [ ] They asked for the FDA to reconsider accepting the crushed tablet method because developing a further method would take a significant amount of time.

Dr. Marroum reiterated that the crushed tablet test is not acceptable and that the whole tablet test needs to be performed. He will speak to others within the Agency to see if an exception could be made, but in the interim Shire needs to explain the difference in the behaviors of tests and present their arguments accordingly. In regard to using a different method for — testing, they should show that they are able to reject a bad batch using this approach. Shire argued that they have previously shown that.

[ ]

[ ]

Metal Specification

After consulting the USP, Shire reevaluated all metal impurities in API and selected — metal impurities including the — instead of the — metals recommended by the Agency, as they felt this was justifiable based upon the toxicology review, analytical method capability, and batch data. Shire stated that the analytical method for all — metals has been validated and that testing is a challenge because of the low levels and not many elements are detected in the drug substance.

The Division requires seeing all — metal impurities included in the specification with limits. If some metal impurities out of — are not present in the current lots, there is still a possibility that

they could appear later. USP is not a good example because most monographs need to be updated. Shire was advised to use the same methodology to look at all — Having the limits for these metal impurities would give some assurance that batches would not have — exceeding the toxic limit. It is expected that there will be some analytical variability in values and levels cannot be controlled. The Division reiterated that Shire is to list all — with appropriate limits based on methods sensitivity. Lanthanum carbonate is a mineral and the Division needs to know what metal impurities the future batches will contain. We should have enough control of the drug substance because of its mineral nature so that outlier batches are not used in the drug product. Some lots may show elements at higher amounts, possibly at toxic levels, therefore specified limits on all — metals are a requirement.

Shire stated that they submitted full justification for —metal impurities in Volume 2/4-219 with a table of evaluation results and proposed recommended limits based on analytical capabilities.

The Division will take into account that listing all —impurities may be a burden and will discuss it further with upper management and inform Shire of the discussions at a later date. The USP is good to refer to for some elements listed, but the USP does not address other elements.

Drug Substance

ICH Guidance for Industry requires 12 months long-term stability data at 5°C ± 3°C and 6 months accelerated stability data at 25°C ± 2°C 60% RH for drug substance stored at refrigerated conditions. Shire was asked to provide up to 12 months stability data at 5°C for three lots (F030001, F30002 and F03003) manufactured at [ ]

Shire was also asked to submit a stability data for 12 months at 5°C and for 6 months at 25°C/60%RH for at least three batches of the drugs substance manufactured at [ ]

Drug Product

[ ]

Shire was also asked to clarify why the closure system [ ] for the [ ] container has been changed for the current formulation.

Two year expiry dating for the drug product cannot be assigned based on the stability data of current formulations .[ ]

[ ] should be submitted, as recommended by the Stability Guidance, in order to assign a two year expiration date.

Shire stated that the current [ ] stability data is up to 12 months and [ ] is to be generated shortly. Stability data for the current formulation is supportive and they have sufficient data to support a 2 year shelf life.

/S/

Meeting recorder: _____
Denise M. Hinton

/S/

Meeting concurrence: _____
Kasturi Srinivasachar, Ph.D.

/S/

_____
Patrick Marroum, Ph.D.

Draft: 12Mar04
Final: 20Apr04

RD:
Dorantes 3/30/04
Marroum3/30/04
Raman 4/15/04
Srinivasachar 4/19/04

Shire Attachment

Enclosed is a preliminary response to Dr. Dorantes' question regarding fecal excretion data from orally-dosed subjects. The response was sent by Shire via email on March 8, 2004.

Informal question

Why are excretion data not available from the oral study?

Response

Our understanding is that this question relates to the oral arm of Study SPD405-117, an open-label, parallel group, single-dose oral and intravenous pharmacokinetic study in healthy male subjects.

In previous meetings with the Agency (9th January 2003, 11th January 2003), we highlighted a concern that an oral mass balance approach would not have adequate sensitivity to determine the extent of absorption or excretory routes for absorbed lanthanum in man. At the time, this concern was based on systemic bioavailability values determined in animals, indicating an absorbed fraction of approximately 1/1000th of 1% compared to a typical error for drug recovery in a human mass balance study of +/- 5 to 10% (see Table 1 for examples).

Furthermore, three Phase 1 studies (Studies LAM-IV-108, LAM-IV-109 and LAM-IV-111) established that urinary excretion of lanthanum after oral dosing in healthy subjects was extremely low (e.g. 0.000031% of the dose in Study LAM-IV-109), indicating that non-renal clearance mechanisms were likely to be most important. Animal data supported this view, the main excretory mechanisms in an intravenous rat study being the bile and direct gut transfer (Study R00185-LAM-IIIG). Consequently, a mass balance approach would also not provide information on major excretory routes for absorbed lanthanum, as any lanthanum in the feces arising from bile would be indistinguishable from the much larger quantity of lanthanum arising from the unabsorbed dose.

A bioavailability approach was therefore suggested to the Agency as an alternative, culminating in Study SPD405-117. The aims of this study were to investigate the bioavailability and non-renal excretory routes for systemic lanthanum. As such, the focus was to obtain oral and intravenous pharmacokinetic data and intravenous excretion data. Fecal excretion data from the oral arm were not considered necessary or helpful to fulfill these aims.

The results from Study SPD405-117 confirmed the profile predicted from the animal data and endorsed the approach taken to investigate absorption and excretion. The systemic bioavailability after an oral was calculated to be just 0.00127% (highest value in any subject 0.00294%) and renal clearance <2% of total clearance, demonstrating very low absorption and the predominance of non-renal clearance mechanisms for the absorbed fraction. In the event, it was not possible to quantify the fecal component arising from elimination of systemic lanthanum owing to relatively high background fecal lanthanum concentrations and ethical constraints on the size of the intravenous lanthanum dose that could be given to the subjects.

Summary Table of Mean Recovery Data Obtained in Volunteer Studies Conducted

With Radiolabelled Test Materials

(Source [redacted] s Conducted 2003)

[redacted]					
Anti-Rheumatic Agent	Oral	6	Carbon-14	11	21
GCS Inhibitor	Oral	6	Carbon-14	9	83
Anti-Atrial Fibrillation	Oral	5	Carbon-14	7	65
Anti-Atrial Fibrillation	Intravenous	5	Carbon-14	7	58
Anti-Coagulant	Oral	4	Carbon-14	7	66
Anti-Cancer	Oral	4	Carbon-14	14	19
Endothelin Receptor Antagonist	Oral	6	Carbon-14	8	55
Anti-Fungal	Oral	6	Carbon-14	28	12
Anti-Cholinergic agent	Oral	6	Carbon-14	8	66
5-HT Antagonist	Oral	6	Carbon-14	12	90
Anti-Depressant	Oral	6	Carbon-14	8	90
Coronary Stenting	Intravenous	5	Tritium	12	6
Angiogenisis Inhibitor	Intravenous	6	Carbon-14	7	85

* = Excretion still ongoing (*ca* 1%) at the end of the collection period.

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/s/

Denise Hinton
4/21/04 03:12:25 PM

Patrick Marroum
4/21/04 03:29:15 PM

Kasturi Srinivasachar
4/23/04 12:06:53 PM

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	240-453-6404
Attention:	Dr. Lisa Wittmer (US Agent)
Company Name:	Shire Pharmaceutical Development Inc.
Phone:	240-453-6400
Subject:	NDA Meeting Minutes
Date:	December 19, 2003
Pages including this sheet:	6

From:	**Denise Hinton**
Phone:	**301-594-5333**
Fax:	**301-594-5494**
E-mail address:	**hintond@cder.fda.gov**

You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

Please let me know you received this.

Thank you.

Teleconference between Shire and the FDA Division of Cardio-Renal Drug Products

Drug:	**Fosrenol (Lanthanum Carbonate)**
Sponsor:	**Shire Pharmaceutical Development Inc.**
NDA:	**21-468**
Date of meeting request:	**February 25, 2004 (Division request)**
Date of Briefing Document:	**NA**
Date Meeting Confirmation Faxed:	**NA**
Type:	**C**
Classification:	**Guidance**
Meeting Date:	**March 2, 2004**

FDA Participants:

Douglas C. Throckmorton, M.D.	**Director, Cardio-Renal Drug Products**
Akinowole Williams, M.D.	**Medical Officer**
James Hung, Ph.D.	**Supervisory Statistician**
Valeria Freidlin, Ph.D.	**Statistician**
Denise Hinton	**Regulatory Health Project Manager**

Shire Participants:

Simon Tulloch, M.D.	**Senior Vice President US R&D**
Yuxin Zhang, Ph.D.	**Senior Director, Biostatistics**
Rick Lilley, Ph.D.	**Senior Vice-President, Regulatory Affairs**
Ray Pratt	**Vice President, Clinical**
Ian Cockburn	**Worldwide Director, Pharmacovigilance**
Wilson Totten	**Executive Vice President of RND**
Isobel Webster	**International Project Leader**
Lisa Wittmer, Ph.D.	**Associate Director, Regulatory Affairs**

Meeting:

The Division asked Shire to explain why the mortality data for people exposed to lanthanum carbonate had not been updated since December 2002. The long term data was of critical importance to understand mortality and for long term follow up of bone and adverse events.

Shire stated that it was difficult to collect additional follow up information because the studies were not designed to collect that specific data, attrition of those discontinued was lost to follow up, and they believed they could not retrieve the data from the sites after the trials were completed due to HIPPA regulations preventing further information, outside of what was required in the protocol, to be divulged.

The Division stated that the information added since the December 2002 submission did not add meaningfully to our understanding of the mortality data, as it included only those patients who continued to take study drug. We know from other data that there is a differential drop-out rate for the treatment groups that will skew these data. The comparison of mortality rates in Table A-1 in the December 20, 2002, submission (SN 042) suspected an adverse effect of lanthanum on mortality. The sponsor felt that the shape of the survival curves provided reassurance as to an effect on mortality.

Shire stated that the importance of the mortality follow up was not clearly communicated in the February 28, 2003 approvable letter, however they did recognize that the Division had discussed the importance of this issue separately with them.

The Division stated that we had not finalized our review

Shire was asked to provide updated and complete long term mortality data after the December 2002 date for all patients who have enrolled in the trials of lanthanum, including patients no longer in active trials. If that is not possible, the sponsor should submit written communication explaining why they would not be able to provide more long term mortality information and a precise description of difficulties encountered with trying to obtain the necessary information. They should also make a case in support of their previous arguments of why the Agency should not be concerned about the follow up data. The Agency will review that response as a part of the current submission.

/S/

Meeting recorder: _____
Denise M. Hinton

Meeting concurrence: /S/
Douglas C. Throckmorton, M.D.

Draft: 5Mar04
Final: 10Mar04
RD: 8Mar04
Freidlin 3-8-04
Hung 3-9-04
Williams 3-9-04
Throckmorton 3-10-04

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/s/

Denise Hinton
3/10/04 03:10:55 PM

Doug Throckmorton
3/11/04 07:31:45 AM

NDA Meeting Minutes

Meeting Date:	December 3, 2003
Type of Meeting:	NDA Meeting
NDA Application:	21-468
Sponsor:	Shire Pharmaceutical Development Inc.
Classification:	B
Meeting Request Date:	November 10, 2003
Confirmation Date:	November 10, 2003
Briefing Package Received:	November 10, 2003
Meeting Chair:	Douglas C. Throckmorton, M.D.
Meeting Recorder:	Dianne C. Paraoan

Attendees:

Division of Cardio-Renal Drug Products

Douglas C. Throckmorton, M.D.	Director, Division Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Deputy Director, HFD-110
James Hung, Ph.D.	Team Leader, Statistician, HFD-710
Akinwole Williams, M.D.	Medical Officer, HFD-110
Kris Raman, Ph.D.	Chemist, HFD-810
Angelica Dorantes, Ph.D.	Clinical Pharmacologist/Biopharmaceutist, HFD-860
Xavier Joseph, D.V.M.	Pharmacologist, HFD-110
John Koerner, Ph.D.	Pharmacologist, HFD-110
Valeria Freidlin, Ph.D.	Statistician, HFD-710
Denise Hinton	Regulatory Health Project Manager, HFD-110
Dianne C. Paraoan	Regulatory Health Project Manager, HFD-110

Shire Pharmaceutical Development Inc.

Iain Cockburn M.D.	Worldwide Director of Pharmacovigilance
Stephen Damment, Ph.D.	Director, Preclinical Sciences
[ ]	Shire Consultant
[ ]	Shire Consultant
Michael Pennick, Ph.D.	Manager, Preclinical Sciences
Raymond Pratt, M.D.	Vice President, Clinical Research
Wilson Totten, M.D.	Group Research and Development Director
Simmon Tulloch, M.D.	Senior Vice President, US Research and Development
Isobel Webster	Project Leader
[ ]	Shire Consultant
Lisa Wittmer, Ph.D.	Associate Director, Regulatory Affairs
Yuxin Zhang, Ph.D.	Senior Director, Biostatistics

BACKGROUND

Shire Pharmaceutical Development Inc. requested this meeting to discuss whether the additional preclinical and clinical data submitted constitutes a complete response to the approvable letter dated 28 February 2003. Pending the result of this meeting, the sponsor intends to resubmit the NDA by the end of the year.

DISCUSSION POINTS

Shire Pharmaceutical Development Inc. provided a brief PowerPoint presentation to graphically outline the additional Absorption, Distribution, Metabolism, Excretion (ADME) information they plan to include in their NDA resubmission. (See attached). The sponsor concluded their presentation in the last slide by making several points:

1. Lanthanum is naturally present in bone of dialysis patients.
2. Additional deposition occurs over time in patients treated with lanthanum carbonate.
3. Lanthanum is cleared from bone with an estimated half-life of 1.9 – 3.4 years.
4. Predicted bone levels after 15 years are within the range evaluated in animal studies, without adverse effects on bone cells or structure.
5. No evidence of aluminum-like or other adverse effects on bone in patients treated for 4+ years.

Overall

Dr. Throckmorton informed, based on the summaries provided, the sponsor has sufficient sufficient, reviewable additional data to constitute a complete response to the approvable letter dated 28 February 2003. The Division, however, had several recommendations prior to their resubmission.

Clinical Pharmacology/Pharmacology

Dr. Throckmorton stated that changes in the serum concentrations of lanthanum are largely without clinical relevance. We know that the drug is absorbed and is deposited in relevant tissues. Whether the serum levels are low or high does not alter that fact or make the drug more or less 'safe'.

ADME

It was discussed that (1) lanthanum deposition occurs in the bone, liver, and gastrointestinal (GI) tract, (2) remains in those tissues over an extended period of time, and (3) that no steady state has been achieved.

Dr. Throckmorton stated that studying the lanthanum deposition in bone is sufficient data assuming that:

1. The bone samples show deposition that is uniform and universal.
2. The small number of subjects and the bone biopsies represent the total population.
3. We are able to conclude that bone is a reasonable tissue to look at to understand deposition.

Gastrointestinal

Dr. Koerner stated that the animal studies showed that the GI tract had considerably more lanthanum than in the bone. The sponsor stated that they chose to study lanthanum deposition in the bone rather than the GI tract because it is more difficult to get GI tissue samples from subjects. In addition, it was discussed that more subjects would drop out of the study because of obvious GI side effects. The sponsor stated that they are reevaluating the data of those subjects who discontinued the study because of GI side effects. Dr. Throckmorton encouraged the sponsor to reevaluate the data to show evidence that there were no long term GI effects.

Bone studies

The sponsor has collected additional relevant bone samples from patients taking lanthanum for longer periods of time. The critical additional piece this allows is a calculation of the 'on-' and 'off-' kinetics of lanthanum absorption. The patients, of course, will also provide some limited safety information. As the number of patients is small, the bone biopsies will be critical. The number of samples is likely too small to detect subtle effects on bone histology---our need is to exclude toxicity of the relative magnitude of aluminum. We need, then, to be convinced that the available biopsies are sufficient to have detected such an injury, if one were present. A part of this argument should be a thorough review of what we know about the time-course of the development of histologic bony injury with aluminum, to make the case that these biopsies (looking for lanthanum) are at a sufficiently long period of exposure to be informative.

[

]

Biowaivers

[

]

Stability Data

Stability data will be included per previous agreements with the Agency.

Mortality

Dr. Throckmorton suggested that the sponsor provide mortality analysis for all subjects in this study, including those subjects on lanthanum for a short time. The mortality analysis provided should be as extensive as that submitted at the time of the approvable letter dated 28 February 2003.

Safety

Dr. Throckmorton recommended that the sponsor send updates on any adverse events involving bone. This should include an assessment of such injuries from all patients with available data, even those no longer taking lanthanum.

Post Approval Evaluation

The sponsor inquired as to whether or not the number of subjects in their sample was sufficient [ ] Dr. Throckmorton replied that a small sample may limit them but is sufficient as long as adequate long term follow up is completed and that all adverse events are monitored and reported. Given the longterm nature of lanthanum deposition and the relatively rare adverse events we are worried about (e.g., pathologic bony fractures), it is more than usually attractive to [ ] providing good information in this setting.
Dr. Throckmorton recommended that the sponsor include [ ] monitoring both subjects and adverse events at the time of resubmission.

Other Discussion Points

Short-Term vs. Long-Term Issues

A brief discussion of the age of patients to be used in the study, risk of malnutrition, and elevated liver enzymes were mentioned. The sponsor stated that children are excluded in the study. Dr. Throckmorton could not comment on the LFT material formally [redacted] but the Division had not identified liver toxicity as an issue previously. The sponsor should continue to focus on the long-term issues of the bone and tissue deposition.

Labeling

The sponsor stated that they have heightened knowledge of lanthanum and asked the Division for recommendations on how to give advice to physicians through labeling and if they will need to propose a new label. Dr. Throckmorton recommended the sponsor describe how and what they intend to provide to physicians and that a new label should be submitted with the resubmission.

CONCLUSIONS/ RECOMMENDATIONS

The Division recommended that the sponsor consider the discussions and suggestions described above in preparing the NDA resubmission. We encouraged the sponsor to contact the Division if they need additional assistance.

At the time of NDA resubmission, the sponsor needs to consider the following:

- Include extensive mortality analysis equivalent to that submitted at the time of the approvable letter dated 28 February 2003.
- Include the method(s) of monitoring both subjects and adverse events.
- Support the contention that the new bone biopsies will inform the risk of serious bony injury following long-term lanthanum deposition. A part of this will be a comparison with what is know about the toxicities of aluminum.

/S/

Signature recorder: _____
Dianne C. Paraoan

/S/

Concurrence, Chair: _____
Douglas C. Throckmorton, M.D.

Draft: 12/5/03 Final: 12/18/03
RD: 12/10/03

Throckmorton: 12/18/03
Stockbridge: 12/17/03
Williams: 12/16/03
Hung: 12/17/03
Dorantes: 12/15/03
Koerner: 12/15/03
Raman: 12/12/03
Hinton: 12/10/03

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/s/

Denise Hinton
12/18/03 03:57:25 PM

Doug Throckmorton
12/19/03 02:16:08 PM

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9/25/03

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-468	Efficacy Supplement Type SE- NA	Supplement Number NA	
Drug: Fosrenol (lanthanum carbonate hydrate) Chewable Tablets		Applicant: Shire Pharmaceutical Development	
RPM: Denise Hinton		HFD- 110	Phone # (301) 594-5333
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	Phosphate Binder
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	October 26, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	NA
• OC clearance for approval	NA
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	Enclosed
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	October 1 and 15, 2004
❖ Actions	
• Proposed action	**(X)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE on 28Feb03
• Status of advertising (approvals only)	**(X)** Materials requested in AP letter **(NA)** Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(X)** Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**(X)** None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	4Oct04
• Most recent applicant-proposed labeling	20Oct04
• Original applicant-proposed labeling	26Jan04
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC: 30 Jun03 and 30Jun04 DMETS: 2Jan03 and 2Jul04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Renagel and Phoslo
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	26Jan04 and 11Aug04
• Reviews	See Dr. Raman's review 14Sep04
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Yes
• Documentation of discussions and/or agreements relating to post-marketing commitments	In action letter
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Enclosed
❖ Memoranda and Telecons	Enclosed
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	26May1999 (CMC) 27May1999
• Pre-NDA meeting (indicate date)	18Sep01
• Pre-Approval Safety Conference (indicate date; approvals only)	12Oct04
• Other	Enclosed

❖ Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	NA
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	NA
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Dr. Temple 27Feb03 and 26Oct04 Dr. Throckmorton 25Feb03 Dr. Stockbridge 3Feb03/ 13Oct04 Dr. Karkowsky 12Oct04
❖ Clinical review(s) *(indicate date for each review)*	24Dec02 and 14Jul04
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	NA
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	26Jan04 15 mo. Safety Update 14Jul04 See Dr. William's review See Dr. Freidlin's 17May04 review
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	See Dr. William's review -14Jul04
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Enclosed
❖ Demographic Worksheet *(NME approvals only)*	NA
❖ Statistical review(s) *(indicate date for each review)*	27Aug, 3 and 8Oct, 5Nov02; and 17May04
❖ Biopharmaceutical review(s) *(indicate date for each review)*	18Nov02, 10Jan03, 24Sep03, 22Mar04, and 19Aug04
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	20Feb03
• Bioequivalence studies	6Jul04
❖ CMC review(s) *(indicate date for each review)*	31Dec02, 16Jan03, 27Feb03, 14Sep04
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	31Dec02-acceptable and 23Feb04
• Review & FONSI *(indicate date of review)*	31Dec02
• Review & Environmental Impact Statement *(indicate date of each review)*	31Dec02, 2Feb04
❖ Microbiology (validation of sterilization & product sterility) review(s)	NA
❖ Facilities inspection (provide EER report)	Date completed: 8Jun04 **(X)** Acceptable ( ) Withhold recommendation
❖ Methods validation	**(X)** Completed ( ) Requested ( ) Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	4Dec02, 13Jan03, and 10Jun04
❖ Nonclinical inspection review summary	13Jan03
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	15Oct02
❖ CAC/ECAC report	5Nov02

Meeting between Shire and the FDA Division of Cardio-Renal Drug Products

Sponsor:	Shire Pharmaceutical Development Inc.
Drug:	(Fosrenol) Lanthanum Carbonate Hydrate
NDA:	21-468
Date requested:	June 25, 2003
Date of confirmation:	July 3, 2003
Briefing document received:	July 22, 2003
Date of meeting:	August 7, 2003
Time:	9:30 –11:00 AM
Type:	C
Classification:	CMC
Meeting Chair:	Kasturi Srinivasachar, Ph.D.
Meeting recorder:	Denise M. Hinton

FDA Participants:

Kasturi Srinivasachar, Ph.D.	Chemistry Team Leader, HFD-810
Kris Raman, Ph.D.	Chemist, HFD-810
Angelica Dorantes, Ph.D.	Clinical Pharmacologist and Biopharmaceutist, HFD-860
Xavier Joseph, Ph.D.	Pharmacologist, HFD-110
Denise Hinton	Regulatory Health Project Manager, HFD-110

Shire Participants:

Jo Ferdinando, Ph.D.	Director of Pharmaceutical Sciences
Steve Damment, Ph.D.	Director, Preclinical Sciences
Lisa Wittmer, Ph.D.	Associate Director, Regulatory Affairs
Linda Mota	Regulatory Affairs Associate

Background:
Shire requested this meeting to discuss outstanding chemistry issues from the February 28, 2003 Approvable Letter.

Discussion:

The Division stated that

1 The current formulation

Shire gave a brief overview of the activity and results of the API. The API evaluated on stability and retention samples resulted in the impurity [redacted] Due to difficulties with obtaining [redacted] Shire proposes to specify [redacted] since the limit of detection is [redacted] and has been validated. The Division stated that [redacted] should be included in the specification. [redacted] batches of the drug substance have been made without detection of [redacted] at [redacted] while there has been detection of the impurity at the [redacted] site. They are assuming that there has been no detection of degradant [redacted] in API manufactured at [redacted] because their [redacted] is superior to [redacted].

Shire has stability up to [redacted] without detectable [redacted] impurities. The level is shown to be high at [redacted], therefore they will only use API with undetectable levels of this impurity initially. Toxicity studies are being conducted with API containing [redacted] versus lanthanum carbonate hydrate. If the toxicity results are comparable, they propose specification limits for the [redacted] in the API of <LOD.

The Division suggested that acceptance testing be done when manufacturing the tablets and each time when testing API. Shire agreed to retest API for [redacted] before manufacturing the drug product. Shire commented that the product would be stored at 15-25°C and they are also considering [redacted] or may qualify why it [redacted]

The Division responded to the following questions:

The relevant section of the briefing document is provided in parentheses.

1. **Is the quantification and planned qualification of [redacted] sufficient for determination of a suitable specification and shelf-life for the 250 mg and 500 mg tablets of lanthanum carbonate (Item 9)?**

The Division will need to see the complete and final results of the toxicity study before commenting on whether the quantification and qualification of [redacted] is sufficient to determine the specification limits.

The Division asked if the retained samples were checked for these impurities. Shire stated that if they retrospectively looked back at the samples, they would not be able to quantify them since it has been over 3 years.

2. **Shire has the following questions regarding specifications for metal impurities (Item 9):**

   a. **Is it a requirement to set specifications for all — potential metal impurities or is it sufficient to specify for the — metals identified in the NDA?**

Specifications should be set for all — potential metal impurities. The Division inquired about unlisted impurities such as [ ] Shire stated that the current technique is set to test for — metal impurities and they would find out why [ ] and possibly other impurities were not included.

b. If it is a requirement to set specifications for all — potential metal impurities, are the proposed specifications acceptable?

The amounts of impurities are generally low compared to the average human daily intake from the diet. The Division recommended that the specifications for [ ] should be set at lower levels. The Division suggested that Shire look at the USP monographs and keep within the posted limits for [ ] similar to lanthanum carbonate. Shire agreed to tighten the specification limit for metal impurities [ ]

Shire agreed to provide justification of current specifications on the basis of additional toxicity information.

3. **Regarding the [ ] method, is the specification proposed in the briefing package acceptable (Item 10)?**

[ ]

4. **Is the proposed whole tablet dissolution method that achieves — dissolution in 45 minutes acceptable (Item 10)?**

The proposed whole tablet dissolution method ([ ] with paddle at — rpm) is acceptable, however the proposed specification of — at 45 minutes is not acceptable. Before a final specification is set, the Division recommends that Shire collects additional data for [ ]

In regard to the dissolution medium, the Division considers that [ ] is more appropriate than [ ] because its pH value is about — which is closer to physiologic conditions.

In response to Shire's question of how to switch from the old method to the new, the Division stated that the number of timepoints to be used for each duplicate test would depend on the stability data of the crushed tablets. The Division suggested that they test both methods for the current batches and use the whole tablet method on the new batches. Shire has [ ]

The data will be submitted and additional discussions with the Division will be necessary to reach agreement on the specifications.

5. **Assuming adequate demonstration of bioequivalence, is the amount of stability data planned for inclusion in the resubmission (outlined in the briefing package) sufficient for approval of the 500 mg tablet (Item 11)?**

The amount of stability data will be sufficient provided it includes [ ] of real time stability data and [ ] accelerated data.

6. **Shire has the following questions relating to a proposed change in packaging of the 500 mg product (current formulation) (Item 12):**

   a. **Is it acceptable for Shire to include the CMC information relating to the packaging change in the resubmission for review prior to approval? If yes, is [ ] of accelerated stability data and available real-time data sufficient to support the proposed packaging change ([ ]**

The Division stated that Shire could change anything in the resubmission as long as they have enough data to support it or they can propose to make changes post approval. Shire was advised to collect a sufficient amount of background stability data and state how much data they have [ ]

Shire stated that they would have [ ]

   b. **If the packaging change must be submitted as a post-approval supplement, is [ ] of accelerated stability data and available real-time data sufficient to support the proposed packaging change [ ]**

The Division will accept [ ] of accelerated stability data for the new packaging as long as Shire has conducted all required testing. Shire was asked to compare packaging materials and show that the change is comparable or better.

Shire agreed to do [ ] tests and provide [ ] stability data.

/S/

Meeting Chair: _____
Kasturi Srinivasachar, Ph.D.

Meeting recorder: /S/
Denise M. Hinton

Draft: 8Aug03
Final: 5Sep03

RD: 8Aug03
Srinivasachar 5Sep03
Raman 2Sep03
Dorantes 11Aug03
Joseph 11Aug03

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/s/

Kasturi Srinivasachar
9/5/03 04:46:34 PM

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(240) 453-6456
Attention:	Lisa Wittmer, Ph.D.
Company Name:	Shire Pharmaceutical Development
Phone:	(240) 453-2032
Subject:	**NDA 21-468** **July 3, 2003 Meeting Minutes**
Date:	July 31, 2003
Pages including this sheet:	4

From:	**Denise M. Hinton**
Phone:	**301-594-5333**
Fax:	**301-594-5494**

Teleconference between Shire and the FDA Division of Cardio-Renal Drug Products

Sponsor:	Shire Pharmaceutical Development Inc.
NDA:	21-468
Drug:	Fosrenol (lanthanum carbonate)
Date of request:	June 19, 2003
Date of confirmation:	June 26, 2003 via telephone
Date of teleconference:	July 3, 2003
Meeting chair:	Douglas C. Throckmorton, M.D.
Meeting recorder:	Denise M. Hinton

FDA Participants:

Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D.	Division Director, Division of Cardio-Renal Drug Products
Juan Carlos Pelayo, M.D.	Medical Officer
Kris Raman, Ph.D.	Chemist
Angelica Dorantes, Ph.D.	Clinical Pharmacologist and Biopharmaceutist
Denise Hinton	Project Manager

Shire Participants:

Isobel Webster	International Project Leader
Wilson Totten, M.D.	Group Director R&D
Simon Tulloch, M.D.	Senior Vice President US R&D
Alex Michaels, M.D.	Vice President US Post-marketing
Iain Cockburn, M.D.	Worldwide Director Pharmacovigilance
Steve Damment, Ph.D.	Director, Preclinical Sciences
Michael Pennick	Manager, Preclinical Sciences
Jo Ferdinando, Ph.D.	Director, Pharmaceutical Sciences
Maggie Gill	Clinical Research Manager
Lisa Wittmer, Ph.D.	Associate Director, Regulatory Affairs

Background:

Shire requested a teleconference to discuss the requirements [ ] to obtain feedback on the proposed 3b study (312) entitled "A Multi-Center, Open-label Clinical Experience Study Assessing the Efficacy and Tolerability of Lanthanum Carbonate in the Reduction of Pre-dialysis Serum Phosphate in End Stage Renal Disease Patients Receiving Dialysis." Protocols [ ] 312 were submitted for review on [ ] and April 25, 2003.

Discussions:

3b Study (312)

After introductions, the Division asked for a more detailed explanation of the purpose of protocol synopsis 312. Shire explained that they conducted the study under IND 55,054 and that the design intervention for the study was to assess higher doses of Fosrenol from 3 grams to 4.5 grams daily. The rationale behind increasing the dose was that 60% of the patients receiving the treatment in the clinical program achieve control in doses between 750 mg and 3 gm, by increasing the dose they may achieve a greater target level. Secondly, they aimed to comply with the new draft K/DOQI guidelines and are confident that the new formulation can allow for increasing the dosage with ingestion of less tablets.

To answer the Division's question of how the study could be interpreted, Shire explained that the study would not confirm efficacy but would assess and interpret tolerability. The patient's response would be interpreted by the occurrence of adverse events and tolerability at higher doses. The study is described as exploratory, not definitive, thus assessments for safety and tolerability will allow a sense of what patients experience at certain dose levels.

The Division strongly encouraged that Shire capture any person that drops out due to the occurrence of adverse event(s) be followed until complete resolution and submit the complete information to the Agency. Collection of this data may provide adequate safety information, which was addressed in the February 28, 2003 Approvable letter. The Sponsor was also advised to detail specific tracking of the events in the protocol.

The Division referred back to the proposed 3b study, explaining that it was limited in value and that a comparator would be necessary in order to allow the trial to be more interpretable. Shire may submit a proposal to do an in vitro binding assay test, however, the Division cannot comment on what the conditions should be without further information, as there are a number of factors that influence binding. Additionally, the study seems very unlikely to support any changes in labeling. Shire agreed to the Division's recommendation to revise the study to require investigators to follow patients who discontinue from the study due to adverse events and follow them until resolution.

Shire stated that they would submit a new dissolution method.

Meeting recorder: /S/
Denise M. Hinton

Meeting concurrence: /S/
Douglas C. Throckmorton, M.D.

Draft: 11Jul03
Final: 30Jul03

RD:
Dorantes 7/23/03
Raman 7/25/03
Pelayo 7/25/03
Stockbridge 7/28/03
Throckmorton 7/30/03

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/s/

Denise Hinton
7/31/03 01:05:41 PM
CSO

Minutes signed by Dr. Throckmorton and faxed to the sponsor on July 31, 2003.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(240) 453-6456
Attention:	Lisa Wittmer, Ph.D.
Company Name:	Shire Pharmaceutical Development
Phone:	(240) 453-2032
Subject:	**NDA 21-468** **June 26, 2003 Meeting Minutes**
Date:	August 5, 2003
Pages including this sheet:	4

From:	**Denise M. Hinton**
Phone:	**301-594-5333**
Fax:	**301-594-5494**

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and/or confidential

commercial information

(b5)

6/10/03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-468

Shire Pharmaceutical Development Inc.
Attention: Lisa Wittmer, Ph.D.
1801 Research Boulevard, Suite 600
Rockville, MD 20850

Dear Dr. Wittmer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosrenol (lanthanum carbonate hydrate) 250 and 500 mg Chewable Tablets.

[ ]

We have reviewed the referenced material and have the following comments and recommendations:

1.

[ ]

2. We recommend that you submit [ ] for review and comment [ ]

If you have any questions, please call:

Denise M. Hinton
Regulatory Health Project Manager
(301) 594-5333

Sincerely,

{See appended electronic signature page}

/S/

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doug Throckmorton
6/10/03 07:40:18 AM

Minutes of a meeting between Shire and the FDA Division of Cardio-Renal Drug Products

Sponsor:	**Shire Pharmaceutical Development Inc.**
Drug:	**(Fosrenol) Lanthanum Carbonate Hydrate**
NDA:	**21-468**
Date requested:	**March 7, 2003**
Date of confirmation:	**March 21, 2003**
Type:	**C**
Date of teleconference:	**April 2, 2003**
Time:	**10:30 –11:30 AM**

FDA Participants:

Kasturi Srinivasachar, Ph.D.	**Chemistry Team Leader**
Kris Raman, Ph.D.	**Chemist**
Patrick Marroum, Ph.D.	**Biopharmaceutics Team Leader**
Denise Hinton	**Regulatory Health Project Manager**

Shire Participants:

Jo Ferdinando, Ph.D.	**Director Pharmaceutical Sciences**
Lisa Wittmer, Ph.D.	**Associate Director, Regulatory Affairs**

Background:
Shire requested this meeting to discuss the [ ] in the manufacture of the Drug Product, dissolution methodology, and acceptance of a bio-waiver for the 500 mg Tablet.

CHEMISTRY

- **Shire was asked to refer to their response from the December 16, 2003 deficiency letter in Volume 1.3, page 4-065. In that response, Shire agreed not to adjust the amount of lanthanum in the tablet based on the lanthanum assay, but to target to — of label claim. Shire's recent proposal to [ ] in order to achieve full potency of the drug product at the time of manufacture is unacceptable.**

Dr. Jo Ferdinando stated that she misunderstood the agreement and thought they were to [ ] responding to the lanthanum assay. Shire's aim was to [ ]

- **Dr. Srinivasachar advised Shire to use a calculation in batch documents to achieve adequate potency for every batch of API. Instead of basing the calculation on the assay, which will have analytical error in the measurement because it is not an absolute value, Shire was told that they could correct for the [ ]**

- **The Division also asked Shire to provide detailed calculations from batches to show Certificate of Analysis results, adjustments, and how the amount of lanthanum carbonate is calculated and adjusted for in each batch.**

In response to Dr. Srinivasachar's comment on the specifications for [ ] being too wide, Shire stated they wanted to incorporate the stability range. Stability under accelerated conditions may cause the drug substance to [ ] therefore, the specifications were increased to incorporate the [ ] Shire agreed to reevaluate and provide the data of all assays and present the details [ ]

BIOPHARMACEUTICS

Shire sought guidance for obtaining a waiver for the higher 500 mg tablets which is stated to be exactly double the 250 mg tablet they propose to market upon approval.

[ ]

- [ ]

[ ]

- [ ]

Shire stated that during their review of all chewable USP tablets they learned that none had a dissolution requirement for locally acting drugs and asked if they could adopt a [ ] test instead of a dissolution test.

- **Shire was advised to refer to the ICH guideline Q6A. The approach for adopting [ ] test is acceptable if they are able to show that the [ ] test is able to reject lots that are deemed to be unacceptable.**

Meeting recorder: /S/
Denise M. Hinton

Meeting concurrence: /S/
Kasturi Srinivasachar, Ph.D.

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/s/

Denise Hinton
5/21/03 10:12:11 AM
Minutes signed off by Dr. Srinivasachar and faxed to the sponsor.

Meeting between Shire and the FDA Division of Cardio-Renal Drug Products

Drug:	**Fosrenol (Lanthanum Carbonate Hydrate)**
NDA:	**21-468**
Date Meeting Requested:	**March 7, 2003**
Date Meeting Confirmation Faxed:	**March 21, 2003**
Date Briefing Document Received:	**March 24, 2003**
Date of Meeting:	**March 27, 2003**
Time:	**12:00 – 1:00 PM**
Type:	**C**

FDA Participants:

Robert Temple, M.D.	**Director of Drug Evaluation I**
Douglas C. Throckmorton, M.D.	**Director, Cardio-Renal Drug Products, HFD-110**
Juan Carlos Pelayo, M.D.	**Medical Officer**
Norman Stockbridge, M.D., Ph.D.	**Deputy Director, Cardio-Renal Drug Products, HFD-110**
Angelica Dorantes, Ph.D.	**Clinical Pharmacologist & Biopharmaceutist**
Denise Hinton	**Project Manager**
John Koerner, Ph.D.	**Pharmacologist**
Valeria Freidlin, Ph.D.	**Statistician**

Shire Participants:

Steve Damment, Ph.D.	**Director of Pre-Clinical Sciences**
Jo Ferdinando, Ph.D.	**Director, Pharmaceutical Sciences**
Neil Frazer, M.D.	**Vice President, Clinical Development**
Rick Lilley, Ph.D.	**Senior Vice President, Regulatory Affairs**
Wilson Totten, M.D.	**Group Director, R&D**
Simon Tulloch, M.D.	**Senior Vice President, US R&D**
Isobel Webster	**International Project Leader**
Lisa Wittmer, Ph.D.	**Associate Director, Regulatory Affairs**
Yuxin Zhang, Ph.D.	**Senior Director, Biostatistics**
[ ]	[ ]

Background:
Shire Pharmaceutical Development requested this meeting to discuss their proposals for addressing the clinical and biopharmaceutics deficiencies listed in the February 28, 2003 Approvable Letter.

Meeting:
Shire presented slides (see attachment) with proposals for addressing the Agency's concerns related to the safety evaluation of lanthanum carbonate. Shire sought input for establishing

whether the long-term adverse event profile is adequate to establish fair and balanced labeling and defined the data needed to establish the long-term safety profile of lanthanum carbonate post-approval based on the possible outcomes of characterizing absorption, deposition, and elimination profile.

In response to Shire's proposal regarding their approach for addressing adverse events, the Division stated that the adequacy of follow up of adverse events leading to discontinuation of patients is at issue. Shire was asked to provide information describing the time to resolution and any permanent sequelae for all events leading to discontinuation.

Shire sought agreement on whether the data to be provided to describe effects of lanthanum carbonate on QT interval and assess its link to cardiac death will sufficiently address the clinical prolongation of QT interval on the surface electrocardiogram.

- **The Division stated that the analysis of the small database Shire submitted on the 24-month group is unclear, leaving some uncertainty as to its meaning. Shire was provided with the Division's analysis of the outliers and was advised to show the mean effect and outlier analyses when they reevaluate QT prolongation. Shire stated that they did not see an apparent difference between the lanthanum therapy and standard therapy groups, but they agreed to provide a revised table of the list of patients identified with a QT prolongation as part of the full response to the Approvable Letter.**

Shire presented its proposal to provide additional data to establish the time-course of the expected absorption, deposition and elimination following chronic use of lanthanum carbonate. They stated that they expect to see steady state in 12 months, but they have been unable to demonstrate steady-state in tissue samples.

- **The Division stated that bone may provide a conservative estimate (because lanthanum may persist longer there) of deposition, and asked whether bone biopsy data could be used to establish when steady state was reached. Shire said they believe that that bone achieves steady state at 26 weeks, and that they believed bone accumulation and loss was a reasonable marker in the absence of data from other tissues.**

  The Division stated that it would be important for Shire to show what factors influence lanthanum absorption, especially through the GI tract. Shire discussed the possibility of doing an IV study in humans and noted that the rate of absorption was similar in healthy volunteers and animals and they do not expect the data of patients with residual renal function to be much different.

There was some discussion regarding the absence of aluminum like effects in patients receiving lanthanum carbonate after one year of treatment. Aluminum shows small effects at one year. The Division was not certain that one year of exposure was sufficient to have detected a toxic effect of lanthanum in the number of biopsies the sponsor had conducted, but the sponsor should make that case if they can. The clearest way forward is to collect longer-term (e.g., 2-3 year follow-up) bone biopsies to describe the time to steady state. This same cohort, along with the clinical data from all patients who had received lanthanum, could then be use to support

approval. If the 3-year group demonstrated that steady state is achieved and the previously discussed concerns prove to be unfounded, based on those data, then longer-term data may be submitted post-approval. If adverse effects are seen after four years, Shire would need to provide data showing broader exposure. Data showing decreasing lanthanum concentration in the bone would provide additional safety assurance.

As regards the long-term clinical safety database, the Division suggested that Shire locate patients who were exposed to lanthanum carbonate and have had biopsies, and follow them for a minimum of three years or until steady state is reached. Shire should also assess all patients exposed to lanthanum for signs of bony disease. It will be necessary for Shire to document that steady state is reached in bone before the application can be considered for approval. After approval, they will need to continue to monitor long-term safety. There will be a focus on the accumulation of lanthanum carbonate, bone effects, and signs of decrease of lanthanum in bone after steady state.

Shire stated that they could provide the results from patients exposed to lanthanum carbonate within the last 3 years. The Division told Shire to provide sufficient evidence with a sample size adequate enough to be able to detect osteomalacia.

Shire will discuss Chemistry and additional Biopharmaceutic issues at a later date.

Meeting recorder: /S/
Denise M. Hinton

Meeting concurrence: /S/
Robert Temple, M.D.

Draft: 28Mar3
Final: 11Apr03

RD: 1Apr03
Temple 11Apr03
Throckmorton 9Apr03
Stockbridge 8Apr03
Pelayo 8Apr03
Dorantes 8Apr03
Koerner 2Apr03
Freidlin 2Apr03

Attachments

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/s/

Denise Hinton
4/11/03 03:36:27 PM
Minutes signed off by Dr. Temple and faxed to the sponsor on April 11, 2003.

Douglas C. Throckmorton, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Tel (301) 594-5365, FAX (301) 594-5494

Memorandum

DATE: 2.25.03

FROM: Douglas C. Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products (DCRDP), HFD-110
FDA

TO: Robert Temple, M.D., Director
Office of Drug Evaluation-I
FDA

SUBJECT: NDA 21-468
NAME OF DRUG: Lanthanum Carbonate (Fosrenol)
SPONSOR: Shire Pharmaceutical Development Inc.

DOCUMENTS USED FOR MEMO:

1. Medical Review by Juan Carlos Pelayo, M.D., dated 12.31.02.
2. Secondary Medical Review by Norman Stockbridge, M.D., Ph.D., dated 2.3.03.
3. Chemistry Review by Kris Raman, Ph.D., dated 12.31.02 and 1.16.03 (Reviews #1 and 2 respectively).
4. Clinical Pharmacology and Biopharmaceutics Review by Angelica Dorantes, Pharm.D., dated 2.03.
5. Statistical Review of Clinical Data and Addendum by Valeria Friedlin, Ph.D., dated 11.5.02 and 12.30.02.
6. Pharmacology/Toxicology Review by John E. Koerner, Ph.D., dated 12.4.02.
7. Pharmacology/Toxicology Review by Xavier Joseph, Ph.D., dated 1.13.03.
8. Clincal Inspection Summary by Robert B. Shibuya, M.D., Pharmacologist, dated 2.20.03.
9. Proprietary Name review by Carol Holquist, R.Ph., Division of Medication Errors and Technical Support (DMETS), dated 12.20.02.
10. Sponsor's submission summarizing effects of lanthanum on bony parameters, NDA 21-468 volume 1.189 (study LAM-IV-301).
11. Sponsor's Integrated Safety Summary, NDA 21-468 volume 1.79.
12. Aluminum and bone disease in chronic renal failure by Jartmut H. Malluche, Nephrol Dial Transplant (2002) 17 (suppl 2): 21-24.
13. Intestinal absorption of aluminum in renal failure by Tilman B. Drueke, Nephrol Dial Transplant (2002) 17 (suppl 2): 13-16.

CONCLUSIONS

This memorandum constitutes the Divisional memorandum recommending that an approvable action be taken for the NDA named above for lanthanum as a phosphate binder. With one exception, discussed below, the deficiencies identified by the primary reviewers have been summarized in other reviews, and the reader is referred to the primary reviews as well as the secondary medical review by Norman Stockbridge for a summary. Lanthanum is a phosphate binder, but there are substantial issues related to its safety in the dialysis population that should be addressed prior to its approval. There are three major areas of uncertainty that remain:

1) **Chemistry, Manufacturing and Controls**: a variety of issues remain to be clarified, including:
    a. issues related to the proposed levels of metallic impurities in the product.
    b. the need for a USAN name for lanthanum.
    c. the need for adequate data to support the approval of the 500 mg tablet (the 250 mg tablet is approvable).
    d. the completion of one inspection, the results of which are anticipated today or tomorrow.
2) **Clinical Pharmacology**: the sponsor has been unable to quantify the absorption of lanthanum in humans although it is known to occur (based on bone biopsy material in humans and extensive animal data). Hence, the sponsor has not been able to perform a standard ADME or to assess the extent to which other factors can influence the absorption and elimination of lanthanum. When this is coupled with the observation that lanthanum is not removed with hemodialysis, the result is that in a person with ESRD lanthanum may continue to accumulate with no apparent route of elimination or defined 'steady-state' level of lanthanum accumulation in the body.
3) **Clinical**: the prominent clinical deficiencies relate to the unknown consequence of long-term accumulation of lanthanum in the various parts of the body where it is deposited (prominently the GI tract, bone and heart). As discussed by the various reviewers and below, while no clear signal for toxicity of this lanthanum deposition has been identified, the database is inadequate to evaluate the long-term consequences of such deposition on tissues of interest, including the bone and heart. Given the history of substantial human suffering that occurred following the bony deposition of another metal (aluminum) in patients with ESRD, a suitable way must be devised to conduct a long-term assessment of the consequences of lanthanum deposition, including adequate assessment of effects on bone. The exact nature of such a follow-up remains to be elucidated, but should incorporate a through follow-up of all patients who received lanthanum as part of the NDA trial database.

BACKGROUND AND OVERVIEW

Hyperphosphatemia is a significant source of morbidity and mortality in patients with end stage renal disease (ESRD). The treatment of hyperphosphatemia involves the use of phosphate binders to complex with phosphate in the gut, thereby preventing its absorption. At present, there are two phosphate binders in common use: one approved drug (Renagel) and off-label use of calcium-containing antacids. Historically, antacids containing aluminum were also used. These were later shown to cause a devastating form of bone disease, resulting in anemia and bony fractures. While controlled trial data are not available, these effects were evident clinically only after 3-5 years of treatment with aluminum-containing antacids. The present NDA proposes the use of a novel phosphate binder: lanthanum carbonate.

To support the use of lanthanum carbonate as a phosphate binder the sponsor has studied it in patients undergoing either peritoneal dialysis or hemodialysis. There is no doubt: lanthanum binds phosphate, although not 'better' to any degree than available therapies.

What remains, then, is to characterize the safety of lanthanum. For this NDA, the sponsor has collected a reasonable number of patient exposures, (around 550 > 1 year, 150 >2 years, see Dr. Pelayo's review, page 13 for details). Under normal circumstances this database would suffice for a chronic therapy. The present application, however, is not 'normal' in two critical ways that limit the adequacy of the available data to support the clinical safety of lanthanum:

- the poorly-characterized but prolonged time to steady-state concentrations for lanthanum.
- the limitations in the clinical data that result from the differential discontinuations due to adverse events.

Need for Data at Steady-State Concentrations

Typically, the time to stead-state serum concentrations for a new drug (and active metabolites) is determined early in the development program. This information is used as a base for understanding the relationship between concentration and adverse events observed in the later stages of the development. Where there are long-lived metabolites (*e g.*, levosimendan) or unusual tissue distribution (*e.g* , amiodarone) this is taken into account when looking at the time needed for clinical safety follow-up. The current program is handicapped in this regard: originally it was thought that lanthanum was not absorbed. It is now apparent that:

1. The fraction of an oral load of Lanthanum that is absorbed is not know for humans, but it is known from bone biopsy material to be absorbed in humans. From non-clinical data, it is deposited in multiple tissues with repeat administration. Serum concentrations of lanthanum are a poor marker of tissue levels, and remain constant even with varying tissue levels in animals.
2. This build-up of lanthanum results in levels in various tissues in animals that are extremely high (*e.g.*, into the micrograms/gram tissue for stomach, teeth and liver in dogs, see John Koerner's review, page 5). We don't know when steady state levels are achieved in humans, but in healthy animals it requires around 6 months of lanthanum administration.
3. We know relatively little about how lanthanum is metabolized/ excreted, although it does not involve the CYP 450 system, and is likely to be via biliary excretion. Renal clearance is not a large component in animals.
4. We know, whatever the route of elimination is, that tissues levels fall very slowly following drug discontinuation (*e.g.*, 87% remains in the femur growth plate of dogs 6 months after discontinuation of lanthanum).
5. We know very little about what factors might affect the absorption/ deposition/ metabolism/ and elimination of lanthanum. The interaction studies conducted to date have used serum concentrations of lanthanum to look for interactions, which are poorly correlated with changes in tissue in animals.

Why does this matter? Most critically, these deficiencies mean that we don't whether the available safety database follows patients long enough to reach steady state as far as tissue concentrations. For a drug to be used chronically, one that accumulates in tissues that are identified as of particular concern for the population (*i.e.*, bone in patients with ESRD), this is a deficiency that must be addressed. We also have no understanding of the factors that might influence the pharmacology of lanthanum (*e.g.*, extent of absorption from the gut). Should a safety consideration be identified, such interactions would be critical to understand.

Impact of Differential Withdrawal Rate

As discussed by other reviewers, there was a differential withdrawal rate in all of the trials of lanthanum, such that patients on lanthanum were much more likely to discontinue for adverse events (especially GI adverse events). For details, see Juan Carlos Pelayo's review page 18 and the sponsor's table 8.8-12. The sponsor asserts that this observation was due, in part, to an accident of trial design that allowed people on the comparator therapy to remain in the trial and switch to another agent, while patients on lanthanum were discontinued if they didn't tolerate the drug. While a partial explanation, the withdrawal rates on lanthanum exceed the comparator for <u>all</u> trials, regardless of duration, and the pattern of adverse events is consistent across the trials (all focused on GI intolerances) indicating that the use of lanthanum is significantly less well tolerated than the comparator phosphate binders. This differential exposure has to be taken into account for all long-term safety assessments.

CLINICAL SAFETY OF LANTHANUM CARBONATE IN ESRD

For the present application, two safety concerns predominate: mortality effects and effects on bone. There is a third, less well-defined effect to prolong the QT interval on which I will have little to say because I'm not sure we know much for certain. The two factors discussed above both play into the decision regarding the adequacy of the current database with regard to these events.

With regard to the comparative effects of these agents on mortality, the sponsor first submitted data that suggested a favorable effect of lanthanum on mortality (based on a follow-up of 85% of the patients in their trials). As additional data became available, it became clear that the initial reporting was biased, and that there was no evidence of a favorable effect of lanthanum on survival. As Norman Stockbridge points out (page 6 of his review), while there is no clear <u>adverse</u> effect (although the crude mortality rate is in favor of standard therapy), the confidence limits around the estimates are broad.

The sponsor also examined the available data (clinical and non-clinical) for evidence of bone toxicity. The inadequacies of the animal testing have been commented on elsewhere. For the most important trial, the animals treated with standard phosphate binders and lanthanum both developed bony disease due to hypophosphatemia. Because of this, the ability to detect bony injury due to another mechanism (*e.g.*, lanthanum toxicity) was significantly reduced, and the absence of a signal in this trial cannot be interpreted as dispositive. The sponsor has also assessed the possible effects of lanthanum on bone in the clinical studies. Here, the data are also limited. First, the sponsor performed study LAM-IV-301, which included the collection of baseline and follow-up bone biopsies after one year of therapy in patients with ESRD (on hemodialysis and peritoneal dialysis). These data are reviewed in Dr. Pelayo's review. The results from these studies are equivocal, and suffer from the small number of biopsies (around 30 pairs) and the design of the trial. The trial was designed to allow patients to go without phosphate binders for 4 weeks, at which time they were randomized to either calcium carbonate or lanthanum carbonate (a standard design for this type of trial). Unfortunately, uncontrolled hyperphosphatemia itself affects bony deposition. As a result, all patients had disordered bone metabolism at baseline, and both groups tended to improve on therapy. As the trial was not intended to find a difference between the two groups and obtained relatively few biopsies, this design had a very high likelihood of finding 'no difference', whether or not a difference was there to find.

The sponsor also looked for clinical adverse events suggesting bony toxicity. Here, as discussed above, the differential dropout rate and the shorter exposure to lanthanum could minimize our ability to detect a difference between the two treatment groups (follow for patients who discontinued therapy is only available for mortality). There is also the issue of how long a bony toxicity takes to be manifest clinically (aluminum took years). With these limitations, no safety signal emerged for lanthanum and bone toxicity from the data.

So, what can we say about the risk for bony toxicity in patients taking lanthanum? We can say there was no clear signal with the available data, but that the available data are almost certainly inadequate to assess the concern. I do, however, think, that the patients exposed to lanthanum for even short periods of time may provide relevant safety information if they are followed long enough. Based on the discussion above, lanthanum is quite likely to persist in the bone for months to years after drug discontinuation. If this is shown to be true, the early dropouts will have received less lanthanum (that is, we can't assess the effect of steady-state concentrations of lanthanum), but they will continue to have significant lanthanum in their bones and potentially be a source of data on bony disease.

Consequences of Patient Discontinuations

There is one additional safety concern that has not been addressed fully by the previous reviewers that needs mention: the resolution of adverse events in the clinical trial database. As discussed previously, there were significantly more adverse events leading to discontinuation in patients receiving lanthanum. For most applications, it is reasonable to assume that the discontinuation of the drug will quickly lead to resolution of the symptoms (*e.g.*, nausea with erythromycin). Here, the link between drug discontinuation and resolution of symptoms is less clear, given the large amounts of lanthanum that persist in the tissues long afterwards. The submission does not address the time to resolution of the symptoms reported in the clinical trials. If the GI symptoms for lanthanum persist for weeks or months after discontinuation, they become more than simply symptoms leading to discontinuation. For this population, where food intake is often diminished as a consequence of their disease, a drug that exacerbates this has the very real potential to lead to significant malnutrition. Here, again, more data are required in the form of follow-up information for those patients that discontinued from the trials in the submission.

SUMMARY AND RECOMMENDATION

The issue for this package is not whether lanthanum binds phosphate in the GI tract, and hence is effective as a phosphate binder in patients with ESRD. Instead, the issue is whether we understand enough about the safety of its chronic use. For the reasons discussed above, I believe substantial issue remain regarding the long-term use of lanthanum centered around the effects of chronic deposition of lanthanum in a variety of body tissues, our imperfect understanding of the factors influencing that deposition, and our imperfect understanding of the consequences of the adverse effects reported for patients taking lanthanum. I believe that a three pieces of information are critical to assist our understanding of the safety of this drug:

1) A better understanding of the clinical pharmacology of lanthanum (*e.g.*, absorption, deposition and elimination).

2) Longterm follow-up data from patients that have been exposed to lanthanum. Given that lanthanum is deposited and excreted (if at all) very slowly in patients with ESRD, the sponsor should C

T all patients who took lanthanum and be able to follow all of them for clinical outcomes. Obviously, the

control patients in the trials might serve as a useful comparator group to allow for examination of clinical safety long-term.

3) Long-term follow-up data from the ongoing study LAM-IV-307, from patients on lanthanum and standard therapy for up to 2 years. This trial intends to collect bone biopsy material at baseline and after 1 and 2 years of therapy. These data could provide important information on two critical aspects of lanthanum safety: when 'steady-state' tissue concentrations are achieved and whether there is a long-term safety risk for patients on lanthanum. The sponsor should be strongly encouraged to revisit the details of the data collection in that trial to make it as robust as possible with regard to safety data collection.

These two long-term datasets, combined with the additional work on the clinical pharmacology of lanthanum, could fill in critical pieces need to more fully understand the overall risks and benefits of lanthanum in patients with hyperphosphatemia. Would it be possible to approve the drug pending these data (presumably with a Phase IV commitment)? Given our experience with aluminum-containing antacids, the availability of an approved phosphate binder, and the imperfect state of our understanding of the kinetics of lanthanum, I'm reluctant to recommend such a course and would prefer to wait until the results of the 2-year bone biopsies and the long-term follow-up from the patients exposed to lanthanum to date are available and analyzed. Were additional information to become available that resolved many of our uncertainties about when steady-state lanthanum concentrations are achieved in bone, it might be possible to approve this before the trial is complete, especially if steady-state is achieved in less than a year of chronic therapy.

One last point needs to be discussed, which is the recommendations of the primary and secondary medical reviewers. The primary medical reviewer recommends against approval of lanthanum carbonate. He argues that lanthanum is inferior to currently available (if unapproved) therapy---calcium carbonate with regard to phosphate binding, based on study LAM-IV-301. He also, and most importantly, concludes that 'the drug's safety is not adequately evaluated, and the current safety evaluation shows that long-term exposure to lanthanum carbonate may be unacceptably toxic.' Inferiority to available therapy is not a basis for refusing to approve an agent, although superior efficacy would be an advantage for this compound (one that is absolutely not demonstrated in these data). He agrees that the lanthanum effectively binds phosphate and can control hyperphosphatemia in patients on dialysis (*e.g.*, see page 39 of his review). I am in agreement with his argument regarding the inadequacy of the current safety evaluation, but absent a clear signal of increased risk, I see this absence as an issue for additional study rather than a basis for a non-approval.

The secondary medical reviewer, Norman Stockbridge, suggests that the long-term data are inadequate for approval as a chronic therapy, but that approval for short-term treatment is an option. There are three reasons that I disagree with this approach. First, of course, we have no evidence that lanthanum is effective in patients who are 'resistant' to other binders, so this argument would need to be made on the basis of 'too few' options for patients being currently available for the short-term treatment of hyperphosphatemia (*i.e.*, Renagel, calcium and aluminum-containing antacids). I know of no data suggesting that there are individual who cannot be controlled on the current therapies, which would be needed for this argument. Second, even if we were to conclude that lanthanum was effective in this population, the issue how long to allow the treatment to continue would be difficult to answer. First, hyperphosphatemia is a chronic condition for patients with ESRD, and initiation of therapy with a new phosphate binder typically takes 2-3 weeks to see clear effects (that is, 'short-term' use can't be all that short-term). Given this, and the concerns over the deposition of lanthanum (and its slow elimination), a course of therapy lasting a few months might still result in a substantial total-body burden of lanthanum and a risk of long-term toxicity (yet to be determined). Lastly, I disagree in general with the notion of a short-term approval for the treatment of any condition that is by its nature chronic; it is an open invitation to off-label and potentially dangerous use.

To conclude, then, sufficient uncertainty remains with regard to the clinical pharmacokinetics of lanthanum and the clinical consequences of long-term oral use of lanthanum carbonate that additional clinical information is required before the Division can recommend approval. The application as submitted is approvable. The timing of approval relative to the collection of these clinical data ([redacted] from the on-going clinical study) relies on first determining more fully the kinetics of lanthanum following oral administration in ESRD.

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/s/

Doug Throckmorton
2/25/03 01:39:02 PM
MEDICAL OFFICER

1/16/03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-468

INFORMATION REQUEST LETTER

Shire Pharmaceutical Development Inc.
Attention: Lisa Wittmer, Ph.D.
Associate Director, Regulatory Affairs
1801 Research Boulevard, Suite 600
Rockville, MD 20850

Dear Dr. Wittmer:

Please refer to your April 30, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosrenol (lanthanum carbonate) 250 mg and 500 mg Chewable Tablets.

We also refer to your submission dated December 20, 2002.

We have reviewed the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests.

I. Regarding the Drug Substance

1. Is [ ] method provided in the original NDA and the alternative method proposed in the amendment for [ ] are same or different? If different, please provide methods validation. Also provide method validation for [ ] determination by [ ] method.

2. Please refer to NDA Serial # 041, December 20, 2002 and explain the three new peaks observed at [ ] in the [ ] of drug substance lot 0G0493 manufactured by [ ] which are not present in [ ] lot 0G0492 and [ ] lots F020004 and F020005.

3. Please provide more recent reference(s) to evaluate the toxicology and biological monitoring of metals in humans.

II. Regarding the Drug Product

1. Batch Analysis Results (Volume 1.3, Page 4-085-86): Please justify why all the tests established in the specifications for the drug product were not applied to 500 mg tablet (lanthanum identity and carbonate identity) manufactured at [ ]

2. Please provide the stability data on 250 mg and 500 mg tablets containing the drug substance manufactured by [ ].

3. Please specify the names of the [ ] in the package insert. Please revise the package insert to reflect this.

If you have any questions, please call:

Ms. Denise M. Hinton
Regulatory Health Project Manager
(301) 594-5333

Sincerely,

/S/

{See appended electronic signature page}

Kasturi Srinivasachar, Ph.D.
Chemistry Team Leader, DNDC I for the
Division of Cardio-Renal Drug Products, HFD-110
DNDC DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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

/s/

Ramsharan Mittal
1/16/03 05:06:26 PM
For Kasturi Srinivasachar

********** -COMM. JOURNAL- ********** DATE JAN-16-2003 ***** TIME 17:08 *********

MODE = MEMORY TRANSMISSION START=JAN-16 17:08 END=JAN-16 17:08

FILE NO.=163

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
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-FDA,CDER,OND,ODE1,DCRDP -

********** -CARDIO RENAL - ***** - 301 594 5494- **********

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(240) 453 6456
Attention:	Lisa Wittmer, Ph.D.
Company Name:	Shire Pharmaceutical Development
Phone:	(240) 453-2032
Subject:	**CMC Information Request 16Jan03**
Date:	January 16, 2003
Pages including this sheet:	4

From: **Denise M. Hinton**
Phone: **301-594-5333**
Fax: **301-594-5494**

1/10/03

Redacted 3

page(s) of trade secret

and/or confidential

commercial information

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(b5)

Redacted 11

page(s) of trade secret and/or confidential commercial information (b4)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 18

Amir A. Malik, M.D.
204 Southpark Circle East
St. Augustine, Florida 32086

Dear Dr. Malik:

On September 9, 10, and 11, 2002, Ms. Barbara T. Carmichael, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol #LAM-IV-302 entitled: "A Phase III, Dose Titration, Randomized, Double-Blind, Placebo Controlled, Parallel Group Study to Assess Efficacy and Safety of Lanthanum Carbonate for Reduction and Maintenance of Serum Phosphorus Levels in Chronic Renal Failure Patients Receiving Hemodialysis") of the investigational drug Fosrenol™ (lanthanum carbonate), performed for Shire Laboratories, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your response dated October 7, 2002, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Ms. Carmichael presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not follow the investigational plan as required by 21 CFR 312.60 in that for subject 003, you increased the dose of Calcijex™ in the dialysis fluid after the subject started the titration phase of the study.

2. You did not maintain adequate and accurate case histories as required by 21 CFR 312.62(b) in that for subjects 002, 003, and 005 the date for the start of the washout period was not correctly documented in source documents. The date was originally written as 11/29/99, crossed out and changed to 12/3/99. This gave the appearance that less than one week transpired between the start of the washout period and the beginning of the titration phase as these subjects began the titration phase on 12/8/99.

Please make appropriate corrections/changes in your procedures to ensure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Carmichael during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter, at the address given below.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003754077
Field Classification: VAI
Headquarters Classification:
_____1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_X__ 4)VAI-response received
_____5)OAI

Deficiencies noted:
_X___failure to adhere to protocol (05)
_X___inadequate and inaccurate records (06)
Deficiency Codes: 5, 6

cc:
HFA-224
HFD-110 Doc.Rm. NDA#21-468
HFD-110 Review Div.Dir./Throckmorton
HFD-110 MO/Pelayo
√HFD-110 PM/Hinton
HFD-46/47c/r/s/ GCP File #10734
HFD-46/47 GCP Reviewer/Shibuya
HFD-46/47 CSO/Slavin
HFR-SE250 DIB/Gallant
HFR-SE250 Bimo Monitor/Torres
HFR-SE2570 Field Investigator/Carmichael
GCF-1 Seth Ray

r/d: (AS):11/19/02
reviewed:KMU:11/20/02;11/26/02
reviewed:AEH:12/9/02
f/t:ml:11/27/02;12/9/02

o:\Slavin\Malik letter

Reviewer Note to Rev. Div. M.O.

This was a routine pre-approval inspection of a clinical investigator. This site screened 17 subjects and enrolled 13 subjects. Eight subjects completed the study. The record review confirmed that each screened subject signed a consent form prior to participation. Four subjects' records were reviewed in depth for data integrity. A 3-item 483 was issued at the completion of the inspection for failure to adhere to protocol, increasing Calcijex for one subject after the titration phase started, failing to adhere to the one week time period between the washout phase and the titration phase for 3 subjects, and failing to maintain adequate and accurate records for the date the phosphate binder was stopped for 4 subjects. Data are acceptable in support of NDA 21-468.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC - 4 2002

D. Hinton

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

William F. Fathauer, M.D.
10390 E. Jenan Drive
Scottsdale, Arizona 85260

Dear Dr. Fathauer:

Between April 12 and July 8, 2002, Mr. Randall Johnson, representing the Food and Drug Administration (FDA), met with you to investigate allegations of regulatory noncompliance and to review your conduct of a clinical study (protocol #LAM-IV 307) entitled, "An Open Label, Randomized, Multicenter, Phase III, Comparator Controlled Parallel Group Study to Assess the Long-Term Safety and Efficacy of Lanthanum Carbonate in Chronic Renal Failure Patients Receiving Hemodialysis," of the investigational drug lanthanum carbonate, performed for Shire Pharmaceuticals. Mr. Timothy Kapsala, also representing the FDA, witnessed an interview with you on June 5, 2002. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to ensure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to FDA regulations governing your conduct of clinical investigations and the protection of human subjects. We recognize that Dr. Jeffrey Feldstein was the principal investigator for this study from July 14, 1999 until you assumed responsibility on June 8, 2000 and that some of the violations noted in this letter were his responsibility. We note that at the conclusion of the inspection, Mr. Johnson presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We note your responses and wish to emphasize the following:

1. You did not supervise the study as you committed to do when you signed Form FDA 1572 (21 CFR 312.60).

   a. You made the following statements during the inspection:

      1) that you performed your duties largely at the direction of the employees of Southwestern Clinical Research, the servicing site management organization;

      2) that you never visited [redacted] the dialysis center where study subjects were actually seen; and

3) that you did not work with [redacted] who were listed on your Form FDA 1572 as subinvestigators. These individuals were staff physicians at [redacted] In addition, you stated that [redacted] were supervised or directed by employees of Southwest Clinical Research.

b. For 14 of the 18 subjects screened, neither you nor your subinvestigators signed page 107 of the case report form entitled, "END OF STUDY." Had the document been signed, it would have indicated that, at the conclusion of the subject's participation, you had personally reviewed the document for accuracy.

2. You did not promptly report serious adverse events (SAEs) to the sponsor (21 CFR 312.64(b)).

Details of these events are in the following table:

Subject	Nature of SAE	Date of SAE	Reported to sponsor
11113	hospitalized for abdominal pain		6/15/00
11102	pelvic fracture		7/2/01
11104	hospitalized for diverticulitis		4/24/01
11115	death		6/16/00
11109	hospitalized for CHF		3/22/01
11109	death		3/29/01
11108	death		4/3/01

3. You did not have control over the investigational drug (21 CFR 312.61). In the interview with Investigators Johnson and Kapsala, you stated that you did not have control over the study medication in that you did not have access to Southwestern Clinical Research, where the drug was stored.

4. You did not prepare and maintain adequate and accurate case histories (21 CFR 312.62(b)).

a. Study documents for the following subjects did not indicate the individual performing the examination or reviewing the data.

- 11105 EKG reports dated [redacted]
- 11105 Screening physical examination
- 11113 Screening physical examination
- 11113 Early termination physical examination
- 11102 Screening physical examination
- 11102 Visit 12 physical examination
- 11118 Screening physical examination

b. Discrepancies between source documents and case report forms (CRF) were noted for the following subject:

- 11105 Interval data for EKG reports dated [redacted],
- 11105 The history of gastrointestinal bleed noted on the CRF was not substantiated in the medical history section of the source documents.

c. Changes were made to study documents with no indication of who made the modifications, when they were made, or why the changes were made. These changes to study records include:

- Dates on the EKG for subject 11102 visit 15;
- EKG report for subject 11105 dated [redacted]
- Date on the lab report for subject 11118 visit W3 changed between [redacted]
- Vital signs on the screening physical examination form for subject 11104; and
- Screening medical history form for subject 11105.

We wish to remind you that, as principal investigator, you are ultimately responsible for the conduct of a study. Proper oversight or supervision of medical personnel is necessary to ensure the investigation is conducted according to the protocol and in compliance with FDA regulations.

Deviations noted above appear to be a result of a serious lack of supervision of personnel involved in conducting this study. Therefore, we request that you inform this office, in writing, of the actions you have taken in response to the inspection, including- a list of current studies you are conducting and confirmation of whether you plan to conduct future studies, since you indicated to our investigator that you plan to retire or not to conduct clinical studies in the future. Failure to adequately explain your plan may result in further regulatory action.

We appreciate the cooperation shown Investigator Johnson during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter, at the address given below.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003711514

Field Classification: OAI
Headquarters Classification:
_____1)NAI
_____2)VAI- no response required
__X_3)VAI- response requested
_____4)OAI

If Headquarters classification is a different classification, explain why: Ordinarily, this blatant failure to supervise would result in a Warning Letter recommendation. However, Dr. Fathauer stated that he will not engage in any more clinical research. Therefore, we recommend a VAI-R recommendation, specifically asking Dr. Fathauer to commit to ceasing his clinical research activities. Compared to the volume of data collected and documented, the protocol violations and record keeping are not sufficient to shed doubt on the overall validity of the data.

Deficiencies noted:
__X_inadequate study drug accountability (04)
__X_inadequate and inaccurate records (06)
__X_failure to report ADRS (16)
__X_other (18; please specify: failure to personally supervise and conduct the study)
Deficiency Codes: **4, 6, 16, 18**

cc:
HFA-224
HFD-110 Doc.Rm. NDA#21-468
HFD-110 Review Div.Dir. Throckmorton
HFD-110 MO Pelayo
HFD-110 PM ~~Nguyen~~ HINTON
HFD-47c/r/s/ GCP File # 10678
HFD-47 GCP Reviewer Shibuya
HFD-47 CSO Storms
HFR-PA-252 DIB Stokke
HFR-PA-2565 Bimo Monitor Koller
HFR-PA-2530 Field Investigator Johnson

r/d: (RS/8/12/02):
reviewed: AEH;8/20/02
f/t:**ml:9/26/02**

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Reviewer Note to Rev. Div. M.O.

This for-cause inspection was instigated pursuant to a complaint from the sponsor, Shire Pharmaceuticals. The inspection revealed that this site had two principal investigators, Jeffrey Feldstein, M.D. and William Fathauer, M.D. Statements made by Dr. Fathauer indicate that the study was conducted de facto by [redacted] Southwestern Clinical Research, the site management organization that serviced this site.

Inadequate study supervision by the principal investigators, failure to promptly report SAEs to the sponsor, protocol violations, a lack of control of study drug, and record keeping deficiencies were documented. Eighteen subjects were screened and 16 were randomized. Records for 5 subjects were reviewed in detail.

The failure to supervise the study and failure to report SAEs are serious problems. However, the number and severity of protocol violations and record keeping deficiencies documented in the inspection is small compared to the large amount of data collected. For that reason, the data appear acceptable for review. Dr. Fathauer stated that he would cease performing clinical research.

Dr. Feldstein cannot be located for a for-cause inspection. According to the field investigator, Southwestern Clinical Research, the site management organization, is out of business.

Minutes of a meeting between Shire and the FDA Division of Cardio-Renal Drug Products

NDA:	21-468
Sponsor:	Shire Pharmaceutical Development Inc.
Drug:	Fosrenol (Lanthanum Carbonate Hydrate)
Date Meeting Requested:	November 25, 2002
Date Confirmation Sent:	December 2, 2002
Date of Meeting:	December 3, 2002
Type:	C
Meeting Chair:	Douglas C. Throckmorton, M.D.
Meeting Recorder:	Denise Hinton

FDA Attendees:

Douglas C. Throckmorton, M.D.	Director, Div. of Cardio-Renal Drug Products, HFD-110
Juan Carlos Pelayo, M.D.	Medical Officer, HFD-110
Angelica Dorantes, Ph.D.	Clinical Pharmacology and Biopharmaceutics, HFD-860
Patrick Marroum, Ph.D.	Team Leader, Clinical Pharmacology and Biopharmaceutics
Xavier Joseph, Ph.D.	Pharmacologist, HFD-110
John Koerner, Ph.D.	Pharmacologist, HFD-110
Charles Resnick, Ph.D.	Team Leader, Pharmacology, HFD-110
Valeria Freidlin, Ph.D.	Statistician, HFD-710
James Hung, Ph.D.	Team Leader, Statistician, HFD-710
Kris Raman, Ph.D.	Chemist, HFD-810
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemist, HFD-810
Denise Hinton	Regulatory Health Project Manager, HFD-110

Shire Attendees:

Isobel Webster	International Project Leader
Simon Tulloch, M.D.	Senior Vice President US R&D
Neil Frazer, M.D.	Vice-President, Medical Affairs
Yuxin Zhang, Ph.D.	Senior Director, Biostatistics
Sharmen Confer	Manager, Clinical Programs
Steve Damment, Ph.D.	Director, Preclinical Sciences
Rick Lilley, Ph.D.	Senior Vice-President, Regulatory Affairs
Lisa Wittmer, Ph.D.	Associate Director, Regulatory Affairs

Background:

The Division requested a meeting with Shire Pharmaceutical Development Incorporated to discuss the remaining chemistry, clinical, biopharmaceutical, and pharmacology deficiencies identified to date in the Divisional review of the application. The Division met with Shire on September 5, 2002 to inform the sponsor of issues and deficiencies identified during the initial review of the NDA.

Meeting Discussions:

Chemistry
The sponsor's chemist was unable to attend the meeting. A teleconference will be scheduled for a later date to discuss the chemistry issues.

The Division asked the sponsor to provide a detailed justification on all impurities [ ] consistently detected in lanthanum carbonate batches including an explanation of how the specifications were chosen and what would be a permissible level of exposure.

The sponsor stated that they had previously provided justification on the specification limits for the — impurities in the original NDA in addition to the other — potential impurities in the drug substance. Because heterogeneity was seen in the drug substance samples and has the possibility of being present in future batches, the Division asked the sponsor to set analytical standards for the metal impurities that may be potentially undetected by the present specifications. — metals were found through mass spectrometry methods and caused concerns over other potential metal impurities that may be above limits of detection. The Division recommended that a standard of practice be written explaining how the impurities will be addressed.

The Division advised the sponsor to apply for a USAN name other than lanthanum carbonate since there is potential for confusion with the currently marketed drug product (lithium carbonate). The look-alike and sound-alike similarity between the established names and the similarity in dosing could increase the potential for confusion.

The Division asked if [ ] would be the commercial manufacturer for the product. The sponsor stated that they would be used as a [ ] supplier and that it was in the process of being inspected.

The Division will provide the sponsor with a list of chemistry deficiencies to be addressed by the end of December 2002.

Stability Data

The Division informed the sponsor that the stability data submitted for the 500 mg tablet was inadequate and asked the sponsor to submit additional stability data before January 2003.

Pharmacology and Toxicology
The sponsor was asked to provide a table showing tissue levels of lanthanum across different species and an explanation of the calculations for the bioavailability in dogs. The sponsor stated that they will discuss the calculations for bioavailabilty in the dog studies with Dr. John Koerner, and noted that the tissue data was provided in the original

submission of the NDA. The sponsor provided the reference data for the bioavailability calculations to the Division after the meeting.

Clinical Pharmacology
The Division informed the sponsor that the in vitro P-450 data provided in the original submission were sufficient. The sponsor was advised to complete the P-glycoprotein study since lanthanum is taken orally.

The Division asked the sponsor to provide ADME data. The sponsor stated that pre-clinical mass balance studies were conducted in rats and in dogs, but a study was not done in humans because of the difficulty of effectively regulating the drug IV. The sponsor also stated that from their perspective, an ADME study in humans would not provide any additional information for the absorption & elimination of lanthanum. They mentioned that based on animal data, it could be assumed that about 94% of an oral dose is excreted and the rest (about 6%) is absorbed and deposited in different tissues.

Dr. Throckmorton said that he understood why the sponsor could not perform a study with interpretable and meaningful results since the drug is minimally absorbed. However, language regarding absorption, tissue distribution, and excretion of lanthanum would be included in the labeling.

The Division emphasized the need to understand the kinetics of lanthanum in patients without renal function. The sponsor stated that in study LAM-IV-111 they evaluated the pharmacokinetics of lanthanum in dialysis patients. The overall results showed that the plasma levels of lanthanum in subjects with compromised renal function were about 3 times higher than those in control subjects. The gut and transgut were the main routes of excretion. The kidneys excreted negligible amounts of lanthanum with minimal lanthanum in the dialysate.

Dissolution
The Division commented that the newly proposed dissolution test using [redacted] tablets and a specification of [redacted]% of dissolved lanthanum in [redacted] hours was not appropriate for a chewable tablet. It was noted that the guidance recommends the use of whole tablets in case a patient swallows the whole tablet or does not chew the tablet enough. The sponsor answered that the tablet was too big to be swallowed without chewing.

The Division mentioned that perhaps the problems the sponsor is having in getting appropriate dissolution data for their chewable tablets are related to the high values on the hardness/disintegration of their tablets and not due to the solubility of lanthanum in the dissolution medium.

The sponsor noted that they are trying to improve the dissolution methodology and additional dissolution data will be submitted at the end of January 2003.

Clinical
The review at present shows that the controls have differed and show that lanthanum is effective at binding phosphate in patients. .

With regard to the possibility of a mortality effect of lanthanum, at present the database is inadequate because only 85% of the mortality data was provided. The sponsor was asked to submit 100% of the mortality data set and provide a breakdown of who is missing should that not be possible.

The sponsor stated that they now have over 90% of the data and will submit it to the Agency along with an explanation for the missing data. Their rationale was that they were unable to gather data from various sites due to closures and subpoenaed information.

Morbidity (AE Profile)
The Division commented that a major review issue is that the data show the discontinuation rate of patients in Study LAM-IV-307 varied between the lanthanum treated patients and the standard therapy treated patients. It was an open label trial that potentially may have resulted in informative censoring which causes concern over the evaluation of the safety profile.

Dr. Pelayo stated that it was difficult to perform comparisons of the discontinuation, adverse event, and mortality data and asked the sponsor to provide an explanation as to how they interpreted the different time intervals and ended up with equal results. The sponsor was also advised to characterize GI toxicities.

The sponsor stated that they would provide an explanation in writing addressing the large drop out rate. They explained that patients that were randomized to lanthanum could drop out if they experienced an adverse event, while patients on standard therapy could remain in the study.

The Division asked the sponsor to explain why there is a differential drop-out rate in the comparative safety study and recommended that they conduct an analysis looking only at those patients taking their first phosphate binder (either lanthanum or standard therapy). Such an analysis could provide information on the comparative incidence of acute adverse events associated with the products.

Carcinogenicity Assessment Committee
The data from the 104-week rat carcinogenicity study and the 99-week mouse carcinogenicity study were presented to the Executive Carcinogenicity Assessment Committee in November 2002. They agreed that the rat study was adequate and that there were no treatment-related tumor findings. The Committee also agreed that the mouse carcinogenicity study was adequate, but the stomach adenomas in male mice were drug related. The sponsor stated that the results of the study would be included in the label.

Meeting Preparation: /S/
Denise M. Hinton

/S/
Meeting Concurrence: _____
Douglas C. Throckmorton, M.D.

Draft: 10Dec02
Final: 8Jan03

RD:
Throckmorton 8Jan03
Pelayo 7Jan03
Dorantes 18Dec02
Marroum 23Dec02
Joseph 7Jan03
Koerner 3Jan03
Freidlin 12/19/02
Hung 12/19/02
Raman 23Dec02

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

/s/

Denise Hinton
1/10/03 01:50:40 PM

********** -COMM. JOURNAL- ********** DATE JAN-09-2003 ***** TIME 14:43 ********

MODE = MEMORY TRANSMISSION START=JAN-09 14:33 END=JAN-09 14:43

FILE NO.=049

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	a	92404536456	001/010	00:01:54

-FDA,CDER,OND,ODEI,DCRDP -

********** -CARDIO RENAL - ***** - 301 594 5494- *********

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(240) 453 6456
Attention:	Lisa Wittmer, Ph.D.
Company Name:	Shire Pharmaceutical Development
Phone:	(240) 453-2032
Subject:	**Meeting Minutes 3Dec02**
Date:	January 9, 2003
Pages including this sheet:	6

From: **Denise M. Hinton**
Phone: 301-594-5333
Fax: 301-594-5494

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Richard Bilinsky, M.D.
1112 Center West Drive
Springfield, Illinois 62704

DEC - 2 02

Dear Dr. Bilinsky:

This letter informs you that you did adhere to the Food and Drug Administration (FDA) regulations governing the conduct of clinical investigations and the protection of human subjects.

Between September 23 and October 2, 2002, Mr. Mark Peterson, from FDA, met with you to review your conduct of a clinical study (protocol # LAM-IV-307 entitled: "An Open Label, Randomized, Multicenter, Phase III, Comparator Controlled Parallel Group Study to Assess the Long-Term Safety and Efficacy of Lanthanum Carbonate in Chronic Renal Failure Patients Receiving Hemodialysis") of the investigational drug lanthanum carbonate, performed for Shire Laboratories. This inspection, as part of FDA's Bioresearch Monitoring Program, is designed to validate clinical studies on which drug approval may be based and to ensure the protection of the rights and welfare of human research subjects.

Mr. Peterson presented and discussed with you his inspectional findings at the conclusion of the inspection. We evaluated the inspection report and the documents submitted with that report and agree with his conclusions.

We appreciate the cooperation shown Investigator Peterson during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003796899
Field Classification: NAI
Headquarters Classification:
__X__1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-110 Doc.Rm. NDA# 21-468
HFD-110 Review Div.Dir.Throckmorton
HFD-110 MO Pelayo
HFD-110 PM Hinton
HFD-47c/r/s/ GCP File # 10729
HFD-47 GCP Reviewer Shibuya
HFD-47 CSO Storms
HFR-CE-650 DIB Baumgarten
HFR-CE-6520 Bimo Monitor Yuscius
HFR-CE-6520 Field Investigator Peterson

r/d: (RS/11/12/02):
reviewed:AEH:11/13/02
f/t:ml:11/25/02

o:**RS\NDA 21-468\Bilinsky**

Reviewer Note to Rev. Div. M.O.
- This site screened 28 subjects and randomized 17.
- Records for 3 subjects were inspected in detail.
- No regulatory violations were noted.
- All subjects were consented.
- Data appear acceptable.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

HINTON

Leland E. Garrett, Jr., M.D.
Wake Nephrology Associates, P.A.
3604 Bush Street
Raleigh, North Carolina 27609

DEC 30 2002

Dear Dr. Garrett:

On September 10-13, 2002, Ms. Barbara M. Frazier and Mr. Thomas R. Berry, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol LAM-IV-307 entitled: "An Open Label, Randomized, Multicenter, Phase III, Comparator Controlled Parallel Group Study to Assess the Long-Term Safety and Efficacy of Lanthanum Carbonate in Chronic Renal Failure Patients Receiving Hemodialysis") of the investigational drug lanthanum carbonate, performed for Shire Pharmaceutical Development. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, our investigators presented and discussed with you, [illegible] Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not conduct the study in accordance with the approved protocol, in violation of 21 CFR 312.60. Subjects 01004 and 01012, who were randomized to the Lanthanum arm, were not removed from the study after taking another phosphate binder (Phoslo). Records show that Subject 01004 was on the Lanthanum arm 12/7/99 to 12/4/01 and was given Phoslo 3/6-11/01 according to the Concomitant Medications Log for Visits 16-18. Subject 01012 was on the Lanthanum arm 12/7/99 to 12/6/01 and was given Phoslo 5/22-6/12/01 according to the Home Medications Report dated 6/12/01.

2. You did not prepare and maintain adequate and accurate case histories, in violation of 21 CFR 312.62(b). For subject 01012, Calcijex was stopped on 6/20/00 and Zemplar was started on 12/9/00 and for subject 01014, Calcijex was stopped on 6/6/01 and Zemplar was started on 6/11/01. However, Zemplar was not added to the Concomitant Medications Log for both subjects. For subject 01024, the Concomitant Medications Log shows that Calcijex was stopped on 2/2/01 and Zemplar was started on 2/16/01. However, the Physicians Order Sheet shows that Calcijex was stopped on 9/25/00 and the dialysis treatment sheet shows that Zemplar was started on 10/30/00.

Please make appropriate corrections/changes in your procedures to ensure that the findings noted above are not repeated in any ongoing or future studies. Your response dated September 18, 2002 and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigators Frazier and Berry during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address below.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003785~~290~~ 920
Field Classification: VAI
Headquarters Classification:
_____1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_X_4)VAI- response received
_____4)OAI

Deficiencies noted:
_X_ failure to adhere to protocol (05)
_X _inadequate and inaccurate records (06)
Deficiency Codes: 05,06

cc:
HFA-224
HFD-110 Doc.Rm. NDA#21-468
HFD-110 Review Division Director Throckmorton
HFD-110 MO Pelayo
HFD-110 PM Hinton
HFD-46/47c/r/s/ GCP File #10736
HFD-46/47 GCP Reviewer Shibuya
HFD-46/47 CSO Hajarian
HFR-SE150 DIB Todd-Murrell
HFR-SE150 BIMO Monitor Hubbard
HFR-SE1535 Field Investigator Frazier
HFR-SE1535 Field Investigator Berry
GCF-1 Seth Ray

r/d:GRH:11/18/02
f/t:ml:12/19/02
O:\GRH\GARRETT VAI.DOC

Reviewer Note to Rev. Div. M.O.
Thirty-eight subjects were screened and 30 subjects were randomized. Records for 16 subjects were reviewed. Two subjects (01004, 01012) who were on the Lanthanum arm, were not removed from the study after taking another phosphate binder (Phoslo), a protocol violation. Discrepancies were noted between source documents and case report forms in 3 subjects (01012, 01014 and 01024). Overall, the data appear acceptable.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NOV 18 2002

Gregory V. Warren, M.D.
Wisconsin Center for Clinical Research, L.L.C.
2901 West Kinnickinnic River Parkway, Suite 305
Milwaukee, Wisconsin 53215

Dear Dr. Warren:

Between September 3 and 12, 2002, Mr. Ronald Ruff and Ms. Denise Burosh, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #LAM-IV-302 entitled: "A Phase III, Dose Titration, Randomized, Double Blind, Placebo Controlled, Parallel Group Study to Assess Efficacy and Safety of Lanthanum Carbonate for Reduction and Maintenance of Serum Phosphorus Levels in Chronic Renal Failure Patients Receiving Hemodialysis") of the investigational drug lanthanum carbonate, performed for Shire Laboratories. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to ensure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to FDA regulations governing your conduct of clinical investigations and the protection of human subjects. At the conclusion of the inspection, Mr. Ruff and Ms. Burosh presented and discussed with you their observations. We wish to note the following:

The protocol required you to report serious adverse events (SAEs) to the sponsor within 24 hours. You did not report the following SAEs to the sponsor within that timeframe (21 CFR 312.60 and 312.64(b)):

Subject	Nature of SAE	Date of SAE	Date Reported to Sponsor
006/IBL	esophageal ulcer	/	3/9/00
006/IBL	C. difficile colitis	/	3/9/00
006/IBL	sternal wound infection	/	3/9/00
006/IBL	brachial artery thrombosis	/	5/15/00
010/M-L	pneumonia	/	1/14/00

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigators Ruff and Burosh during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter, at the address given below.

Sincerely yours,

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003782320
Field Classification: NAI
Headquarters Classification:
_____1)NAI
__X__2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

If Headquarters classification is a different classification, explain why: The failure to promptly report SAEs is significant and documented.

Deficiencies noted:
__X_failure to notify IRB of changes, failure to submit progress reports (15)
__X_failure to report ADRS (16)
Deficiency Codes: **15, 16**

cc:
HFA-224
HFD-110 Doc.Rm. NDA#21-468
HFD-110 Review Div.Dir. Throckmorton
HFD-110 MO Pelayo
HFD-110 PM Hinton
HFD-47c/r/s/ GCP File #10718
HFD-47 GCP Reviewer Shibuya
HFD-47 CSO Storms
HFR-CE-850 DIB Bigham
HFR-CE-850 Bimo Monitor Matson
HFR-CE-8590 Field Investigator Ruff/Burosh

r/d: (RS/10/15/02):
reviewed:AEH:10/17/02
f/t:ml:10/17/02

o:**RS\NDA 21-468\Warren.doc**

Reviewer Note to Rev. Div. M.O.
- This site screened 12 subjects, titrated 10, randomized 4, and completed 2.
- All subjects consented to the study.
- The documentation was in order with the exception of several serious adverse events that were reported to the sponsor late.
- Data appear acceptable.

10/15/02

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-468

INFORMATION REQUEST LETTER

Shire Pharmaceutical Development Inc.
Attention: Rick Lilley, Ph.D.
1801 Research Boulevard
Suite 600
Rockville, MD 20850

Dear Dr. Lilley:

Please refer to your April 30, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosrenol (Lanthanum Carbonate Hydrate).

We also refer to your submission dated August 5, 2002.

We are reviewing the carcinogenicity section of your submission and have the following comments and information request. Please clarify the following discrepancy:

1. The number of tumor occurrences of histiocytic sarcoma in the liver among the male rats from the data set was not consistent with the number from the study report.

2. From the data set, the reviewer found 0,0,0, and 1 animals in the controls, the low, the mid, and the high dose group, respectively. However, the number of tumors in the study report was 0,1,0, and 4 in the control, the low, the mid, and the high dose group, respectively.

3. We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, please call Ms. Denise Hinton, Regulatory Project Manager, at (301) 594-5312.

Sincerely,

/S/

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Doug Throckmorton
10/15/02 04:55:10 PM

Minutes of a meeting between Shire and the FDA

NDA:	21-468
Drug:	Fosrenol (Lanthanum Carbonate Hydrate)
Date of meeting request:	July 11, 2002
Meeting package received:	August 27, 2002
Date of meeting:	September 5, 2002
Type:	B (Ninety-day conference)
Meeting chair:	Douglas C. Throckmorton, M.D.
Meeting recorder:	Denise Hinton

FDA Participants:

Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical Officer
Juan Carlos Pelayo, M.D.	Medical Officer
Joseph Xavier, Ph.D.	Pharmacologist
Charles Resnick, Ph.D.	Team Leader, Pharmacologist
Angelica Dorantes, Ph.D.	Clinical Pharmacology and Biopharmaceutics
Patrick Marroum, Ph.D.	Team Leader, Biopharmaceutics
Kris Raman, Ph.D.	Chemist
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemist
Valeria Freidlin, Ph.D.	Statistician
James Hung, Ph.D.	Team Leader, Statistician
Denise Hinton	Project Manager

Shire Participants:

Wilson Totten, M.D.	Group Research and Development Director
Simon Tulloch, M.D.	Senior Vice President, US R&D
Neil Frazer, M.D.	Vice President of Medical Affairs
Steve Damment, Ph.D.	Director, Pre-Clinical Sciences
Guillermo Millicovsky, Ph.D.	Director, Pre-Clinical Sciences
Yuxin Zhang, Ph.D.	Senior Director of Biostatistics
Jo Ferdinando, Ph.D.	Director, Pharmaceutical Sciences
Isobel Webster	International Project Leader
Rick Lilley, Ph.D.	Senior Vice President, Regulatory Affairs
Mike Burkin	Regulatory Officer
Suma Krishnan	Senior Manager, Regulatory Affairs

Background:

Shire Pharmaceutical Development Incorporated requested a meeting to discuss deficiencies identified during the initial review of the NDA submission. Shire filed an NDA on April 30, 2002 for Fosrenol (Lanthanum Carbonate Hydrate) for [redacted]

Meeting:
Dr. Throckmorton stated that the meeting was to inform the sponsor of issues and deficiencies found early in the review process. Although the review of the NDA was not complete, the reviewers were prepared to address the most critical issues identified to date.

Chemistry:

Dr. Srinivasachar informed the sponsor that in their recent correspondence with the agency [redacted] 250 mg and 500 mg strengths [redacted]. He also said that a new site had been added for the manufacturing of the drug product. [redacted]

The sponsor clarified that the new site [redacted] Dr. Srinivasachar made it clear that the stability data on [redacted] batches were not acceptable and the agency would like to review the stability data on the [redacted] batches. Dr. Srinivasachar said that the primary stability batches have to be [redacted] of the manufacturing batch size. Any stability data submitted based on the [redacted] batches will be [redacted]

Dr. Srinivasachar requested the sponsor to [redacted]

Dr. Srinivasachar said that in the original submission there were a large number of metal impurities in the API with assay results [redacted] ppm of each impurity. The actual test results should be provided especially since the current specification limits for various metals are well below [redacted] ppm.. In addition, the total metal impurity level must be specified under specifications. Dr. Srinivasachar requested the sponsor to provide a justification on the limits of metal impurities in the specification and asked them to submit an updated version of specification for agency review.

Dr. Srinivasachar asked the sponsor if they had more stability data on 500 mg tablets, because only limited stability data was submitted in the original submission.

The sponsor agreed to provide the following information to the agency:

- [redacted]
- Revised specification for lanthanum carbonate API
- Provide justification for the impurity levels in the specification
- Submit stability data on 500 mg tablets

Dr. Throckmorton stated that no data are to be submitted too late in the review cycle to allow for adequate time for a complete, thorough review. If a substantial submission comes in within 3 months of the goal date, it could be considered a major amendment and cause a 3 month extension. The sponsor stated they would remain with current formulation submitted in the NDA. [redacted]

Pharmacology/Toxicology:

The Division stated that Lanthanum is deposited in normal animals (rats) with an increased deposition of lanthanum carbonate to approximately 26 weeks. Once lanthanum is no longer administered, the serum levels stay up showing that lanthanum is deposited in tissue, plasma and possibly other places. Based on the 12-week data from nephrectomized animals, Lanthanum continues to be absorbed in various organs where not initially deposited. The Division advised the sponsor to think about the consequences of dialysis and to provide the data including estimates of amounts removed. The sponsor was also asked to provide an explanation as to whether a patient who received lanthanum for an indefinite period of time would have lanthanum deposits throughout the body.

The sponsor will submit data to assure the Division that lanthanum can safely be administered in a human population long-term in addition to justification, in writing, showing robust long-term exposure in healthy animals vs. diseased animals. The sponsor stated that it would be difficult to keep nephrectomized animals beyond 13 weeks and agreed to submit a written response. They stated their assurance was based on the long-term tissue exposure data in normal animals compared to the lanthanum tissue concentrations of normal and uremic rats used in the 12-week study. The sponsor stated that if they analyzed lower tissue and plasma concentration, then there would be a fixed concentration giving confidence that steady state could successfully be reached in humans.

Dr. Throckmorton asked the sponsor if any information could be given about tissue deposition in patients with renal failure and if so, that the sponsor provide long range steady state data. The sponsor stated that the tissue levels collected were for bone and the measurements were made at baseline after one year of treatment. The sponsor also stated that there were no signals showing continuous accumulation. They were unable to provide an explanation as to what may happen years after administration. Steady state in

human plasma had been demonstrated in Phase III studies, and with the addition of animal data, the sponsor stated that steady state could be achieved in the tissue of renal patients. Dr. Throckmorton commented that serum levels do not mean much if there is tissue deposition and asked the sponsor to submit the data for review.

Biopharmaceutics:

[redacted]

Dr. Throckmorton asked the sponsor why a mass balance study had not been performed. The sponsor stated that it was difficult to do in humans because lanthanum cannot be effectively regulated, and an oral dose in humans would be lost in the error of technique.

Dr. Dorantes stated that the sponsor provided data showing minimal levels of lanthanum in plasma and urine after oral administration. Nevertheless, a mass balance (ADME) study is needed to show that lanthanum is completely eliminated from the body. Animal data showed lanthanum to be in the tissue, liver, gut, and other tissues.

Dr. Throckmorton stated that another major concern is the use of lanthanum for pre-end stage renal disease. The sponsor was asked to submit a written explanation about the routes of excretion and the clearance of lanthanum in dialysis patients. The sponsor stated that they have pharmacokinetics data in normal patients and to perform a mass balance study in diseased patients would be difficult.

Dr. Dorantes asked for P450 information. The sponsor stated that an in vitro study was conducted and showed no significant effects of lanthanum on P450 chromosomes. With regard to dissolution testing, Dr. Dorantes recommended that the sponsor use a more conservative approach by conducting the dissolution tests with whole tablets instead of the proposed crushed tablets. The sponsor stated that they would consider the use of whole tablets for dissolution and they will test additional dissolution conditions and media with : per the agency's request. Dr. Dorantes asked the sponsor to include solubility data in different media in the validation report of the dissolution methodology.

Clinical:

Dr. Thockmorton conveyed to the sponsor that it was important to show that they have adequate data addressing the potential consequences of deposition of lanthanum in renal

failure patients and that the animal study of Renagel vs. Lanthanum study is inadequate. The targeted toxicity needs to be understood for patients with end stage renal disease and the presence of hypophosphatemia in both arms hinders interpretation of the study.

The sponsor was advised to review the patients' records to see how many had developed bone fractures while receiving lanthanum; counting for every fracture regardless of the occurrence. The sponsor agreed to summarize and submit the data explaining clinical consequences of bony fractures independent of attribution.

Dr. Throckmorton discussed the possibility of a favorable effect of lanthanum on mortality, as suggested by the sponsor. To corroborate this, the Agency needs to have as much information about the cohort of patients that the sponsor used in their analysis as possible, tied to a single date of follow-up (*e.g.*, through May 2002). As the analysis is not prespecified, the patients from LAM-IV-307 should be pooled with the other available mortality data for the first estimate.

Statistics:

Dr. Hung requested data for time to event analysis related to bone fractures and cardiovascular mortality/morbidity.

Conclusion:

At the close of the meeting the sponsor asked if their NDA would need to go before the Advisory Committee. Dr. Throckmorton stated that he does not foresee the need for an advisory panel since the Division's questions are in regard to the safety of the product though Dr. Temple will make the final decision. The reviewers will contact the sponsor as necessary. The sponsor was reminded to submit a written response to the issues raised by each discipline.

/S/

Meeting preparation: _____
Denise M. Hinton

Meeting concurrence: /S/
Douglas C. Throckmorton, M.D.

Draft: 1 Oct02
RD:
Throckmorton 15Nov02
Stockbridge 8Nov02
Pelayo 8Nov02
Xavier 6Nov02
Resnick 6Nov02
Dorantes 7Nov02
Raman 25Oct02
Srinivasachar 5Nov02
Freidlin 7Nov02
Hung 8Nov02
Final: 15Nov02

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

/s/

Denise Hinton
11/20/02 04:06:53 PM

LANTHANUM CARBONATE

RESPONSE TO INFORMAL COMMENTS AND QUESTIONS RECEIVED FROM DR. JOSEPH VIA TELECONFERENCE ON 23 OCTOBER 2002

QUESTIONS/COMMENTS

1. Please provide the number of studies used to compile the historical control data for the Ames test, and the period over which these studies were carried out.

2. Although not a significant issue, it would be helpful to receive an explanation for the large variation in cell survival between experiments in the mammalian gene mutation assay. Survival was 16% and 62% in Experiments 1 and 2, respectively.

3. Please provide a justification for the high dose used in the mouse micronucleus test – was it a limit dose?

4. In the dose justification document submitted for the carcinogenicity studies, ulceration of the stomach in the mouse study is mentioned. This lesion cannot be found in the original study report. Please clarify.

5. Was the concentration of lanthanum in the bone of uraemic rats higher compared to normal rats?

RESPONSES

Ames Bacterial Assay (Report M/AMES/42075)
Historical data

The original study report (page 34) contains the historical control data for the strains used. We have established from [redacted], who conducted the study) that these data relate to the 2-year period immediately preceding the study, *i.e.* 1994-1996. The 'n' value shown in the table represents the number of control plates examined for each strain.

CHO Mammalian Gene Mutation Assay (Report M/PMC/42078)
Cell survival

The variation in percentage survival between Experiments 1 and 2 occurred mainly at the highest concentration tested (2000 μg/mL) in the absence of S9 mix, where it was 16% in Experiment 1 and 62% in Experiment 2. In another study (Study V00265-LAM-IIID), we investigated the physicochemical effects of lanthanum in McCoys 5A Medium, the medium used in the CHO gene mutation assay. In this study, it was shown that fine precipitation began to occur at lanthanum concentrations of 389 μg/mL and above when no S9 mix was present. The variable survival in the mutation assay may therefore relate to the poor solubility of lanthanum carbonate at the upper end of the concentration range tested.

Mouse Micronucleus Test (Report M/MMN/42354)
Dose selection

The high dose level of 2000 mg/kg was selected as a 'limit dose'. This is the practicable limit dose recommended in current genotoxicity guidelines for low-toxicity compounds (ICH Guideline S2A, 1995, Note 5 referencing Hayashi *et al* (1994); and OECD guidelines 1997).

In addition, toxicokinetic studies demonstrated saturable absorption at doses above 500 mg/kg/day, which limited the value of administering higher doses. The relevant data are summarised in Table 1 below. After a single dose, there was very little relationship between AUC or Cmax and dose over the range 500 to 2000 mg/kg. After repeated administration, exposure generally increased with increasing dose, but in a sub-proportional manner. For data pooled across studies, doses of 100, 500, 1500 and 2000 mg/kg/day, which represent a dose ratio of 1 : 5 : 15 : 20, resulted in a steady state $AUC_{0\text{-}24}$ ratio of 1 : 5 : 7 : 11 and a C_{max} ratio of 1 : 4 : 5 : 10.

Hayashi M, Tice RR, MacGregor JT, Anderson D, Blakey DH, Kirsch-Volders M, Oleson FB jr, Pacchierotti F, Romagna F, Shimada H, Sutou S and Vannier B (1994)
In viv rodent erythrocyte micronucleus assay
Mutation Research, 312(3), 293-304

Table 1 A Summary of Plasma Lanthanum Exposure in Mouse Studies

Dose (mg/kg/day) and Sample Time	Mean AUC_{0-24}		Mean C_{max}		Study Number
	Male	Female	Male	Female	
500 (Day 1)	23.5	85.8	4.4	4.4	SPD/85
500 (Day 1)	12.3	13.4	1.4	1.5	SPD/86
1500 (Day 1)	28.1	31.1	3.8	3.1	SPD/98
2000 (Day 1)	57.1	58.8	4.6	5.0	SPD/85
2000 (Day 1)	19.2	30.7	2.2	2.7	SPD/86
100 (Day 29)	4.9	2.2	0.58	0.18	SPD/98
500 (Day 14)	20.1	11.1	1.5	2.7	SPD/85
500 (Day 29)	10.6	13.0	0.85	1.4	SPD/98
500 (Week 13)	13.2	26.7	0.95	2.5	SPD/86
1500 (Day 29)	19.2	26.0	1.9	1.8	SPD/98
2000 (Day 14)	43.2	32.8	2.5	3.9	SPD/85
2000 (Week 13)	30.9	44.0	5.3	3.5	SPD/86
Mean of means (sexes combined) for repeat-dose studies					
Dose (mg/kg/day)	AUC_{0-24}		C_{max}		
100	3.5 (n=2)		0.4 (n=2)		
500	15.8 (n=6)		1.7 (n=6)		
1500	22.6 (n=2)		1.8 (n=2)		
2000	37.7 (n=4)		3.8 (n=4)		

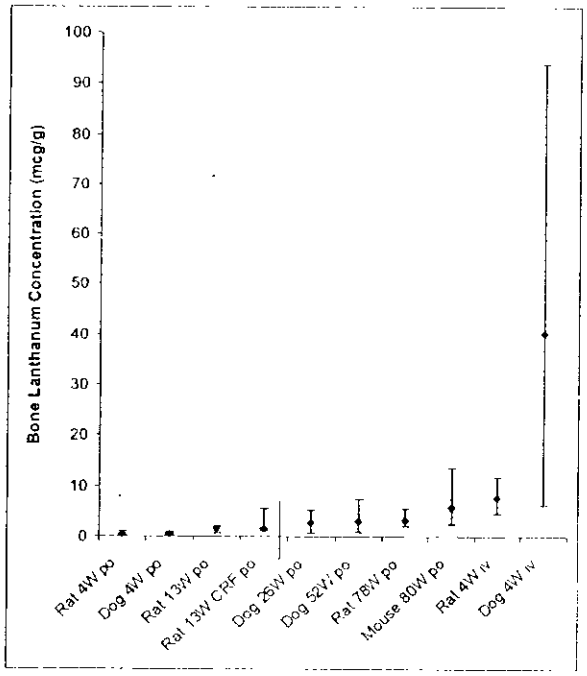
Mouse Carcinogenicity Study (Report SPD/88/C)
Gastric ulceration

There were 3 mice at the high dose, 1 male and 2 females, recorded with ulceration of the stomach. No other treatment groups were affected. The relevant incidence tables can be found on Pages 144 and 159 of the study report (Volume 1) for males and females, respectively.

Study in Uraemic Rats (Report LAN-02)
Bone lanthanum concentrations

The median and range bone lanthanum concentrations in chronic renal failure (CRF) and normal renal function (NRF) rats from the 13-week study (Study LAN-02) are shown in Table 2 below. There was a tendency for the median values to be higher in the uraemic rats compared to the rats with normal renal function, but overall the concentrations were considered to be comparable, given the degree of variability around the median values. As shown in Figure 1, the concentrations measured in the uraemic animals in this study were below those measured in the intravenous and long-term oral toxicology studies, where no bone toxicity was identified, indicating that the bone mineralisation abnormality identified in some uraemic rats was unlikely to have been due to a direct toxic effect of lanthanum on bone.

Figure 1 - Femur lanthanum concentrations in oral and intravenous animal studies of various durations (median and range)



The red box highlights the study in uraemic rats where impaired mineralisation was observed at doses of 1000 and 2000 mg lanthanum carbonate/kg/day (Study LAN-02). The median bone lanthanum concentration in biopsy samples taken from dialysis patients after one year of treatment in Study LAM-IV-303 was 1.8 µg/g (range [redacted] µg/g)

Table 2 - Femur lanthanum concentrations in normal and uraemic rats in Study LAN-02

Species (Report No.)	Route	Duration of Dosing	Dose (mg (salt)/ kg/day)	Range of Medians (µg/g wet tissue)	Overall Range (µg/g wet tissue)
Rat NRF (LAN-02)	po	13 weeks	100	0.17	
			500	0.48	
			1000	0.61	
			2000	1.2	
Rat CRF (LAN-02)	po	13 weeks	100	0.20	
			500	1.2	
			1000	1.4	
			2000	1.6	

CRF – chronic renal fai'ure
NRF – normal renal function

APPEARS THIS WAY
ON ORIGINAL

NDA 21-468
Lanthanum Carbonate

Response to Medical Reviewer's' Request for NDA 21-468

Agency's request:

Provide explanation for the calculation of the total number (n=2421) of patients treated in Phase 2-3 studies as reported in Table 8.8-2 of the 4-month safety update.

The total number of patients treated in Phase 2-3 studies that was reported in Table 8.8-2 of the 4-month safety update involved the following studies: LAM-IV-202, LAM-IV-204, LAM-IV-205, LAM-IV-301, LAM-IV-302, LAM-IV-308, and LAM-IV-307. In order to keep consistency for the entire ISS that integrated data from all but LAM-IV-303 of the Phase 2-3 studies, patients (n=98) treated in LAM-IV-303 were not included in the calculation. This was noted in Table 8.8-2.

To calculate the total number of patients treated in Phase 2-3 studies, we first calculated the exact number of the patients treated for each individual study to match up with each study report. The following rules were used in the calculation:

1) If a patient received more than one treatment in a study, he/she was counted only once under the total column. LAM-IV-202 had, for instance, 59 patients received lanthanum treatment; among them, 19 patients were later randomized to receive placebo. Therefore, there were only 59 patients under the total column.
2) In situations where the number of patients treated in a study may also include those who had been treated in a previous study/part, the number of such patients was calculated and reported inside the parentheses where applicable. LAM-IV-205 had, for instance, 42 patients treated; among them, 40 patients were those who were treated in LAM-IV-204. LAM-IV-308 had, for instance, 77 patients treated; among them, 11 patients were treated previously in LAM-IV-205 and 66 patients in LAM-IV-302.

To obtain the total number of patients treated in Phase 2-3 studies, we added up the number of patients treated in each study involved (except LAM-IV-303), and then subtracted those numbers in parentheses as illustrated below:

Study No.		Patients treated Under the total column In Table 8.8-2	Patients Treated in a Previous Study/Part(s)	
LAM-IV-202		59		
LAM-IV-204		145		
LAM-IV-302		126		
LAM-IV-205		42	(40)	(from LAM-IV-204)
LAM-IV-301	Part 1-3	800		
	Part 4	507	(507)	(from Part 1-3 of the same study)
	Part 5	161	(161)	(from Part 4 of the same study)
LAM-IV-308		77	(11/66)	(from LAM-IV-205 and LAM-IV-302)
LAM-IV-307		1289		
Sum total		3206	(785)	
Total number of Phase 2-3 patients treated without LAM-IV-303:		2421 (3206 - 785 = 2421)		

The same method can be used to calculate for the number of patients treated under other columns in Table 8.8-2 and similar tables throughout the application.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(240) 453-6404
Attention:	Suma Krishnan
Company Name:	Shire Pharmaceutical Development Inc.
Phone:	(240) 453-6400
Subject:	Meeting Confirmation for September 5, 2002
Date:	July 18, 2002
Pages including this sheet:	2

From:	**Denise M. Hinton**
Phone:	**301-594-5312**
Fax:	**301-594-5494**

Meeting Confirmation

Drug:	**Lanthanum Carbonate Hydrate**
NDA:	**21-468**
Date Meeting Requested:	**July 11, 2002**
Date Meeting Confirmation Faxed:	**July 18, 2002**
Type:	**C**

Meeting Date:	**September 5, 2002**
Time:	**1000-1130**
Location:	**WOC 2, Conference Room F, 6th Floor** **1451 Rockville Pike, Rockville, MD**

FDA Participants:

Douglas C. Throckmorton, M.D.	**Director, Cardio-Renal Drug Products, HFD 110**
Juan Carlos Pelayo, M.D.	**Medical Officer**
Norman Stockbridge, M.D., Ph.D.	**Supervisory Medical Officer**
Xavier Joseph, Ph.D.	**Pharmacologist**
Charles Resnick, Ph.D.	**Supervisory Pharmacologist**
Angelica Dorantes, Ph.D	**Biopharmaceutist**
Patrick Marroum, Ph.D.	**Supervisory Biopharmaceutist**
James Hung, Ph.D.	**Supervisory Statistician**
Valeria Freidlin, Ph.D.	**Statistician**
Kris Raman, Ph.D.	**Chemist**
Kasturi Srinivasachar, Ph.D.	**Supervisory Chemist**
Denise Hinton	**Project Manager**

Please provide 12 copies of the background information at least 3 weeks prior to the meeting.

Note: Upon arrival to the Division, please have the security guard call Ms. Aprile Blount at (301) 594-5300 or (301) 594-5367.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Shire Pharmaceutical Development Inc.
1901 Research Blvd, Suite 500
Rockville, MD 20850

2. TELEPHONE NUMBER *(Include Area Code)*

(240) 453-6448

3. PRODUCT NAME

Lanthanum Carbonate (FOSRENOL®)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021468

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO.

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4332

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

[ ] THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

RECEIVED
APR 3 0 2002
CDR/CDER

8 HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

[ ] YES [X] NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	Senior Vice President, Regulatory Affairs	April 19, 2002

FORM FDA 3397 (4/01)

4/20 2

NEW DRUG APPLICATION
21-468

SECTION 19.0: FINANCIAL INFORMATION

SHIRE PHARMACEUTICAL DEVELOPMENT INC.

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19.0 FINANCIAL INFORMATION

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

__ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Rick Lilley, Ph.D.	Senior Vice President, Regulatory Affairs
FIRM/ORGANIZATION	
Shire Pharmaceutical Development Inc.	
SIGNATURE	DATE
	April 19, 2002

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

List of Investigators (US)

Investigators	Affiliation	Address	Participation in Protocols
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Principal Investigator: **Leland Garrett, MD** Sub-Investigators:	Wake Nephrology Associates	3604 Bush Street Raleigh, NC 27609	LAM-IV-204
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Investigators	Affiliation	Address	Participation in Protocols
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Principal Investigator: **Suhail Ahmad, MD** Sub-Investigators:	Scribner Kidney Center	2150 North 107th, #160 Seattle, WA 98133	LAM-IV-307
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Principal Investigator: **Karl Brinker, MD** Sub-Investigators:	Dallas Nephrology	6010 Forest Park Road, Suite 100 Dallas, TX 75235	LAM-IV-307
Principal Investigator: **Jose Canglano, MD** Sub-Investigators:	Clinica Las Americas	400 Roosevelt Ave Hato Rey, PR 00916	LAM-IV-307
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Principal Investigator: **Ronald D. Crock, MD** Sub-Investigator:	Affiliated Hospitals at Canton	1320 Mercy Drive, NW Canton, OH 44708	LAM-IV-307
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List of Investigators (cont.)

Investigators	Affiliation	Address	Participation in Protocols
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Principal Investigator: **William F. Finn, MD** Sub-Investigators:	University of North Carolina Division of Nephrology	CB #7155, 348 MacNider Chapel Hill, NC 27599	LAM-IV-307
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Investigators	Affiliation	Address	Participation in Protocols
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Principal Investigator: **Jacinto Hernandez, MD** Sub-Investigator:	FMC-Central	448 North 2nd Street Memphis, TN 38105	LAM-IV-307
Principal Investigator: **Keith Kapatkin, MD** Sub-Investigator:	PAB Clinical Research, Inc	910 Oakfield Drive, Ste 102 Brandon, FL 33511	LAM-IV-307

List of Investigators (cont.)

Investigators	Affiliation	Address	Participation in Protocols
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Principal Investigator: **Gerald Keightley, III, MD** Sub-Investigators:	MedSource Inc.,	1710 E. Franklin Street, Suite 200 Richmond, VA 23223	LAM-IV-307
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Principal Investigator: **Prof H Thieler** Sub-Investigators:	KfH- Dialysezentrum	Nordhauserstr 74 99089 Erfurt Germany	LAM-IV-301
Principal Investigator: **Dr R Bohm**	KfH-Zentrum	Schurzelter Str. 564 52074 Aachen Germany	LAM-IV-301
Principal Investigator: **Dr T Doll** Sub-Investigators:	Dialysezentrum Sinstorf	Schultwiete 2 21077 Hamburg Germany	LAM-IV-301

List of Investigators (cont.)

Investigators	Affiliation	Address	Participation in Protocols
Principal Investigator: **Dr G Warneke** Sub-Investigators:	Dialysezentrum	Steffensweg 99 37120 Bovenden Germany	LAM-IV-301
Principal Investigator: **Dr DJ Bradley** Sub-Investigators:	Addenbrookes Hospital Renal Unit,	Hills Road Cambridge, CB2 2QQ UK	LAM-IV-301
Principal Investigator: **Dr DA Davenport** Sub-Investigators:	Nephrology Unit Royal Free Hospital	Pond Street, London NW3 2QG UK	LAM-IV-301
Principal Investigator: **Dr THJ Goodship** Sub-Investigators:	Renal Medicine Royal Victoria Infirmary	Queen Victoria Road Newcastle Upon Tyne, NE1 4LP UK	LAM-IV-301
Principal Investigator: **Dr D Hamilton** Sub-Investigators:	Jubilee Renal Unit West Norwich Hospital	Bowthorpe Road Norwich, NR2 3TU UK	LAM-IV-301
Principal Investigator: **Dr I Khan** Sub-Investigators:	Renal Unit Aberdeen Royal Infirmary	Foresterhill, Aberdeen, AB25 2ZN UK	LAM-IV-301
Principal Investigator: **Dr J Kwan** Sub-Investigators:	South West Thames Renal Unit St. Helier Hospital	Wrythe Lane, Carshalton Surrey SM5 1AA UK	LAM-IV-301
Principal Investigator: **Dr R McGonigle** Sub-Investigators:	Department of Renal Medicine, Level 03 Derriford Hospital	Derriford Road Plymouth, PL6 8DH UK	LAM-IV-301
Principal Investigator: **Dr A Palmer** Sub-Investigators:	Renal Directorate St. Mary's Hospital	Praed Street London, W2 1NY UK	LAM-IV-301
Principal Investigator: **Dr H Solomon** Sub-Investigators:	Renal Unit Royal Preston Hospital	Sharoe Green Lane Preston, PR2 9HT UK	LAM-IV-301

List of Investigators (cont.)

Investigators	Affiliation	Address	Participation in Protocols
Principal Investigator: **Dr N Tamimi** Sub-Investigators:	Department of Renal Medicine Kent & Canterbury Hospital	Ethelbert Road, Canterbury, CT1 3NG UK	LAM-IV-301
Principal Investigator: **Dr P Warwicker** Sub-Investigators: None	Department of Renal Medicine Lister Hospital	Coreys Mill Lane Stevenage Herts, SG1 4AB UK	LAM-IV-301
Principal Investigator: **Dr M Wilkie** Sub-Investigators: None	Sheffield Kidney Institute Northern General Hospital	Herries Road Sheffield S5 7AU UK	LAM-IV-301
Principal Investigator: **Professor R Wilkinson** Sub-Investigators:	Renal Medicine Freeman Hospital	Freeman Road, High Heaton Newcastle upon Tyne, NE7 1DN UK	LAM-IV-301
Principal Investigator: **Professor M DeBroe** Sub-Investigators:	Afdeling Nefrologie niversiteit	Ziekenhuis Antwerpen Wilrljkstraat 10 B-2650 Edegem Antwerpen Belgium	LAM-IV-303
Principal Investigator: **Dr Alistair Hutchison** Sub-Investigators:	Renal Unit Manchester Royal Infirmary	Oxford Road Manchester M13 9WL UK	LAM-IV-303
Principal Investigator: **Dr Aleksander Sikole** Sub-Investigators:	Department of Nephrology Clinical Centre Skopje	Vodnjankska 17 Skopje Macedonia	LAM-IV-303
Principal Investigator: **Professor Charles Swanepoel** Sub-Investigators:	E13 Groote Schuur Hospital	Observatory 7925 Cape Town South Africa	LAM-IV-303
Principal Investigator: **Dr Philip Kalra** Sub-Investigators:	Department of Renal Medicine Hope Hospital	Stott Lane, Salford Manchester M6 8HW UK	LAM-IV-303

List of Investigators (cont.)

Investigators	Affiliation	Address	Participation in Protocols
Principal Investigator: **Dr Peter Ackrill** Sub-Investigators:	Artificial Kidney Unit Withington Hospital	Nell Lane West Didsbury Manchester M20 2LR UK	LAM-IV-303
Principal Investigator: **Dr Anibal Ferreira** Sub-Investigators: None	Fresenius Medical Care Hemodial, Clinica de Dialise do Restolo, Lda.	Quinta da Mina, lt, 3 r/c 2600-076 Vila Franca de Xira Portugal	LAM-IV-303
Principal Investigator: **Professor Alessandro Balducci** Sub-Investigators:	U.O.D Centro di Nefrologia e dialisi	Ospedale S. Giovanni in Laterano Via S. Giovanni in Laterano, 155 00184 Roma Italy	LAM-IV-303
Principal Investigator: **Professor Giorgio Coen** Sub-investigators: None	Servizio di Fisiologia Renale e Ipertensione Arteriosa Universita la Sapienza	Policlinico Umberto I Via del Policlinico 00 161 Roma Italy	
Principal Investigator: **Dr Sylvie Sulkova** Sub-Investigators: None	Department of Medicine Strahov 1st Medical Faculty Charles University Prague Department of Internal Medicine	Sermirska 5 169 00 Praha 6 Czech Republic	LAM-IV-303
Principal Investigator: **Professor Waldysaw Sulowicz** Sub-Investigators: None	Department of Nephrology	15 Kopernika Str. 31-501 Cracow Poland	LAM-IV-303
Principal Investigator: **Dr Sarala Naicker** Sub-Investigators:	Dialysis and Transplant Unit	S Block, 2nd Floor Addington Hospital Box 977 Durban 4000 South Africa	LAM-IV-303

List of Investigators (cont.)

Investigators	Affiliation	Address	Participation in Protocols
Principal Investigator: **Professor Ljubica Djukanovic** Sub-Investigators: None	Clinical Centre of Serbia Institute of Urology and Nephrology	Pasterova 2 11 000 Belgrade Yugoslavia	LAM-IV-303
Principal Investigator: **Dr Maurice Laville** Sub-Investigators: None	Unite de Nephrologie Hospital Edouard Heriot	5 Place D'Arsonval 69437 Lyon Cedex 03 France	LAM-IV-303
Principal Investigator: **Professor Milan Popkovic** Sub-Investigators: None	Clinic of Rheumatology and Clinical Immunology	VMA, Crnotravska 17 11 000 Belgrade, Yugoslavia	LAM-IV-303
Principal Investigator: **Professor Slobodan Curic** Sub-Investigators: None	Institute for Internal Diseases Clinical Centre Novi Sad	Hajduk Veljkova 1 21 000 Novi Sad Yugoslavia	LAM-IV-303
Principal Investigator: **Dr Armando Torres** Sub-Investigators: None	Servicio de Nefrologia y Unidad de Investigacion Hospital Universitario de Canarias	Ofra s/n, 38320 La Laguna Tenerife, Spain	LAM-IV-303
Principal Investigator: **Professor Dr Hans-H Neumeyar** Sub-Investigators: None	Medizinische Klinik mit Schwerpunkt Nephrologie Medizinische Fakultat der Humboldt-Universitat zu berlin	Charite, D-10098 Berlin Germany	LAM-IV-303
Principal Investigator: **Dr N Dimkovic** Sub-Investigators: None	Centre for Renal Diseases Zvezdara – University Hospital	Dimitrija Tucovica 161 11000 Belgrade Yugoslavia	LAM-IV-303

Minutes of a meeting

Date of meeting:	October 23, 2001
Application:	IND 55, 054
Product:	Lanthanum Carbonate Hydrate
Sponsor:	Shire Laboratories Inc.
Purpose:	follow-up to pre-NDA meeting
Meeting Chair:	Raymond Lipicky, M.D.
Meeting Recorder:	Colleen LoCicero
Participants:	
FDA	
Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products (HFD-110)
Douglas Throckmorton, M.D.	Deputy Director, HFD-110
Juan Carlos Pelayo, M.D.	Medical Officer, HFD-110
Natalia Morgenstern	Chief, Project Management Staff, HFD-110
Colleen LoCicero	Regulatory Health Project Manager, HFD-110
Shire Laboratories Inc.	
Dr. Simon Tulloch	Senior Vice President, US Research and Development
Dr. Neil Frazer	Vice President of Medical Affairs, US
Dr. Steve Damment	Director, Pre-Clinical Sciences, UK
Dr. Guillermo Millicovsky	Director, Pre-Clinical Sciences
Ms. Isobel Webster	International Project Leader, UK
Ms. Suma Krishnan	Senior Manager, Regulatory Affairs, US

Background

The Division requested this meeting in follow up to the September 18, 2001 pre-NDA meeting to discuss again and reinforce the Division's concerns with the Sponsor's NDA submission plan.

Meeting

The NDA submission proposal

The Sponsor has data from a second rat study that they believe identifies phosphate depletion, not lanthanum carbonate, as the cause of the bone defects observed in the initial rat study. The Sponsor believes this finding allays the concern that lanthanum carbonate might adversely affect bone (i.e., cause osteomalacia). Therefore, the Sponsor wishes to submit the lanthanum carbonate NDA at the end of this year without any human bone biopsy data. They plan to amend the NDA three to four months after it is submitted with data from Study 303, the European study that will provide 97 baseline biopsies with approximately 30 follow up biopsies. The Sponsor no longer plans to submit in the original NDA or at any time during the review of the original NDA the bone biopsy data from of their ongoing long-term safety study (Study 307), as they no longer believe this relevant. Study 307 will provide 30 bone biopsies following one year of exposure and 30 bone biopsies following two years of exposure.

The Division's response

The Division did not find the schedule the Sponsor has outlined for the submission of the NDA reasonable. It would not be reasonable to accept the application when the part we consider most important will not be included in the original submission. While the Sponsor may be comforted by the findings of the second rat study, we cannot say at this point whether these findings will alleviate our concerns or not. The Sponsor has, at this point, one troublesome study in rats and one study that is not troublesome. Therefore, the clinical data is critical and we cannot agree to the submission of an NDA without these critical data.

Bony disease is a very important issue in individuals with renal impairment and it will be necessary to be able to describe in the label the effects of lanthanum carbonate on bone. Even if there had not been a signal in the initial rat study, we would be concerned with the potential effect on bone. It is important that we know what happens to bone in man.

Dr. Pelayo noted that the sponsor will need to demonstrate what lanthanum does in human tissue and prove, without a doubt, that while lanthanum carbonate accumulates in humans, it is not toxic to humans. Dr. Pelayo believes the safety data the sponsor plans to provide will be difficult to interpret, as the data are largely unblinded.

The sponsor noted that although the bone biopsies were open label, the evaluations were blinded. The sponsor believes it impossible to blind long-term safety studies in this setting, noting that they do not believe the safety databases for most NDAs are blinded. The Sponsor further noted that Renagel has the same effect on bone in uremic rats and that Renagel's safety database is small.

The Division is concerned with the possible bone effects, enough to not approve the application, and wants to see this issue resolved. Dr. Lipicky noted that while the sponsor believes the issue has been resolved by the second rat study, they have a study ongoing that would help to resolve definitively the question in man.

The sponsor indicated that they are having difficulty recruiting patients into their ongoing long-term safety study (Study 307) and that the study is proceeding slowly. They hope to achieve the number of biopsies needed by the end of 2001 and plan to submit the data in 2003 and 2004. Dr. Lipicky was skeptical that it would be possible to continue the study if lanthanum carbonate is approved.

The two conflicting rat studies, the fact that lanthanum carbonate accumulates in the bone/body, and the knowledge that there are human bone biopsies pending make it impossible to say that we can make a decision without human bone biopsy data. These data are very important and we cannot agree to a submission that will not include human bone biopsy data.

It would be optimal to delay the NDA submission until Study 307 is completed and to include the bone biopsy data from this study in the NDA, as it is unlikely that we will be able to say decisively, based on 30 biopsies, that our concerns are assuaged. However, the Division will accept an NDA in April of 2002 that contains the data from Study 303, the European study that has 97 baseline biopsies with approximately 30 follow up biopsies.

If the Sponsor wants to submit the application in December, they can do so, but the Division will not file it until they have submitted the results of the 30 human bone biopsies from Study 303. The CMC portion of the NDA can be presubmitted, as provided for in the regulations. Following the submission of the NDA, the Agency will deliberate considerably over what to do. The Division reiterated their preference that the NDA not be submitted until the bone biopsy data from the long-term safety study are available for inclusion in the NDA.

Signature, Meeting Recorder: /S/ Colleen LoCicero

Concurrence, Meeting Chair: /S/ Raymond Lipicky, M.D.

drafted: 11/1/01 finaled: 11/6/01

rd:
Pelayo/11/1/01
Throckmorton/11/5/01

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

/s/

Colleen LoCicero
11/8/01 11:20:11 AM
These final minutes were signed by Dr. Lipicky and faxed to the sponsor on 11/8/01.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(240) 453-6456
Attention:	Suma Krishnan
Company Name:	Shire Pharmaceutical Development Inc.
Phone:	(240) 453-6448
Subject:	meeting minutes
Date:	11-8-01
Pages including this sheet:	4
From:	**Colleen LoCicero**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

Dear Suma,

The minutes of our October 23, 2001 meeting regarding IND 55,054 accompany this cover sheet. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes). Please let me know that you received this fax.

Regards,
Colleen

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(240) 453-6404
Attention:	Suma Krishnan
Company Name:	Shire Laboratories Inc.
Phone:	(240) 453-6448
Subject:	meeting minutes
Date:	10-19-01
Pages including this sheet:	4
From:	**Colleen LoCicero**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

Suma,

The minutes of the pre-NDA meeting for IND 55,054 accompany this cover sheet. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes). Please let me know that you received this fax.

Regards,
Colleen

Meeting Minutes

Meeting Date:	September 18, 2001
Sponsor:	Shire Laboratories
Drug:	Lanthanum Carbonate Hydrate (IND 55,054)
Subject/Meeting Type:	Pre-NDA
Meeting Chair:	Douglas Throckmorton, MD
Meeting Recorder:	John Guzman
Participants:	
FDA	
Douglas Throckmorton, MD	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, MD, PhD	Team Leader, Medical, HFD-110
Juan Carlos Pelayo, MD	Medical Officer, HFD-110
Kasturi Srinivasachar, PhD	Team Leader, Division of New Drug Chemistry, HFD-810
Florian Zielinski, PhD	Chemist, HFD-810
Elena Mishina, PhD	Clinical Pharmacologist and Biopharmaceutist, HFD-860
Xavier Joseph, DVM	Pharmacologist, HFD-110
James Hung, PhD	Team Leader, Statistical, Division of Biometrics I, HFD-710
Natalia Morgenstern	Chief, Project Management Staff, HFD-110
Edward Fromm	Regulatory Health Project Manager, HFD-110
John Guzman	Regulatory Health Project Manager, HFD-110
Shire Laboratories	
Dr. Wilson Totten	Group Research & Development Director
Dr. Simon Tulloch	Senior Vice President, US R&D
Dr. Neil Frazer	Vice President of Medical Affairs, US
Dr. Garrick Fiddler	Medical Director
Dr. Steve Damment	Director, Pre-Clinical Sciences
Dr. Yuxin Zhang	Director of Biostatistics, US
Dr. Rosamund Wilson	Head of International Statistics and Data Management
Ms. Jo Ferdinando	Director, Chemistry, Manufacturing, and Controls
[redacted]	Consultant
Dr. Nigel Atherton	Director, Project Management
Ms. Isobel Webster	International Project Leader
Ms. Scharmen Confer	Clinical Program Manager, US
Dr. Rick Lilley	Head of Global Regulatory Affairs
Ms. Tami Martin	Vice President of Regulatory Affairs, US
Ms. Suma Krishnan	Senior Manager, Regulatory Affairs, US

Background

Shire Laboratories, Inc requested this pre-NDA meeting for Lanthanum Carbonate Hydrate (IND 55,054) for the reduction of serum phosphate in chronic renal failure patients. This meeting was conducted to discuss the content and format of the upcoming NDA submission.

Meeting

Discussion of the Chemistry section

Chemistry Question 1: Is Shire's proposal for CMC acceptable to the Agency for the Release and Stability Specifications for Drug Substance? If not, please comment.

The Division asked the Sponsor if they had identified any other — of the drug substance, and how did these — impact the drug product performance. The Sponsor indicated that by utilizing — no indication — was seen. However, other — were identified, with — being — Studies have shown that the — is more — but after — the performance of — — in the drug product appear equal.

The Division noted that the metals in the impurities list in the specifications appeared to be in high amounts and should be further characterized and justified in the NDA submission. In general, the drug substance specifications should be based on manufacturing and analytical capabilities, driven by the available data, and use the USP rather than PhEur specifications.

Chemistry Question 2: Is Shire's proposal for CMC acceptable to the Agency for the Release and Stability Specifications for Drug Product? If not, please comment.

The meeting package indicates that assays are performed [ ] testing. The Division prefers that all drug product assays be done at every time point. It also appears that there was dissolution data only from the — timepoint. Will there be — accelerated dissolution data? Has any degradation of the drug product been observed? The Sponsor noted that by the time of the NDA submission, — — of dissolution data would be available and submitted. They will commit to doing accelerated dissolution studies with the first validation batch. They have noted that the drug product is extremely stable, but they will continue to look for any degradation.

Discussion of the Non-Clinical Section

Non-Clinical Question: Does the Agency agree that the non-clinical program as described in this briefing document is acceptable to support the NDA?

Dr. Resnick (Pharmacology Team Leader) was not available for this meeting. Both he and Dr. Joseph will review the pre-clinical information and draft table of contents for that section in the pre-NDA package. Any comments they have will be communicated to the Sponsor.

After discussion of the non-clinical question, the Sponsor gave a short presentation regarding the issue of the mineralization defect in bone (osteomalacia) in uremic rats treated with Lanthanum (raised during the end-of-phase 2 meeting in June 1999). The Sponsor has new data that indicates that the lesions in uremic rats occur through an indirect, pharmacologically mediated mechanism related to phosphate depletion, and is not a result of direct bone toxicity. Dr. Throckmorton acknowledged information, but reiterated that Dr. Resnick was not in attendance. He encouraged the Sponsor to submit a brief summary of this information to the IND and request that the Division make comment.

Discussion of the Clinical Section

Prior to answering the clinical questions listed in the meeting package, Dr. Throckmorton opened a discussion with the Sponsor to clarify a few issues the Division had regarding the presentation of the data. When did the Sponsor intend to submit the NDA? According to the package, trials 303 and 307 would not be completed until 2002. Are they planning to submit an interim analysis? The Division discourages rolling submissions. Why not wait until 2002 or 2003 to submit the NDA?

The Sponsor indicated that they plan to submit the NDA by the end of 2001, and a safety update in either March or April of 2002. The NDA will include the full patient data for approximately 982 patients exposed to Lanthanum Carbonate for approximately 1 year. The database for study 307 (which includes 1174 patients) will be locked March 2002 and report those findings in either 2002 or 2003. In the safety update, the Sponsor proposes to submit a full database of the bone analyses done in Study 303 (approximately 30 patients). The Sponsor feels that the immediate benefit of the drug, coupled with the new information regarding the mineralization defect justifies the December 2001 submission date for this NDA and that bone biopsy data from studies 303 and 307 are not as crucial as once thought. Dr. Throckmorton expressed reservations about this assertion.

Dr. Throckmorton noted that the patient database the Sponsor is planning to submit is much smaller in comparison with other approved drugs, and urged the sponsor to strongly consider waiting until the data from study 307 (especially the bone biopsies) are available. A small patient database will increase our safety concerns. Further, most of the studies conducted were open-label, which will limit any analysis of comparative safety. The Division encourages the Sponsor to submit as much data as possible. The dataset should be augmented with follow-up information for ALL patients. Patients in Studies 303 and 307 should be completely followed-up, and any reasons that preclude follow-up should be explained. Since Study 307 is a comparative study, the interim data from that study should be included with the original NDA submission.

Clinical Question 1: Draft tables for the ISE and ISS are presented in the packet. Does the Agency find the content and format of the integrated summary tables acceptable?

The Sponsor noted that they would submit SAS transport files, codes, and annotated CRFs, safety databases in SAS. The Division acknowledged that, and noted that the Draft tables were acceptable.

Clinical Question 2: Does the Agency agree that the attached proposal for the provision of clinical data at the time of the NDA filing, supplemented by additional data during the review period as outlined in this document acceptable? If not, please comment.

See discussion prior to the first clinical question.

Other

The Division noted that they did not review the package insert included in the meeting package; any review of the package insert would be done at the time of the NDA review. Copies of the clinical pharmacology (PK) section (study summaries and data) should be sent in electronic format (MS word and SAS, respectively). References maybe placed at the end of each section and the Statistical section maybe an exact copy of the Clinical section.

Due to current policies in the Agency, the Division encourages studies of investigational drugs in pediatric populations. If the Sponsor chooses to file for a waiver, a strong supporting explanation should be included with the waiver request. The Division encourages the Sponsor to consider c

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Signature, Meeting Recorder: /S/ John Guzman

Signature, Meeting Chair: /S/ Douglas Throckmorton, MD

Drafted: September 27, 2001
Edited, based on reviewers' comments on draft, and finaled by C LoCicero for J Guzman on 10/15/01.

Cc: HFD-110
HFD-110/Guzman

Rd:
J Hung/9/27/01
X Joseph/9/28/01
E Mishina/9/28/01
F Zielinski/10/5/01
K Srinivasachar/10/10/01
J Pelayo/10/5/01
N Stockbridge/10/10/01
D Throckmorton/10/12/01

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

/s/

Colleen LoCicero
10/19/01 12:25:40 PM
These minutes were put into final and signed by Ms. LoCicero for Mr. Guzman, Meeting Recorder. These final minutes were signed by Dr. Throckmorton, Meeting Chair, and faxed to the sponsor on 10/19/01.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(240) 453-6404
Attention:	Suma Krishnan
Company Name:	Shire Laboratories Inc.
Phone:	(240) 453-6448
Subject:	meeting notice
Date:	10-10-01
Pages including this sheet:	2
From:	**Colleen LoCicero**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

Notice of Forthcoming Meeting

Application:	IND 55,054
Product:	Lanthanum Carbonate Hydrate
Sponsor:	Shire Laboratories Inc.
Purpose:	follow-up to pre-NDA meeting
Date meeting request received:	Requested by the Division
Meeting:	**Tuesday, October 23, 2001 @ 11:30 a.m. in conference room "F", 5th floor, WOC II**
Participants:	
FDA	
Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products (HFD-110)
Douglas Throckmorton, M.D.	Deputy Director, HFD-110
Juan Carlos Pelayo, M.D.	Medical Officer, HFD-110
Colleen LoCicero	Regulatory Health Project Manager, HFD-110
Shire Laboratories Inc.	
To be announced	

Meeting arranged by: Colleen LoCicero Phone: (301) 594-5332

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

/s/

Colleen LoCicero
10/10/01 03:31:18 PM
CSO
This meeting notice was faxed to the sponsor on 10/10/01.

FW Zielinski sent "Request for Consultation" to HFD-400 (Sammie Beam, 827-3161) on Oct 6, 2000 to get pre-NDA trade name evaluation of FOZNOL and/or FOSRENOL. Turn around is expected to be n mt 90 days.

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
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US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	240.453.6456
Attention:	Suma Krishnan
Company Name:	Shire Laboratories
Phone:	240.453.6448
Subject:	Meeting Confirmation
Date:	July 17, 2001
Pages including this sheet:	2
From:	**John Guzman**
Phone:	**301-594-5312**
Fax:	**301-594-5494**

Suma,

The notice for our upcoming pre-NDA meeting regarding the Lanthanum Carbonate Hydrate accompanies this cover sheet. This serves as confirmation of the meeting. If you have any questions, please let me know.

Best Regards,

John Guzman

Notice of Forthcoming Meeting

Product:	Lanthanum Carbonate Hydrate
IND:	55,054
Sponsor:	Shire Laboratories
Purpose:	Pre-NDA
Pre-meeting (FDA):	**Tuesday, 18-Sept-2001, 09:30am, Conference Room "F", 5th floor, WOC II**
Meeting:	**Tuesday, 18-Sept-2001, 10:00am, Conference Room "F", 5th floor, WOC II**

Tentative List of Participants:

FDA	
Douglas Throckmorton, MD	Deputy Director, HFD-110
Stephen Fredd, MD	Deputy Director, HFD-110
Norman Stockbridge, MD, PhD	Team Leader, Medical, HFD-110
Juan Carlos Pelayo, MD	Medical Officer, HFD-110
Patrick Marroum, PhD	Clinical Pharmacologist and Biopharmaceutist, HFD-860
Gabriel Robbie, PhD	Clinical Pharmacologist and Biopharmaceutist, HFD-860
Elena Mishina, PhD	Clinical Pharmacologist and Biopharmaceutist, HFD-860
Charles Resnick, PhD	Team Leader, Pharmacology, HFD-110
Xavier Joseph, PhD	Pharmacologist, HFD-110
Kasturi Srinivasachar, PhD	Team Leader, Division of New Drug Chemistry I, HFD-810
Florian Zielinski, PhD	Chemist, Division of New Drug Chemistry, HFD-810
James Hung, PhD	Team Leader, Statistical, Division of Biometrics I, HFD-710
Natalia Morgenstern	Chief, Project Management Staff, HFD-110
John Guzman	Regulatory Health Project Manager, HFD-110

Sponsor	
Garrick Fiddler	Medical Director, Shire Labs
Tami Martin	Vice President, Regulatory Affairs
Rick Lilley	Director of Group Regulatory Affairs
Suma Krishnan	Senior Manager, Regulatory Affairs
Wilson Totten	Group R&D Director
Simon Tulloch	Senior Vice President, US R&D
Isobel Webster	International Project Leader
Yuxin Zhang	Senior Director, Biostatistics
Steve Damment	Director, Pre-Clinical Services
[ ]	Consultant, [ ]
Scharmen Confer	Clinical Program Manager

Meeting arranged by: John Guzman Phone: 301.594.5312

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

/s/

John Guzman
7/17/01 09:27:05 AM
CSO

Redacted 12

page(s) of trade secret and/or confidential commercial information (b4)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH & HUMAN SE

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	240-453-6456
Attention:	**Tami Martin** **VP, Regulatory Affairs**
Company Name:	**Shire Laboratories, Inc.**
Phone:	240-453-6450
Subject:	November 2, 2000 Teleconference Minutes
Date:	November 7, 2000
Pages including this sheet:	3

From:	**Sandy Birdsong**
Phone:	**301-594-5312**
Fax:	**301-594-5494**

The minutes from our November 2, 2000 teleconference accompany this cover sheet.

You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

Please let me know you received this facsimile. Thank you.

Sandy

Minutes of a Teleconference

Date:	November 2, 2000
Application:	IND 55,054 Lanthanum carbonate
Sponsor:	Shire Laboratories, Inc.
Purpose:	Discuss Meeting Request

Participants:

FDA

Norman Stockbridge, M.D., Ph.D., Medical Team Leader, HFD-110
Sandra Birdsong, Regulatory Health Project Manager, HFD-110

Shire Laboratories, Inc.

Tami Martin, Vice President, Regulatory Affairs

Background

The sponsor requested a meeting with the FDA statistician to discuss analysis of bone evaluation in the proposed protocol.

Meeting

Dr. Stockbridge stated that the Division does not often deny a meeting, but in this case, the primary analysis of the trial will not determine how a decision is made. The Division is prepared to respond to a concrete proposal, but lacks expertise in development of this type of drug. He stated a decision is made which balances a perceived benefit versus a perceived risk. Safety issues become more important when a surrogate endpoint is used, than when a clinical benefit is demonstrated.

Dr. Stockbridge recommended that the sponsor evaluate a variety of parameters, choose a primary endpoint and several secondary endpoints, then submit a proposal that describes their rationale. The sponsor stated [ ] and Dr. Stockbridge agreed that this may give them an opportunity to obtain more open label data. The sponsor agreed that further discussion with the FDA statistician would not be helpful.

Signature, Meeting Recorder _____

Concurrence, Chair _____

RD: slb/11/2/00 Final: 11/6/00
Stockbridge/11/3/00

/s/

Sandra Birdsong
11/7/00 08:32:13 AM
CSO
Dr. Stockbridge reviewed rough draft on 11/3/00 and concurrence on 11/6/00

Minutes of a Meeting

Type of Meeting:	IND
Date Requested:	FDA
Date Confirmed:	March 17, 2000
Date of Meeting:	April 10, 2000
Product:	Lanthanum Carbonate IND 55,054
Sponsor:	Shire Laboratories, Inc.
Purpose:	Discussion of toxicology
Meeting Chair:	Raymond Lipicky, M.D.
Meeting Recorder:	Sandra Birdsong

Participants:

FDA

Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products (HFD-110)
Norman Stockbridge, M.D.	Medical Team Leader, HFD-110
Shaw Chen, M.D.	Medical Team Leader, HFD-110
Juan Carlos Pelayo, M.D.	Medical Officer, HFD-110
Xavier Joseph, Ph.D.	Pharmacologist, HFD-110
Edward Fromme	Consumer Safety Officer
Sandra Birdsong	Regulatory Health Project Manager

Shire Laboratories, Inc.

Nigel Atherton, Ph.D.	Director of Project Management (UK)
Steve Damment, Ph.D.	Director of Pre-Clinical Sciences (UK)
Garrick Fiddler, MBIRA	Medical Director SPD (UK)
[ ]	Independent Consultant, [ ]
Rick Lilley, Ph.D.	Director of International Regulatory Affairs (UK)
[ ]	
	] (Advisor to Shire)
Tami Martin, R.N., Esq.	Vice President, Regulatory Affairs (USA)
James Pedicano, B.A.	Clinical Program Manager (USA)
Simon Tulloch, M.A.	Senior Vice President, Research and Development (USA)

Isobel Webster, R.G.N. International Project Leader (UK)

Background

The sponsor is developing lanthanum carbonate as an oral phosphate-binding agent for [redacted] in patients undergoing dialysis. Previous pharmacodynamic studies indicate that the duration of action of lanthanum carbonate is similar to that of currently used phosphate binding agents. An end of phase II meeting was held on May 27, 1999.

The November 16, 1999 medical reviews of the sponsor's pre-clinical data and safety report stated that the Division is concerned about treatment-related osteomalacia in uremic rats treated with lanthanum carbonate. Single and multiple oral doses were associated with measurable plasma levels of lanthanum. Accumulation of the drug in brain, bone, kidney, and other organs was also noted. The sponsor was asked to revise the investigator brochure and informed consent form according to the results of the pre-clinical studies.

In the review of amendments made to Protocol LAM-IV-302 dated November 22, 1999, the medical reviewer stated that the proposed change from a double blind to open label design in humans would compromise the study.

This meeting was called by the Division to discuss the toxicological and protocol design issues described above.

Meeting

Discussion of Pre-Clinical Data

The sponsor's consultant discussed the European rat studies and reported that there are substantial problems related to technique and standardization in slide preparation. For example, the width of the growth plate varied due to poor technique in taking the slices. On qualitative evaluation, the animals receiving a dose of 2,000 mg/kg/day for a duration of 12 weeks showed clear signs of osteomalacia that is histologically consistent with hypophosphatemia-induced osteomalacia. He stated that a 6-12% decrease in phosphorous level can induce osteomalacia. The Division noted that the previously presented data indicated that the drug induced osteomalacia irrespective of hypophosphatemia. Therefore, osteomalacia in the rats appears to be unrelated to hypophosphatemia.

Discussion of Protocol Design and Hypothesis

Protocol LAM-IV-303 is a one-year study of 100 patients with end-stage renal disease undergoing hemodialysis randomized to calcium carbonate or lanthanum carbonate. Patients will have a bone biopsy at baseline and at one year. The sponsor believes that 29 patients in each arm must complete both biopsies, for adequate power. The sponsor stated that it is difficult to find patients in this population and the dropout rate is significantly higher in the U.S. than in Europe.

Concern was expressed by the Division regarding the justification for inducing osteomalacia. There appears to be an additional risk involved in administering this drug. By treating hyperphosphatemia, patients will be put at risk for fractures.

The Division discussed several hypotheses. If the hypothesis being tested is that renal osteodystrophy will get better because the patient is not hyperphosphatemic and the study fails to document that, the assumption is that it became worse. If the hypothesis is that the osteodystrophy did not get worse, we must rely on the sensitivity of the assay and the parameters that interpret the quantification. If the hypothesis is that osteomalacia will not develop, no change will be seen. However, not being able to detect the change doesn't mean there was no change, but that the study was under-powered to detect a change. A necessary question for the sponsor to answer is what number of patients are needed in the study and what method of assessment will show that osteomalacia is not produced by the drug.

The Division stated that the sponsor must be able to assess changes in bone quantitatively and then decide how much of a difference can be reliably detected. The Division suggested that there could be multiple histomorphic parameters that go into deciding who has significant bone pathology. The Division believes that bone alkaline phosphatase is a reasonable marker to observe, but another measure is needed as a "decision-maker". The sponsor asked if, in terms of bone data, a study of inpatients treated with the drug for two years would be acceptable. The Division stated this would be acceptable if the trials and the pathology are blinded.

Discussion of Statistical Power

The Division clarified that with only one study of bone biopsies, a p on the order of 0.00125 would be needed. A one-year European study would be acceptable to the Division, but an n of 300 is too small.

Conclusions

Decisions to be made by the sponsor were listed by the Division:

1. What parameters will be used for measuring osteomalacia in humans? One or two quantitative measures should be chosen as the decision-makers.

2. How much of a change in that parameter has to be ruled out?

3. What size study will ensure adequate power?

4. If an open-label design is used, can it be documented that clinical treatment of the patients is not biased?

Since it appears that more than one discussion may be needed, the Division suggested the sponsor meet internally to decide on one to three quantitative measures and obtain one or two reprints that justify this decision. This material should be sent to the Division and when it is received, the Division Statistician can also review the material. Dr. Lipicky suggested that the sponsor contact the Division to arrange another meeting to for further discussion.

/S/

Signature, Minutes Recorder: _____
Sandra Birdsong

Concurrence, Meeting Chair /S/
Raymond Lipicky, M.D.

Cc: Original NDA 20-540
HFD-110
HFD 110/SBirdsong
HFD 110/SMatthews
HFD-110/ABlount

Drafted: 4/13/00 Final: 4/28/00

RD:		
	Stockbridge	4/13/00
	Chen	4/27/00
	Pelayo	4/27/00
	Joseph	4/27/00

Minutes of a meeting

Date of meeting:	May 27, 1999
Product:	Lanthanum Carbonate Hydrate (IND 55,054)
Sponsor:	Shire Laboratories Inc.
Purpose:	End of phase 2
Meeting Chair:	Robert Temple, M.D.
Meeting Recorder:	Colleen LoCicero
Participants:	

FDA

Robert Temple, M.D.	Director, Office of Drug Evaluation I (HFD-101)
Robert Fenichel, M.D., Ph.D	Deputy Director, Division of Cardio-Renal Drug Products (HFD-110)
Charles Ganley, M.D.	Team Leader, Medical, HFD-110
Juan Carlos Pelayo, M.D.	Medical Officer, HFD-110
James Hung, Ph.D.	Statistician, Division of Biometrics I, HFD-710
Emmanuel Fadiran, Ph.D.	Clinical Pharmacologist and Biopharmaceutist, Division of Pharmaceutical Evaluation I (HFD-860)
Albert DeFelice, Ph.D.	Team Leader, Pharmacology, HFD-110
John Koerner, Ph.D.	Pharmacologist, HFD-110
Colleen LoCicero	Consumer Safety Officer, HFD-110

Shire Laboratories Inc.

United Kingdom	
Dr. Wilson Totten	Director, Group Research and Development
Dr. Nigel Atherton	Director, Project Management
Dr. Ian Howe	Medical Director
Dr. Elaine Morten	Manager, Regulatory Affairs
Mr. Rob Haslam	Director, Pharmaceutical Development
United States	
Dr. Simon Tulloch	Vice President, Medical Affairs
Ms. Tami Martin	Vice President, Regulatory Affairs
Ms. Sandy Geroux	Assistant Director, Regulatory Affairs
Dr. Yuxin Zhang	Director, Biostatistics

Background

The sponsor is developing lanthanum (a rare earth) carbonate as a phosphate-binding agent for [redacted]
They requested this end of phase 2 meeting to discuss their proposed phase 3 plan, which consists of three studies. The first is an ongoing, European, open-label, randomized,

parallel-group study to compare safety and efficacy of lanthanum carbonate with calcium carbonate. The second is a dose-titration, parallel-group, double-blind, placebo-controlled study in the US that is designed to confirm the efficacy of lanthanum carbonate. The third is an open-label safety study in the U.S. designed to collect long-term safety data.

The meeting

Discussion Point #1: Safety concerns

The information provided in the briefing document indicates that there is substantial accumulation of lanthanum in the human body, a cause for concern as not much is known about what lanthanum does when it accumulates. There are treatments available for this indication that are relatively safe and do not result in the accumulation of a foreign substance in the body. The Agency is concerned about the accumulation of lanthanum because of the toxicities (bone disease, central nervous system abnormalities, etc.) associated with chronic aluminum administration and the resulting accumulation of aluminum in the body in this patient population.

Discussion Point #2: Long-term safety study

As proposed, the phase 3 program would provide long-term safety data for approximately 800 patients, but not all the data will be from controlled studies. The Agency believed it important that the safety data be controlled, as it will be impossible to tell whether bone disease seen during the study is a result of exposure to lanthanum, other therapeutic interventions, uncontrolled phosphate levels, or renal disease itself. If there is no control group, the data are subject to every twist and turn of this complex patient population.

The Agency also did not believe the proposed duration of the safety study would be sufficient, based on the experience with aluminum.

The Agency's recommendation with regards to the safety study is that the sponsor, after assessing the animal toxicology data to determine upon what toxicities to focus, conduct a long-term safety study (one to two years of exposure) of lanthanum and a comparator. The study should consist of at least one thousand patients with 500 patients in each arm. During the study, the sponsor should look for expected adverse events, as well as unexpected adverse events.

Discussion Point #3: Comparator data from the European study

The Agency noted that, as proposed, the European study would provide data for one year of exposure to lanthanum and six months for calcium carbonate, thereby providing only six months of head-to-head comparator data. The Agency asked whether it would be possible to increase the duration of exposure on comparator in this study from six months

to one year. The sponsor has already reached an agreement with the European regulatory agency on this protocol and hesitates to renegotiate this with them.

Discussion Point #4: Selection of a comparator for the efficacy and safety studies

The Agency asked whether it would be possible to change the comparator in the ongoing European study to calcium acetate or another US approved phosphate-binding agent, as we have data on these products. Since calcium carbonate is not approved in the US as a phosphate-binding agent, we do not have efficacy data for it for this indication, although we do not dispute its usefulness in this setting. Any alternative phosphate-binding agent would be acceptable as the comparator for the proposed efficacy and safety studies. If, however, the sponsor uses calcium carbonate, the Agency might request the sponsor to provide available efficacy data for calcium carbonate.

Discussion Pont #5: Evaluation of safety study

The sponsor should look for the following three types of adverse events during the safety study:

1. unexpected adverse events
2. those adverse events associated with aluminum toxicity. If the model is aluminum it might be possible to look at some of these short term.
3. those adverse events associated with the disease itself

In the open-label trials, the sponsor should proactively look for toxicities such as, but not limited to, CNS abnormalities (i.e., cognitive function) and bone disease. The Agency could not say exactly what tests for these toxicities should be performed. The sponsor suggested performing cognitive function tests, but was not sure (and neither was the Agency) how frequently these tests should be performed.

Discussion Point #6: Comparison to aluminum

The sponsor is close to completion of protein-binding work that they believe will demonstrate whether lanthanum is transported similarly to aluminum. The sponsor has additional work ongoing that should further differentiate the two. The sponsor noted that they have found the levels of lanthanum in the body to be lower than those of aluminum. The sponsor further noted that aluminum was seen in the brains of rats administered aluminum chronically over a period of several months in the aluminum animal toxicology studies. In the toxicology studies performed thus far with lanthanum, the sponsor saw no brain exposure over a 78-week treatment period. The sponsor plans to perform additional studies to evaluate this further.

Discussion Point #7: Pre-clinical studies

In the animal toxicology studies, the sponsor should be paying particular attention to those toxicities associated with chronic administration of aluminum (i.e., bone disease, dementia, etc.)

The sponsor plan to analyze the brain, spinal cord, and other tissues from the 52-week dog study for evidence of lanthanum accumulation. The available literature indicates that lanthanum does not cross the cell membranes into the cells.

Dr. DeFelice noted that the Agency has only been provided snapshots, and has been unable to develop a trajectory of blood or tissue levels from the data provided. The sponsor noted that they had discussed performing evaluations at steady state, but had not followed through on this, as they were unsure how important this was to the Agency. The Agency noted that it is important to achieve a level of lanthanum exposure in the animals at least ten times that of the anticipated human exposure. It is also important to know if and where in the animals lanthanum is accumulating, as it will determine where we will look for this in humans.

The sponsor suggested that an analysis of the tissue from their 26- and 52-week dog studies might allow for some assessment of accumulation. Analyzing tissues taken at terminal kill in the ongoing rat carginogenicity study might further assess accumulation. The terminal tissue from the 104-week rat study could be analyzed for this as well.

Regardless of how reassuring the results of the animal toxicology studies are, the Agency would still want to see considerable human safety data. If the sponsor believes the animal toxicology studies are conclusive and that it should not be necessary to provide the suggested additional human safety data, they should make a case for this. These animal toxicology studies and analyses could be conducted in parallel with the phase 3 clinical studies.

Discussion Point #8: Clinical Pharmacokinetic data

The Agency reminded the sponsor that the clinical formulations must be bioequivalent to the formulation to be marketed. The sponsor responded that the two formulations are identical and that the issue was discussed at the chemistry, manufacturing, and controls meeting with the Agency on May 26, 1999.

The Agency believed the proposed pharmacokinetic program, as described in Question #3 in the briefing package (see attached), was acceptable, but suggested that samples be taken over the 24-hour dosing interval. The sponsor has developed a sensitive assay for lanthanum in plasma.

Discussion Point #9: Dialysis Patient Population

The sponsor noted that they proposed to include only hemodialysis patients in the US phase 3 program as opposed to peritoneal dialysis patients because the former were easier to monitor. The Agency agreed that it would not be necessary to include peritoneal dialysis patients in the US phase 3 studies and that the findings from these studies could be applied to both hemodialysis and peritoneal dialysis patients.

Discussion Point #10: Geriatric Population

The Agency did not believe it necessary for the sponsor to conduct a separate study in geriatric patients, although a separate analysis of geriatric patients in the proposed phase 3 studies could be performed. The Agency further noted that, as discussed previously, a test of cognitive function should be incorporated into the protocols.

Discussion Point #11: Pediatric Population

The sponsor does not plan to perform pediatric studies and intends to apply for a deferral and/or waiver. It will be necessary for the sponsor to justify their exclusion of patients under 18 years of age from the study in the protocol. The Agency believed this would be difficult to do, as there are a substantial number of patients of this age group in this patient population. The Agency recommended that the sponsor consider lowering the age limit and apply for a deferral. If the sponsor can make a case for a waiver, they should do so [redacted]

Discussion Point #12: Drug Interaction Studies

If the ongoing in vitro studies confirm the absence of in vitro drug interactions, the sponsor proposes to perform no additional studies to evaluate the potential for drug interactions with lanthanum. The ongoing studies involve the classic substrates that affect metabolism. The Agency found this acceptable as it follows the guidance. The sponsor believes lanthanum might be similar to antacids in that it might chelate other drug products in the gut. For this reason, and the fact that they also believe lanthanum might affect the pH of the stomach, the sponsor intends to recommend in the product labeling that lanthanum be administered two hours before or after other medications. The sponsor did not plan to perform drug interaction studies to assess this, but assumes that it does occur and plans to address this in the the labeling. The Agency asked how the sponsor knew that a two-hour interval between the dosing of lanthanum and other medications was sufficient to prevent any drug interactions. The sponsor did not know.

The Agency believed it important for the sponsor to monitor and follow up on concomitant medications administered during the planned phase 3 studies. It would be concerning if, for example, many people lose control of their blood pressure while on study drug concomitantly with their blood pressure medication. It will be important to monitor and collect these data. The sponsor should monitor and assess any changes in the doses of concomitant medications during the studies to determine whether the change was necessitated by the addition of study drug. The Agency also suggested that the sponsor might want to look at those medications most commonly taken by patients with renal impairment and perform drug interaction studies with those drugs.

Discussion Point #13: Efficacy

The primary endpoint of the clinical program used the reduction of plasma phosphate levels as a direct measurement of the efficacy of lanthanum carbonate. The Agency agreed that the measure of plasma phosphate alone would be sufficient to prove product efficacy.

Discussion Point #14: Indication

The sponsor wanted to know if the proposed indication statement "[redacted] was acceptable, based upon the proposed clinical development plan. The Agency noted that our bias is to limit the indication to dialysis patients, as the proposed clinical program will not provide data on patients with end-stage renal disease not undergoing dialysis. The Agency added that because the clinical program includes only dialysis patients, it would not be known whether lanthanum is nephrotoxic. If the sponsor wants to expand the label population, they will probably need to expand the patient population studied, although this might be negotiable.

Discussion Point #15: Adequacy of proposed studies to support efficacy

The Agency agreed that two proposed efficacy studies (LAM-IV-301 and LAM-IV-302) would be acceptable for the evaluation of efficacy for the NDA.

Signature, Meeting Recorder: /S/ Colleen LoCicero

Concurrence, Meeting Chair: /S/ Robert Temple, M.D.

cc: orig IND 55054
HFD-110
HFD-110/LoCicero
HFD-110/SBenton

drafted: 6/8/99 finaled: 6/21/99

rd:
Temple 6/16/99
Fenichel 6/14/99
Ganley
Pelayo 6/10/99
Hung 6/10/99
Fadiran 6/11/99
DeFelice 6/14/99
Koerner 6/14/99

Minutes of a meeting

Date of meeting:	May 26, 1999
Product:	Lanthanum Carbonate Hydrate IND# 55,054
Sponsor:	Shire Laboratories Inc.
Purpose:	End of phase 2 CMC
Meeting Chair:	Charles Hoiberg, Ph.D.
Meeting Recorder:	Colleen LoCicero
Participants:	

FDA

Charles Hoiberg, Ph.D.	Director, Division of New Drug Chemistry I (HFD-810)
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-810
Joseph Piechocki, Ph.D.	Chemist, HFD-810
Patrick Marroum, Ph.D.	Team Leader, Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation I (HFD-860)
Colleen LoCicero	Consumer Safety Officer, Division of Cardio-Renal Drug Products (HFD-110)

Shire Laboratories Inc.

United Kingdom

Dr. Wilson Totten	Director, Group Research and Development
Dr Nigel Atherton	Director, Project Management
Dr. Elaine Morten	Manager, Regulatory Affairs
Ms. Kerry Toone	International Project Leader
Mr. Rob Haslam	Director, Pharmaceutical Development

United States

Dr. Rick Couch	Vice President, Pharmaceutical Sciences
Ms. Tami Martin	Vice President, Regulatory Affairs
Ms. Sandy Geroux	Assistant Director, Regulatory Affairs
Mr. Robert Pullen	Senior Director, Analytical Sciences

Background

The sponsor requested this meeting to discuss their phase 3 CMC plans for lanthanum carbonate, an oral phosphate-binding agent being developed [redacted].

The meeting

Discussion Point #1: Site of manufacture

The site of manufacture for drug substance and product differ for the studies performed in Europe and those performed in the US. Drug substance and product specifications and the manufacturing process that will be used at the US manufacturing site(s) are identical to that used in Europe. The sponsor therefore believes there are no significant differences between the clinical materials used in Europe and those used in the US in the drug development program and intends to submit long-term safety data to the NDA that were obtained from the European studies. The sponsor asked whether the Agency believed this was acceptable.

The Agency noted a difference in impurities between the latest batch, manufactured in the U.S., and previous batches, manufactured in Europe, in the briefing package. In particular, a difference in the [ ] was detected. Because this product will be taken chronically, the [ ] might be a cause for concern and the pharmacology/toxicology reviewers have been consulted regarding this item. The sponsor believed the difference in the [ ] detected between batches might be attributed to a better level of detection in the later batches. They also noted that the level detected was still extremely low. The Agency will follow-up on this with the sponsor, once the pharmacology/toxicology reviewers have completed their assessment.

The sponsor verified that the drug substance has been tested for the presence of [ ] but that the level was below the level of detection, so it was not included in the table in appendix 3 of the briefing document. The level was below [ ]

Discussion Point #2: [ ] test

In the [ ] test, the tablets were not tested in water, but were tested at a [ ] The tablet, even when crushed, did not dissolve. The sponsor does not believe dissolution testing is necessary for these tablets because they are chewable and therefore did not attempt classical dissolution testing in the standard mediums.

The Agency could not say, from the information provided in the briefing package, whether the proposed [ ] test would be an acceptable alternative to dissolution testing for the tablets. From the information about this test provided in the briefing document, the Agency was not able to determine whether the test was sufficiently sensitive to detect differences between batches or to detect a bad batch. The Agency would be concerned about the absence of a test that could detect these differences, because, although not intended, some absorption of lanthanum does occur. It would be important to be able to detect whether absorption varies from batch to batch, since increased absorption in one batch may lead to toxicity. Dissolution testing (or a sufficiently sensitive alternative) is particularly important if it is shown that absorbed lanthanum is toxic. If it is shown that lanthanum is not toxic when absorbed, dissolution testing (or a sufficiently sensitive alternative) is not as important. The importance of this

testing will therefore be determined by the degree of lanthanum absorption and whether lanthanum is toxic when absorbed.

The Agency further noted that if the sponsor switches manufacturing sites, post-approval, it will be important that they have a test that has been shown to be discriminating. Substituting the [ ] test for the standard dissolution testing might prove to be a problem, post-approval, if the sponsor plans to use the SUPAC guidelines for site changes. The sponsor believed it would be difficult to come up with [ ] dissolution media needed for standard dissolution testing. It was noted, however, that it might be possible to do this by adding [ ] to facilitate dissolution in these media. The Agency suggested the sponsor establish a protocol for this and submit it to the Agency for review.

Alternatively, the [ ] test might be acceptable to the Agency, however, the sponsor needs to further validate it.

If the sponsor is able to provide dissolution data in the NDA, the Agency would prefer to see dissolution data for both the crushed and intact tablet, in various media. If the sponsor is not able to provide dissolution data, and substitutes the [ ] test for the dissolution testing, they should justify this in the NDA.

Discussion Point #3: Particle size

The particle size of the raw materials and drug product itself will affect product solubility and absorption and, therefore, the Agency believed the sponsor should develop particle size specifications for this. The acceptance criteria for the particle size specifications should be justified. The sponsor agreed to develop particle-size specifications for the active and formulated product [ ]

Discussion point #4: Impurity profile of starting materials

As this compound is derived from —— it is possible that the sponsor might switch suppliers for the starting material. The Agency therefore believes there is a potential for the impurities (— metals) to change each time the supplier changes. The sponsor did not believe the impurity profile would differ for starting material from different suppliers and that provided the starting material complies with the established specifications, it would be suitable to use.

Discussion Point #5: Removal of impurity test from specifications for drug substance

Because the impurities will be adequately defined for the starting material, the sponsor believed it would not be necessary to redefine them for the drug substance, as the only source of the impurities for the drug substance would be the starting material.

The Agency expressed some concern with this proposal, noting that the sponsor seemed to expect differences in the impurities, as their specifications differed for the two. As previously noted, the sponsor might change the supplier for the starting material and could do so without our knowledge. The Agency's concern with this is that the established specifications might not be relevant to starting material from a different supplier.

The sponsor believe they might, at this point, be able to tighten the specifications to the same level for both drug substance and starting material and do not believe it necessary to define these impurities for the drug substance, provided they adequately define these impurities in the starting material.

The sponsor assured the Agency that they will require that all new suppliers comply with the established specifications and that they would not accept new starting material that did not fit the established specifications. The sponsor also agreed not to change suppliers without first consulting the Agency and without first qualifying the new vendor.

The estimated upper end of the clinical dose range (3000 mg/day) would be considered a megadose and would therefore fall under the high dose specifications in the ICH Q3A guideline. The thresholds for impurity characterization and qualification for a much higher than normal dose would be lower than those seen with regular doses.

If the sponsor does not believe the level of metals significantly increases from the starting material to the drug substance and that, provided they define the impurities in the starting material, they should not have to redefine them for the drug substance, they should provide such an argument in the NDA. They should provide batch analysis to support this and tighten the drug substance specifications to be the same as those for the starting material.

Discussion Point #7: Identity test for ——

The Agency noted the lack of an identity test for the — in the drug substance and recommended that the sponsor add this test to the specifications for the drug substance. The sponsor has already included this test for the drug product and agreed to also do so for the drug substance.

Discussion Point #8: References

The Agency noted that since we are a US regulatory agency, the sponsor should refer to the USP/NF for the specifications. The Agency recommended that the sponsor refer only to USP/NF, as a reference to both (EP and USP) might be misinterpreted as either/or.

Discussion Point #8: Environmental Assessment

Since the source of this product is natural and it is not a newly synthesized chemical, the Agency believes the guidance on Environmental Assessment applies to this application and recommended that the sponsor apply for a waiver.

Discussion Point #9: Stability-indicating test for lanthanum

The sponsor believed lanthanum unlikely to degrade at temperatures [ ] and therefore did not believe a stability-indicating test necessary for lanthanum. The Agency was concerned, from a safety and efficacy perspective, with what might happen if the tablets are subjected to extreme conditions (i.e., temperature). The Agency was concerned with how the lanthanum might be influenced by the other components in the product under extreme conditions, noting that the tablet excipients might change the specifications for the lanthanum carbonate. [ ] analysis would not be adequate tests for this as they are not considered stability indicating. The sponsor noted that they did perform [ ] to quantitatively measure all of the other metals. The sponsor believes that only under very extreme circumstances would this become something other than lanthanum and does not believe a stability-indicating test necessary for the lanthanum. The sponsor agreed to provide their justification for this in the NDA.

Discussion Point #10: Moisture

The sponsor currently monitors for moisture in the stability program for the drug substance and agreed to also do so for the drug product (tablet).

Discussion Point #11: Hardness

The sponsor intends to include a specification for hardness of the chewable tablet in the future, so as to ensure that the tablet is not too hard to chew.

Discussion Point #12: Stability protocol

The sponsor agreed to put a notation in the stability protocol of the number of samples of each bottle and tablet size to be put on stability.

Discussion Point #13: Solubility profiles

The sponsor intends to provide solubility profiles for the anhydrous material and its hydrates in the NDA.

Discussion Pont #14: Tablet marking

The marketed tablet, but not the clinical preparations, will have identifying marking. There will be a break mark in the tablet for both the clinical and marketed formulations. If the labeling allows [ ] tablet, dissolution testing would also be required for the [ ] tablet or any suitable alternative that would detect differences in pK. An

acceptable alternative might be to carefully monitor the regimens in the clinical studies that use the — tablet doses to ensure that phosphate control is demonstrated.

The medical reviewers might request that any dosing regimen the sponsor proposes to include in labeling be tested (the regimen) in the clinical studies, and that the sponsor tease out the results from the different regimens to determine whether they are efficacious before allowing the regimen to appear in labeling. The Agency also suggested that the sponsor test whether the tablet can be broken in ways other than 50-50 — and retain efficacy. It will be a clinical decision as to whether the sponsor needs to justify each dose regimen advocated in the labeling.

Signature, Minutes Preparer: _____Colleen LoCicero

Concurrence, Meeting Chair: _____Charles Hoiberg, Ph.D.

cc: orig IND 55054
HFD-110
HFD-110/Locicero
HFD-110/Roeder
HFD-110/Sbenton

Drafted: 6/15/99 finaled: 6/23/99

rd:
Hoiberg
Srinivasachar 6/18/99
Piechocki 6/18/99
Marroum 6/21/99