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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-468

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

Division of Pharmaceutical Evaluation I

NDA:	**21-468**
SUBMISSIONS DATES:	Resubmission dated January 26, 2004 Orig Amed N000(BB) submitted on May 6, 2004 Orig Amed N000(BB) submitted on May 28, 2004 Orig Amed N 000(BB) submitted on July 8, 2004 Orig Amed N 000(BZ) submitted on July 23, 2004
BRAND NAME:	FOSRENOL™
GENERIC NAME:	Lanthanum Carbonate Hydrate
STRENGTHS	250 & 500 mg Chewable Tablets
SPONSOR:	Shire Pharmaceutical Development, Inc.
PK REVIEWER:	Angelica Dorantes, Ph.D.
TEAM LEADER:	Patrick Marroum, Ph.D.
OCPB DIVISION:	Pharmaceutical Evaluation I
ORM DIVISION:	Cardio-Renal Drug Products
SUBBMISSION TYPE:	Resubmission of a New Molecular Entity
INDICATION:	t

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III. SUBMISSION:

Reference is made to the FDA's approvable letter for NDA 21-468 dated February 28, 2003 for Fosrenol (lanthanum carbonate) 250 mg and 500 mg Chewable Tablets. The submission dated January 26, 2004 provides Shire's resubmission for the above NDA. The sponsor has included their response to the issues raised in the approvable letter and they included additional CMC, human pharmacodynamic/ bioavailability, clinical data, and revised labeling.

Lanthanum carbonate hydrate is an inorganic salt that acts in the lumen of the gut by binding to dietary phosphorus released from the food during digestion. Fosrenol is indicated for [ ] The recommended initial total daily dose of lanthanum in adults is 750 mg. In clinical studies, most patients required a total daily dose between 1500 and 3000 mg of lanthanum carbonate to reduce plasma phosphate levels to less than 6.0 mg/dl.

IV. RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPEI) has reviewed the overall information provided in the resubmission to NDA 21-468 for Fosrenol (Lanthanum Carbonate) dated January 26, 2004 and subsequent amendments dated May 6, May 28, and July 8, 2004. OCPB has the following comments:

Reviewer Comments:

A. Clinical Pharmacology

Mass-Balance:

Study SPD405-117 showed that following intravenous administration of lanthanum chloride to healthy male subjects, less than 10% of the total dose of lanthanum was recovered in 7 days (i.e., 1.75±1.08% in urine and 5.55±5.28% in feces). Note that the amount of lanthanum excreted in feces after oral administration was not evaluated in this study, Therefore, OCPB's concern for mass-balance information for lanthanum carbonate following oral administration was not fully addressed by the sponsor.

Bioavailability: Similar to previous studies, study SPD405-117 showed that the absorption of lanthanum following oral administration was very low with an absolute bioavailability of 0.00127±0.0008%. However, note that lanthanum's bioavailability is not a useful/relevant parameter, because lanthanum systemic levels are not predictive of Fosrenol's absorption and total body exposure. An exposure-response relationship with respect to lanthanum plasma levels and its efficacy & safety does not exist. The plasma data collected in several clinical pharmacology and clinical studies do not provide adequate information regarding lanthanum's total body exposure.

Tissue Disposition: Animal studies have demonstrated that bone, liver and GI are the main sites for lanthanum's deposition. For humans, bone was selected as the tissue to study bone deposition. The bone biopsy samples from studies LAM-IV-301, LAM-IV-303, and LAM-IV-107 had provided evidence that there is accumulation of lanthanum in the bone. The bone samples showed that lanthanum

concentrations increased with time with an estimated mean bone half-life of 3.4 years, reaching steady state in about 17 years.

The sponsor's "worse case" prediction (assuming a bioavailability of 0.00294% and no clearance out of bone) for the lanthanum concentrations in bone after treatment for 15 years was 13,900 to 46,000 mcg/kg. These concentrations exceed those measured in long-term animal studies. The sponsor claimed that these concentrations are below the levels measured in multiple dose IV toxicity studies (mean 54,483 mcg/kg) in which bone histology was reported to be normal. However, it should be noted that lanthanum bone-toxicity was identified by Dr. Williams, the Medical Reviewer of DCRDP and an external consultant who reviewed the slides of rats with normal renal function given lanthanum has confirmed the opinion of the medical reviewer that there is bone damage.

Overall, there is very limited data on the concentrations of lanthanum in bone after long time exposure, thus, there are concerns regarding the actual deposition, accumulation, and toxicity of lanthanum in bone. Therefore, in view of the fact that lanthanum is accumulating in the body and more specifically in the bone, the long term safety profile of lanthanum is at best uncertain.

B.

1. [

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2. [

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3. [

C. **Dissolution:**

Regarding the provided dissolution data using USP Apparatus 2 [ ], OCPB has the following specific comments:

1. ***USP Apparatus 2:***

With respect to the proposed — dissolution testing submitted in the resubmission dated January 26, 2003, OCPB considered that the sponsor's proposal of two consecutive tests for the same product was not appropriate. Therefore, on March 10, 2004, OCPB informed the sponsor that their resubmission's proposal of using a — **dissolution test on whole tablets** ([ ] using Apparatus 2 at — rpm; Specification of Q= —, in 45 minutes) followed by a — **dissolution test on crushed tablets** [ ] using Apparatus 2 at — rpm; Specification of Q= — in 45 minutes), if any tablet fails to meet the Q value requirement for — for the evaluation of Fosrenol tablets was not acceptable.

Recommendation: OCPB considers that the already validated whole-tablet method (USP Apparatus 2, [ ], and — rpm) is an appropriate method to be used for the dissolution testing of the 250 and 500 mg "Current Formulation" tablets. With respect to the dissolution specification, the overall data for the "Current Formulation" showed that more than — is dissolved in 45 minutes (except Lot 2D6710; 500 mg). Thus, a dissolution specification of Q= — at 45 minutes would be more appropriate for the stability and lot release testing. Therefore, it is recommended that the sponsor consider the option of using the above method and specification for the testing of the 250 and 500 mg "Current Formulation" Fosrenol tablets.

2. [

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With respect to the proposed target specification of [ ] in [ ] this value appears to be appropriate. However, taking into account that the currently proposed whole tablet [ ] test has not been accepted, OCPB cannot comment on the acceptability of the proposed specification at this time

D. **Biowaivers:**

1. In this submission the sponsor requested **1)** a biowaiver for the 500 mg tablets using the current formulation [redacted]

2. To support the biowaiver request for the 500 mg current formulation the sponsor provided: **1)** formulation data showing that the 250 mg and the 500 mg tablets are compositionally proportional, **2)** clinical data showing that the 500 mg dose is within the clinical range, and **3)** comparative dissolution data showing that the dissolution profiles of the 500 mg vs. the 250 mg current formulations are similar at the following testing conditions: whole tablets-Apparatus 2, [redacted] rpm and Apparatus 2, [redacted] rpm. Based on the review of the overall information, OCPB considers that the sponsor has provided appropriate supportive data and their biowaiver request for the 500 mg current formulation is granted.

3. [redacted]

E. **Labeling:** (A copy of the proposed labeling is included in Attachment 1)

1. The following changes are recommended for the "**Pharmacokinetics**" part of the "**CLINICAL PHARMACOLOGY"** section of the proposed labeling:

Pharmacokinetics:

Absorption:

[redacted]

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

]. No information was provided regarding the mass balance of lanthanum in humans after oral administration. However, mass balance data showed that in rats, the mean total recovery of an IV dose of lanthanum over a 42 days period was 76.4% of the administered dose. In rats and dogs, the mean recovery of lanthanum after an oral dose was about 99% and 94%, respectively. Animal studies indicate that biliary excretion is the predominant route of elimination for circulating lanthanum.

Animal data indicate that following chronic administration, lanthanum carbonate was absorbed and deposited in most tissues from which it is eliminated very slowly. Lanthanum concentrations in tissues were several orders of magnitude higher than plasma concentrations. Animal studies have demonstrated that bone, liver and GI are the main sites for lanthanum's deposition. For humans, bone was selected as the tissue to study bone deposition. The bone biopsy samples from clinical studies provided evidence that there is accumulation of lanthanum in the bone. The bone samples showed that lanthanum concentrations increased with time with an estimated mean bone half-life of 3.4 years, reaching steady state in about 17 years.

Metabolism:
Lanthanum is not metabolized and is not a substrate of CYP450. In vitro metabolic inhibition studies showed that lanthanum at concentrations of 10 and 40 mcg/ml did not have relevant inhibitory effects on any of the CYP450 isoenzymes tested (1A2, 2C9/10, 2C19, 2D6, & 3A4/5).

Special Populations:
Renal Dysfunction: A study evaluating the pharmacokinetic of lanthanum in dialysis patients showed that plasma levels of lanthanum in patients with compromised renal function were about 3 times higher than those in control subjects. The kidneys excreted negligible amounts of lanthanum with minimal lanthanum in the diasylate. Thus, patients with compromised renal function may accumulate higher concentrations of lanthanum in tissues.

Lanthanum trough levels were evaluated in ESRD patients receiving hemodialysis during the clinical studies. The overall results from these studies showed that during chronic administration for up to 1 year, lanthanum mean concentrations were about 0.6 ng/ml, there was minimal increase in plasma lanthanum concentration with dose, and there was no accumulation with time (up to 52 weeks). Lanthanum was rapidly cleared from plasma following discontinuation of therapy.

In Vitro- Drug Interactions:
Gastric Fluid: The potential for a physico-chemical interaction (precipitation) between lanthanum and six commonly used medications (warfarin, digoxin, furosemide, phenytoin, metoprolol, & enalapril) at the stomach (simulated gastric fluid, SGF) was investigated. The overall results showed that the probability of having precipitation of insoluble complexes of X-drug-lanthanum in the stomach is low.

In Vivo- Drug Interactions:
Lanthanum carbonate is highly bound to plasma proteins (>99%) and is not a substrate or an inhibitor of CYP450 enzymes. Thus, the possibility that Fosrenol will precipitate any interaction by the perturbation of plasma protein binding or cytochrome P450 mediated metabolism, two very common sources of adverse drug-drug interaction, is low.

The interaction of lanthanum with the following concomitant medications was investigated.

Citrates: The co-administration of citrate containing products (orange juice & Effercitrate tablets) did not have any effect on the pharmacokinetics of a single 1000 mg oral dose of lanthanum carbonate.
Digoxin: The co-administration of multiple 1000-mg oral doses of lanthanum carbonate did not have any effect on the pharmacokinetics associated with a single 0.5-mg oral dose of digoxin.
Metoprolol: The co-administration of multiple 1000-mg oral doses of lanthanum carbonate did not have any effect on the pharmacokinetics associated with a single 100-mg oral dose of metoprolol.
Warfarin: The co-administration of multiple 1000-mg oral doses of lanthanum carbonate did not have any effect on R & S-warfarin's pharmacokinetics associated with a single 10-mg oral dose of warfarin. The pharmacodynamic interaction between these drugs (bleeding time or prothrombin time) was not evaluated.

2. The following changes are recommended for the "**PRECAUTIONS; Drug Interactions**" section of the proposed labeling:

   Drug Interactions:
   Studies in healthy subjects have shown that lanthanum does not adversely affect the pharmacokinetics of warfarin, digoxin or metoprolol. The pharmacokinetics of lanthanum are unaffected by co-administration of citrate-containing compounds (see **CLINICAL PHARMACOLOGY: In Vitro dug Interactions** and **In Vivo dug Interactions**).

   Within the ESRD clinical setting, although Fosrenol may have a low potential for clinical interactions, there is a theoretical possibility that co-administration of Fosrenol with antibiotics, gabapentin, cardiac glycosides, anti-histamines and levothyroxin might result in changes in pharmacokinetic profiles. It would be prudent to exercise caution when considering such combinations.

3. For the "**DOSAGE AND ADMINISTRATION**" section of the proposed labeling, it is recommended that the sponsor include an appropriate statement indicating that intact tablets should not be swallowed and the tablets should be chewed for an appropriate length of time (i.e., 1-2 minutes), in order to ensure that the tablets are properly crushed before they are swallowed.

Please convey the Recommendation and Reviewer comments as appropriate to the sponsor.

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation I, OCPB
Office of Clinical Pharmacology and Biopharmaceutics

/s/

FT Signed by Patrick Marroum, Ph.D.
cc: Resubmission-NDA 21-468, HFD-110 (Raman), HFD-860 (Dorantes, Metha, Rahman).

ATTACHMENTS

ATTACHMENT 1

Includes:

Deposition of Lanthanum in Bone

BONE DISTRIBUTION

Background:

Pharmacokinetics: Lanthanum is very poorly absorbed after oral administration of lanthanum carbonate. Bioavailability in man is variable, with a mean of 0.00089%. Only a small proportion of the absorbed dose is excreted via the kidneys; approximately 2% of the absorbed lanthanum is excreted in the urine (as measured after intravenous dosing). Excretion via the bile has been shown to be an important route of elimination of absorbed lanthanum in rats, together with direct secretion across the gut wall. In man, about 5.5% of fecal elimination of lanthanum was obtained after intravenous dosing of lanthanum chloride.

Total systemic clearance of lanthanum, determined after intravenous dosing, was low at 54.7 ± 15.6 ml/min (mean ± SD). As renal clearance only accounted for about 2% of this total, the majority of this systemic clearance probably reflects clearance into tissues as well as non-renal elimination.

Clinical Data

Bone Distribution: Bone was selected as the marker tissue to investigate the tissue deposition of lanthanum in patients. Use of bone as the primary tissue to investigate lanthanum deposition, also provided the opportunity for histologic examination to check for possible effects on mineralization. Bone has a particular significance for ESRD patients due to the prevalence of osteodystrophy, and history of aluminum bone toxicity, in this population.

Source and Evaluation of Biopsies: Human bone biopsies were collected from 3 long-term clinical studies, LAM-IV-301, LAM-IV-303 and LAM-IV-307.

Study LAM-IV-307: This was a 24 month open label, randomized, multicenter, Phase 3, comparator controlled, parallel group study of the long-term safety of lanthanum carbonate for controlling hyperphosphatemia in chronic renal failure patients undergoing hemodialysis three times per week. Five hundred patients per group with a 1:1 allocation ratio of lanthanum carbonate vs. standard therapy were to be enrolled. The study consisted of three phases: a screening and one-to three-week washout phase (Part 1), followed by a six-week dose-titration phase (Part 2), and finally, a long-term maintenance phase (Part 3), for a total of 24 months of study participation. The primary objective of the study was to evaluate long-term safety of lanthanum carbonate in chronic renal failure patients with hyperphosphatemia on hemodialysis. Safety was evaluated by monitoring biochemical and hematological parameters, adverse events (AEs), vital signs, physical examinations, and cognitive function assessments.

Eligible patients were randomized in a 1:1 ratio to receive either lanthanum carbonate or their pre-study standard phosphate binder. Patients randomized to the lanthanum arm received a starting dose of 750mg or 1500mg lanthanum daily. Doses were titrated as necessary up to a maximum of 3000 mg/day, and were adjusted based on the results of the phosphate levels taken at the first dialysis session of the week. Patients randomized to standard therapy had their dose of phosphate binder titrated according to the drug's label and current clinical practice. On completion of titration, all patients received their dose of phosphate binder up to 24 months of treatment.

This protocol also included a subgroup of 100 patients randomized per treatment group to receive a baseline bone biopsy followed by a second biopsy after either 1 or 2 years of study treatment (n=29 for each) to measure differences in bone mineralization between patients treated with lanthanum carbonate

and standard therapy. The end-points of the study focus on bone mineralization, in particular osteoid seam thickness and mineralization lag time.

A total of 209 patients were enrolled in the bone biopsy sub-study. Twelve patients (12/209; 5.7%) were terminated prior to randomization. The remaining 197 patients were randomized to one of the two treatments. Of those randomized, 100 patients (100/209; 47.8%) were randomized to receive lanthanum carbonate, and 97 patients (97/209; 46.4%) were randomized to standard therapy.

All bone biopsy samples were assessed for **lanthanum content** and histomorphometry.

Study LAM-IV-301: This study was a prospective multi-centre, randomized open-label 6 month comparative design, lanthanum vs. calcium carbonate, followed by 30 months open label extension with all patients continuing to receive lanthanum carbonate, conducted primarily in Europe. Calcium carbonate was selected as the comparator as it is the most widely used calcium-based phosphate binder in Europe. The study comprised washout, titration and maintenance phases and additional extension phases on lanthanum carbonate. Doses of lanthanum carbonate were from 750mg to 3000mg daily.

The primary objective of the extension study was to assess the safety and tolerability of lanthanum treatment following longer-term (2-year) treatment. In total, 1013 hemodialysis patients were screened for study LAM-IV-301 and 805 were randomized 2:1 to lanthanum carbonate or calcium carbonate. One hundred sixty one of these patients entered the extension (Part 5) phase of the study.

An amendment to this protocol was subsequently submitted and approved for the collection of a single bone biopsy from consenting patients either ongoing in a current lanthanum clinical trial (LAM-IV-309) or patients who have previously participated in study LAM-IV-301.

Biopsy samples were assessed for **lanthanum content** and histomorphometry.

Study LAM-IV-303: This study was a prospective multi-centre, randomized, comparator controlled, parallel group study involving patients initiated onto dialysis within 12 weeks of recruitment to the study. The study comprised washout, titration and maintenance phases over a one-year period. One hundred patients were randomized in a 1:1 ratio of lanthanum carbonate to calcium carbonate.

The primary objective of this study was to investigate the effect of lanthanum compared with calcium carbonate on renal bone disease. Secondary objectives were to investigate the concentration of lanthanum and calcium within bone, and to evaluate long-term safety and tolerability of lanthanum in this patient population. The starting dose of phosphate binder was at the discretion of the investigator and doses of up to 3750mg lanthanum and 9000mg calcium per day were allowed. The investigators were not set a target serum phosphate level in this study since assessment of efficacy was not a primary objective. As a result, the investigators titrated patients to a dose that achieved a level of control that they considered satisfactory. The dose of lanthanum carbonate at Week 52 ranged from 500 to 3750mg (median 1250mg).

The study was conducted at 18 centers in 12 countries: Belgium (1), Czech Republic (1), France (1), Germany (1), Italy (1), Macedonia (1), Poland (1), Portugal (1), South Africa (2), Spain (1), United

Kingdom (3), Yugoslavia (4). A total of 98 patients entered the study and received at least one dose of lanthanum or calcium carbonate (49 in each group).

Following completion of this study a protocol amendment was submitted to local IRBs in order to obtain approval to allow collection of a 3rd bone biopsy from patients who participated in the original treatment phase and have subsequently been off treatment for a period of 18 months to 2 years. The objective of this amendment is to evaluate the long-term effect of lanthanum on cellular activity and its kinetics in bone. Histomorphometry and bulk **lanthanum content** has been analyzed for bone samples collected from this study.

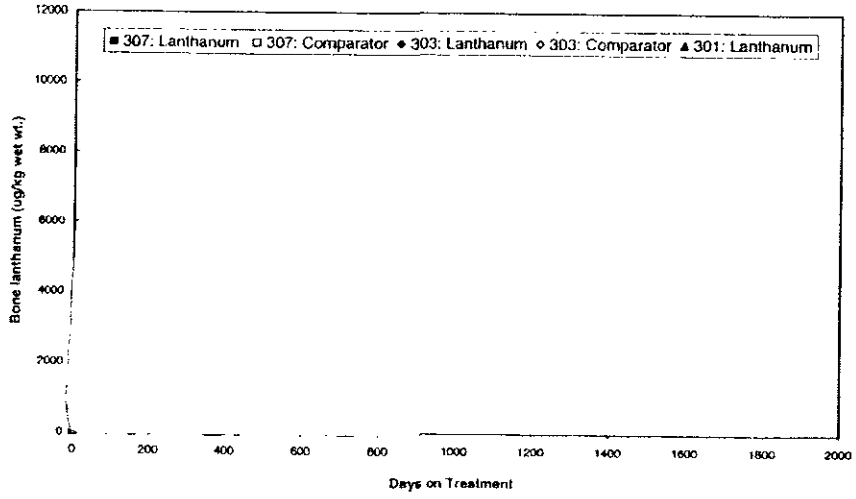
Bone Lanthanum Results

Note that all graphical presentations used wet weight concentrations and, where average values are shown, the median and range have been used.

Patients Receiving Comparator Treatment: Individual bone concentrations varied considerably among control patients within a range of — mcg/kg, which overlapped with the lanthanum-treated population. A trend towards slowly increasing bone lanthanum concentrations with time on comparator treatment was evident from the averaged data, the median rising 3-fold from a baseline of 53 mc/kg to 176 mcg/kg at 24 months.

Patients Receiving Lanthanum Carbonate: The results are shown graphically in Figure 1. Note that the longest-term group of patients from LAM-IV-301 had only one biopsy, therefore comparative biopsies from earlier time-points are not available.

FIGURE 1. Scatter Plot of Bone Lanthanum Concentrations in Patients Taking Lanthanum Carbonate or Standard Therapy



In patients treated with lanthanum carbonate, the median bone lanthanum concentration increased during the first 12 months of lanthanum carbonate treatment up to a median of 1291 pg/kg (range — — pg/kg). Median and range concentrations at 18 and 24 months were similar to 12 months, but at 54 months, the median was approximately 3 fold higher (median 4245 mcg/kg). There was also an increase in the overall range to — mcg/kg at 54 months compared to the shorter treatment periods.

Bone lanthanum results for the individual study populations receiving lanthanum carbonate (LAM-IV-303; LAM-IV-307; and LAM-IV-301) are summarized in Table 1 and shown graphically for each consecutive 6-month exposure period in Figure 2.

TABLE 1

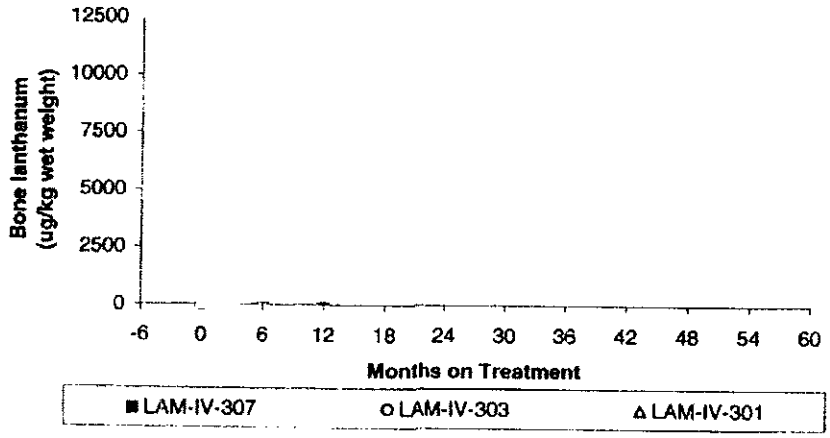
BONE LANTHANUM AMOUNT (WET- MCG/KG) BY TIME SINCE TREATMENT STARTED

Time (Months)	Study LAMIV 307	Study LAMIV 303	Study LAMIV 301	ALL Patients
Baseline	99 ± 174 (n=78)	40 ± 22 (n=43)	-	78 ± 143 (n=121)
6	803 ± 675 (n=2)	1435 ± 893 (n=11)	-	1338 ± 872 (n=13)
12	1494 ± 1106 (n=28)	2425 ± 1438 (n=25)	-	1692 ± 1280 (n=51)
18	1494 ± 1106 (n=13)	-	-	1494 ± 1106 (n=13)
24	1869 ± 1243 (n=13)	-	-	1969 ± 1243 (n=13)
30	571* (n=1)	-	-	571 (n=1)
48	3152 (n=1)	-	4896 (n=1)	4024 ± 1233 (n=2)
54	-	-	5897± 3120 (n=11)	5897± 3120 (n=11)
60	-	-	6345 (n=1)	6345 (n=1)

BONE LANTHANUM AMOUNT (DRY- MCG/KG) BY TIME SINCE TREATMENT STARTED

Time (Months)	Study LAMIV 307	Study LAMIV 303	Study LAMIV 301	ALL Patients
Baseline	128 ± 252 (n=78)	66 ± 49 (n=43)	-	106 ± 206 (n=121)
6	1158 ±1069 (n=2)	2140 ±1527 (n=11)	-	1989 ± 1475 (n=13)
12	1461 ± 1030 (n=28)	3180 ± 1713 (n=25)	-	2236 ± 1616 (n=51)
18	2268 ± 1688 (n=13)	-	-	2268 ± 1688 (n=13)
24	2724 ± 1745 (n=13)	-	-	2724 ± 1745 (n=13)
30	722* (n=1)	-	-	722 (n=1)
48	4109 (n=1)	-	9088 (n=1)	6599 ± 3521 (n=2)
54	-	-	8681± 4750 (n=11)	8681± 4750 (n=11)
60	-	-	8321 (n=1)	8321 (n=1)

FIGURE 2. Bone Lanthanum Wet Weight Concentrations (Median, Min, Max) All 'On-Treatment' Biopsies - By Study; Time Categories (±1- 3 Months)



The absence of significant overlap in the exposure periods between studies makes it difficult to rule out an influence of 'study' or geographical region on the results, particularly for the 48+ month exposure patients who, with the exception of a single patient, were all from Study LAM-IV-301, carried out in Europe. Patients on this study had the highest bone lanthanum concentrations, and the 3 patients with

the highest overall values — pg/kg) were among a group of 4 originating from the same centre in Germany.

Bone Deposition Projections

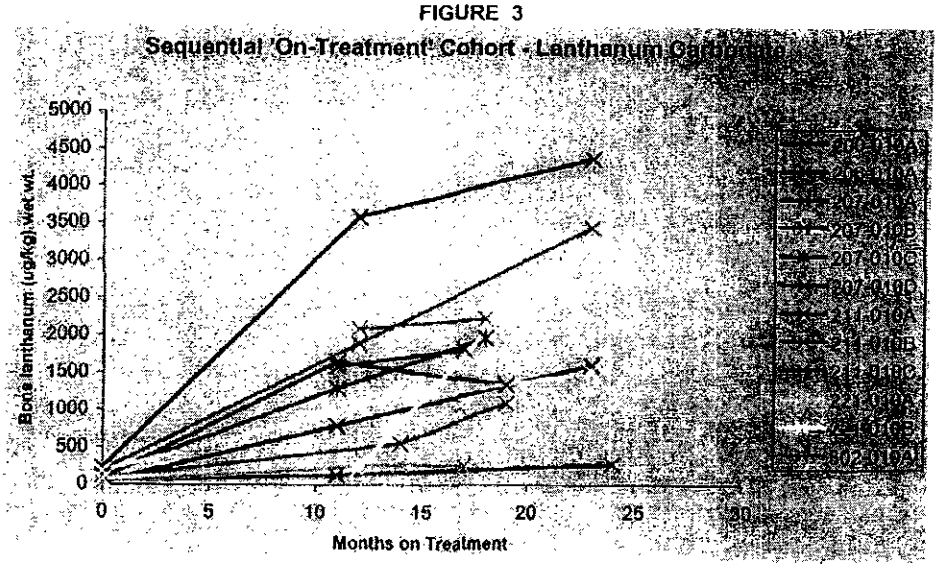
The sponsor performed the following projections of the bone lanthanum concentrations that might occur with long-term use. They used measured values for systemic bioavailability in man and conservative assumptions about rates of bone deposition and clearance.

Half-Life and Time to Steady State in Bone: A half-life for lanthanum in bone was calculated using the bone lanthanum data obtained from the sequential 'off-dose' cohort in Study LAM-IV-303, assuming the elimination observed between the 'on-dose' and 'off-dose' biopsies was linear over time. Steady state was assumed to occur after 5 halt lives.

The bone half-life calculated as 0.693/slope of the concentration-time curve between the 'on-dose' and 'off-dose' biopsies was 1.94 years based on the change in median bone concentrations, and 3.37 years based on the change in mean bone concentrations. Therefore, steady state would be reached in 10 years and 17 years, respectively.

"On Treatment cohort" -Patients Receiving Lanthanum Carbonate: The individual results are shown graphically in Figure 3.

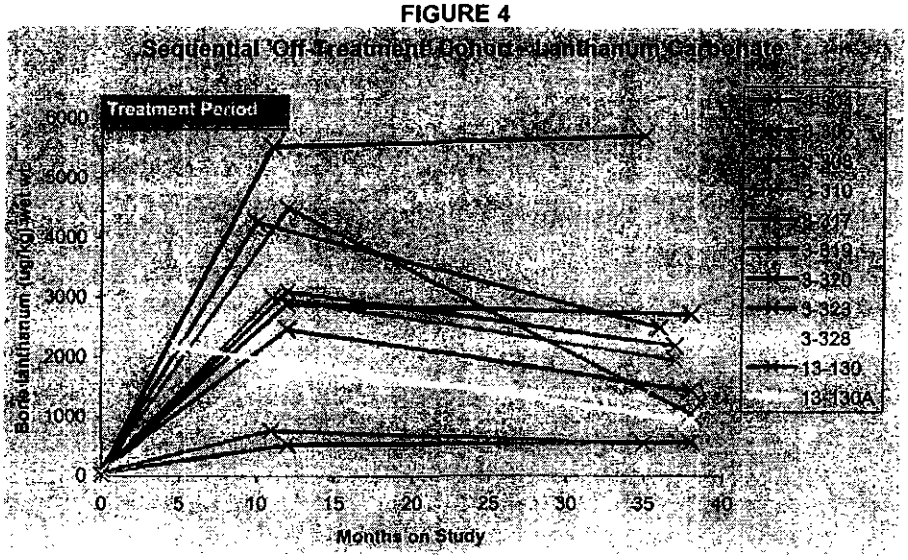
FIGURE 3



Of the 12 lanthanum carbonate patients providing sequential biopsies, the lanthanum concentration was approximately the same (i.e. <20% difference) in 4 patients, higher (i.e. >20% increase) in 7 patients, and lower (i.e. >20% reduction) in 1 patient in the 2nd compared to the 1st 'on-treatment' biopsy (taken after 17 to 24 months, and 11 to 14 months of treatment, respectively). The findings indicate bone lanthanum concentrations increase with time on lanthanum carbonate treatment. In sequential biopsy cohort, the absence of an increase in 5 of 12 patients between the first second 'on-treatment' biopsies suggests some elimination from bone was occurring. This is supported by the sequential 'off-treatment' cohort.

Sequential 'Off-Treatment' Cohort: The results for the cohort of patients from Study LAM-IV-303 who provided sequential biopsies at baseline, at the end of 12 months of treatment with lanthanum carbonate, and approximately 24 months after completing the treatment phase, are illustrated in Figure 4.

FIGURE 4



Of the 11 lanthanum patients providing sequential biopsies, none had higher (i.e. >20% higher), 3 had the same (i.e. 20% difference) and 8 had lower (i.e. >20% lower) bone lanthanum concentrations in the 'off-treatment' biopsy (taken 24 to 26 months after stopping treatment), compared to the 'on-treatment' biopsy (taken after 5 to 12 months of treatment). The median concentration after 24 to 26 months off-treatment was 1441 pg/kg (range — mcg/kg), approximately half that at the end of the 10 to 12 month treatment phase (2946 mcg/kg, range — mcg/kg). This indicates that lanthanum is slowly cleared from bone, allowing tentative estimation of the elimination half-life and time to steady state.

Worst-case' maximum concentration

Assumptions:

1. All absorbed lanthanum accumulates in bone (i.e., using the average systemic bioavailability measured in man, 0.00089% of an oral dose is absorbed and assumed to transfer to bone. Using the highest bioavailability measured in any patient during Phase I trials, 0.00294% of the dose is assumed to transfer to bone.
2. No lanthanum is eliminated from bone
3. Lanthanum is evenly distributed in the skeleton, which accounts for 15% of bodyweight, i.e. 10.5kg of bone per 70kg man.

$$\text{Rate of input into bone} = F \bullet \text{Dose}/\tau \qquad = \frac{0.0000089 \bullet 1000000 \mu g}{8hr}$$

Where F is the systemic bioavailability, τ is the dose interval and the dose is 1 g elemental lanthanum t.i.d.

The transfer rate of lanthanum into bone is thus 1.1125 mcg/hr using the average bioavailability, and 3.675 mcg/hr using the highest measured bioavailability. After 15 years continuous exposure, these accumulation rates would result in average and maximum bone lanthanum concentrations of 13,900 mcg/kg and 46000 mcg/kg, respectively.

Realistic maximum concentration

Assumptions:

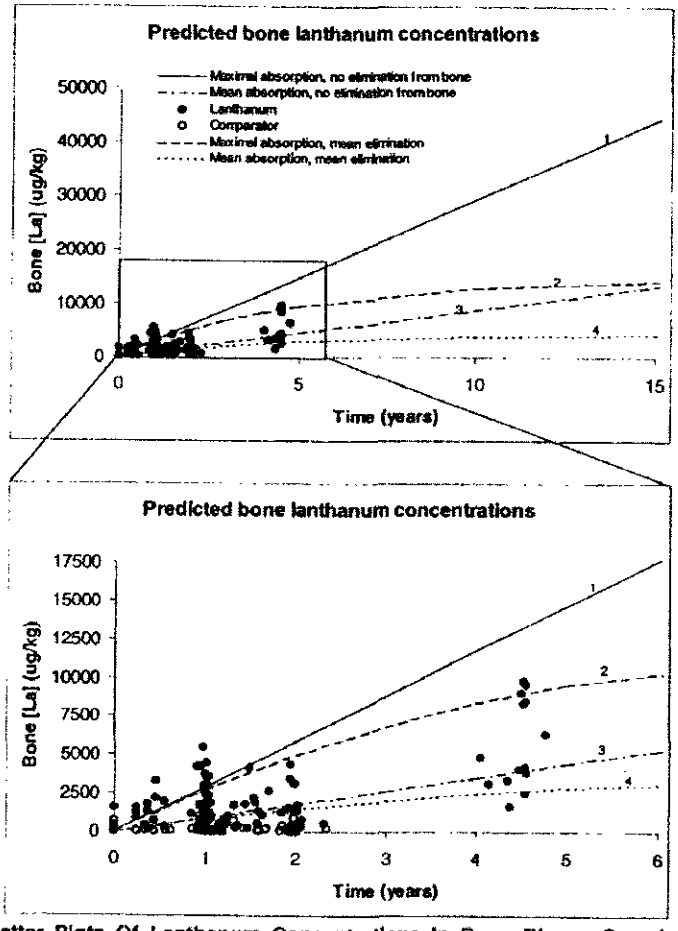
1. All absorbed lanthanum accumulates in bone.
2. Elimination from bone has a 1.94 or 3.37 year half-life (the median and mean estimates from the sequential 'off-treatment' cohort patients in the biopsy program (Study LAM-IV-303).
3. Lanthanum is evenly distributed in the skeleton, which accounts for 15% of bodyweight, i.e. 10.5kg of bone per 70kg man.

$$\text{Maximum amount in bone after Nth dose} = Dose\,to\,bone \bullet \left[\frac{1-e^{-Nk\tau}}{1-e^{-k\tau}}\right]$$

Where Dose to bone = F x Dose (0.0000294 x 1 000000mcg)
N = no. of doses (16425; 15yrs x 365 days x 3 times per day)
k = elimination rate constant from bone (4.081x10-5hr-1 for 1.94 year half-life)
τ = dosing interval (8 hr)

Based on these data, accumulation in bone after 15 years of continuous exposure would be 8,540 mcg/kg (1.94 year half-life) or 14,240 mcg/kg (3.37 year half-life). The 'worst' and 'realistic' case projections are plotted in Figure 5, with the actual bone lanthanum Concentrations overlaid.

FIGURE 5



Scatter Plots Of Lanthanum Concentrations In Bone Biopsy Samples Together With Predicted Bone Levels (Based On Assumed Input And Clearance Rates)

1. Maximal absorption, no clearance; 2. Maximal absorption, 3.37yr half-life ; 3. Mean absorption, no clearance; 4. Mean absorption, 3.37yr half-life

Sponsor's Conclusions

Measurable lanthanum was found in the bone of all dialysis patients receiving the comparator treatment, indicating that this patient population is normally exposed systemically to low levels of lanthanum. This may arise from lanthanum being present in the diet or, more likely, it occurs during disease management due to environmental exposure.

Daily treatment with lanthanum carbonate resulted in rising bone lanthanum concentrations over time. Sequential biopsy samples obtained from patients during, and two years after completing treatment with lanthanum carbonate provided evidence that lanthanum is cleared from bone, with an estimated mean half-life and time to steady state of 3.4 years and 17 years, respectively.

Predictions of bone lanthanum concentrations after treatment for 15 years, assuming all lanthanum absorbed is taken up into bone and is eliminated at the average calculated half-life, ranged between 8,540 and 14,240 mcg/kg. A 'worst case' prediction of 13,900 to 46,000 mcg/kg was obtained assuming no clearance out of bone. These concentrations exceed those measured in long-term animal studies.

Reviewer Comments:

1. For the estimation of the amount of lanthanum deposited in bone, the average and highest bioavailability values were used. OCPB does not agree completely with this approach because the sponsor is assuming that plasma is the central compartment where most of the drug is present. However, this may not be the case for lanthanum, because if lanthanum is rapidly up-taken by other tissue (s), the levels of lanthanum in plasma will be very low and the rate limiting step would be the equilibration from the other tissue (i.e., bone) to plasma. Thus bone may act as a depot compartment with a very slow equilibration to plasma (i.e., flip-flop model) giving a misleading underestimation of lanthanum's bioavailability.

2. It should be noted that the lanthanum data collected in the bone biopsy samples showed that lanthanum concentrations increased with time, but these concentrations are within the range of concentrations predicted by the sponsor using the different models (see Figure 4).

3. Note that pharmacokinetic data are always reported in mean values (arithmetic or geometric) not in median values. Thus, based on the estimated half-life for bone of 3.4 years, lanthanum concentration in bone will increase until the steady state is reached in about 17 years.

4. The analytical site, method, and validation data were not included, thus, based on the BE study past experience, the validity of the bone data may be questionable.

5. The sponsor's "worse case" prediction (assuming no clearance out of bone) for the lanthanum concentrations in bone after treatment for 15 years was 13,900 to 46,000 mcg/kg. These concentrations exceed those measured in long-term animal studies. The sponsor claimed that these concentrations are below the levels measured in multiple dose IV toxicity studies (mean 54,483 mcg/kg) in which bone histology was reported to be normal.

6. It should be noted that the Medical Officer of DCRDP, Dr. Williams, reported bone toxicity in rats. An external consultant who reviewed the slides of rats with normal renal function given lanthanum confirmed the opinion of the medical reviewer, that there is bone damage.

   Specifically the consultant identified 2 significant pathological lesions in these normal rats:

- The subperiosteal surface is highly irregular suggesting increased bone resorption and fibrous replacement but few osteoclasts are present.
- There is slight increase of osteoid seams on trabecular surfaces"

In uremic rats given lanthnaum the consultant found 3 significant lesions, two of these were also seen in normal rats. Specifically the 3 significant lesions seen in uremic rats given lanthanum are:

- "Highly irregular subperiosteal surface with marked increase in osteoclasts and osteoblasts with reparative fibroplasias
- Increased thickness of growth plate
- Striking increase in thickness of osteoid seams on endosteal and trabecular surfaces (Osteomalacia). This probably represents a failure of mineralization rather than demineralization. Similar to that reported in experimental uremic rats fed a low phosphorous diet ".

7. Overall, there is very limited data of concentrations of lanthanum in bone after long time exposure, thus OCPB has concerns regarding the actual deposition, accumulation, and toxicity of lanthanum in bone. Therefore, cannot be ruled out that lanthanum is widespread in the whole body and its retention in some tissues presents a serious safety concern.

ATTACHMENT 2

Includes:

Dissolution Information and Biowaiver Request

DISSOLUTION INFORMATION FOR LANTHANUM CARBONATE TABLETS

ORIGINAL NDA:

In the original NDA submission, the following dissolution methodology and specifications for lanthanum carbonate 250 and 500 mg CRUSHED chewable tablets were proposed:

PROPOSED DISSOLUTION METHOD AND SPECIFICATIONS FOR LANTHANUM CARBONATE CRUSHED CHEWABLE TABLETS	
Variable	**Parameter**
Apparatus Type	USP Apparatus 2 (paddle)
Dissolution Medium	[ ]
Speed of Rotation	[ ] rpm
Sample Pull Times	20, 40, 60, and 120 minutes
Specification	Q= — at —

Note that the sponsor proposal to use crushed tablets was based on the evaluation of the crushing force that was applied to the lanthanum carbonate tablets.

- WHOLE tablet

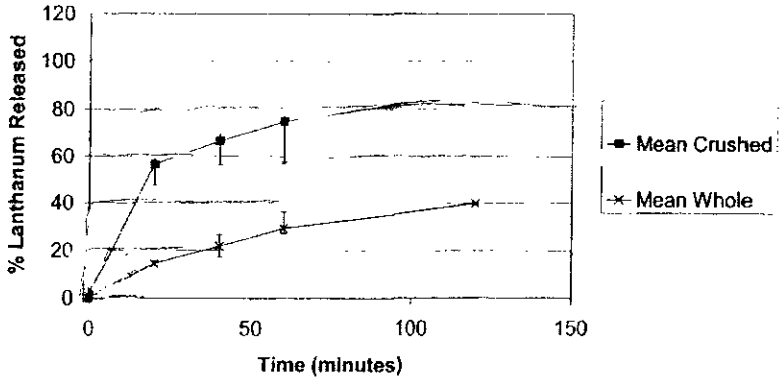
[ ]

- CRUSHED tablet; single tap of a pestle to break each tablet into 4-6 pieces, then each large piece was broken again with a single tap of the pestle

[ ]

The results are presented in the next figure and table.

Dissolution of Lanthanum 250mg Chewable Tablets



	Dissolution Data for Lanthanum Carbonate 250 mg Tablets (Lot No. 0H2772)					
	Testing conditions: USP Apparatus II (paddle), [ ]					
	Percent of Lanthanum Released					
Sampling Time	**Whole tablet**	[ ]		**Crushed tablet**	[ ]	
20 min	14.4 (3.7)			56.7 (10.8)		
40 min	21.8 (14.0)			66.6 (8.5)		
60 min	29.3 (11.9)			74.8 (6.4)		
120min	39.8 (1.2)			87.3 (3.9)		

Mean of 6 tablets (%RSD)

During the review of the original submission, OCPB told the sponsor that the dissolution guidance recommended the use of whole tablets in case a patient swallows the whole tablet or does not chew the tablet enough. OCPB encouraged the sponsor to develop a more appropriate dissolution methodology for the whole tablets (i.e., several dissolution media (including surfactants) and rotation of speed, etc.).

On February 27, 2003, the Agency issued an Approvable Letter for NDA 21-468 and in this Letter the USP Apparatus 2, [ ] rpm method using crushed tablet was accepted on an interim basis for one year with a recommended specification of — at — minutes. FDA told Shire that in that year they should develop an appropriate whole tablet dissolution test.

RESUBMITTED NDA:

In the resubmission dated January 27, 2004, the sponsor submitted method development and validation data for a new dissolution test which uses whole tablets and USP Apparatus 2. Shire undertook extensive dissolution investigations to develop and validate a whole tablet test suitable for Fosrenol chewable tablets. The method development and validation are presented below.

DISSOLUTION METHOD DEVELOPMENT for the WHOLE TABLET- APPARATUS 2

Background information:

Solubility Characteristics: Lanthanum carbonate has — solubility in water (insoluble by normal standards). Solubility studies at varying pH have shown that lanthanum carbonate hydrate has — — solubility at — with increasing solubility in an acid environment. The pH solubility profile is shown below in Table 1.

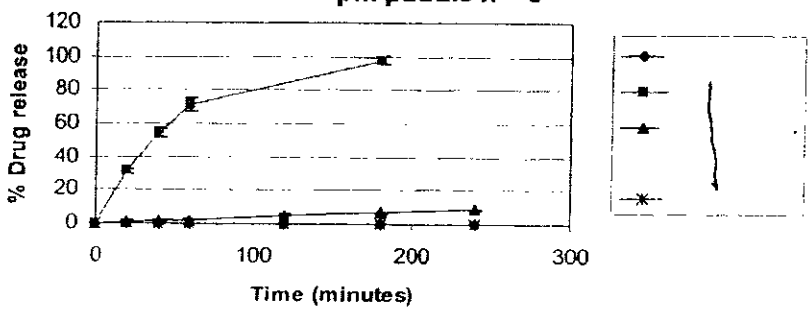
Table 1 pH Solubility Profile of Lanthanum Carbonate Hydrate

pH	Solubility of elemental lanthanum	Media
—	—	—

Dissolution of whole tablets in different pH media: Figure 1 shows the dissolution profiles of batch 96157 for the 250mg whole tablets in various pH aqueous media.

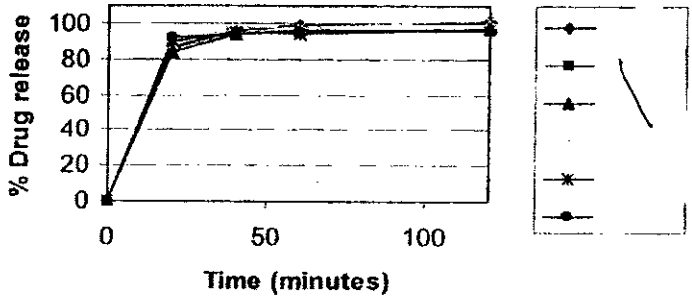
FIGURE 1

Mean dissolution characteristics of whole Fosrenol 250mg tablets in various pH media at — rpm paddle n = 6



Dissolution of crushed tablets: As a consequence of these findings and on the basis that these were chewable tablets, a dissolution method was developed and validated which used crushed tablets. Figure 2 shows the dissolution results of six batches of 250mg Fosrenol tablets using the crushing technique.

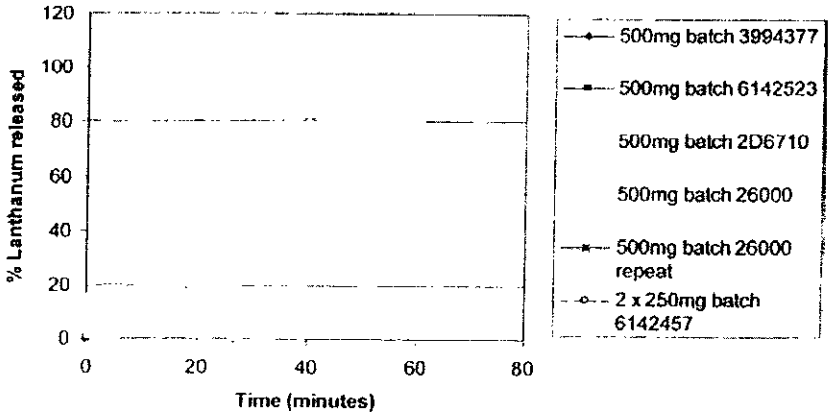
FIGURE 2
Mean dissolution characteristics of crushed Fosrenol 250mg tablets in [ ] rpm paddle n = 6



Note that better reproducibility is apparent but the crushed tablet technique is vulnerable to sample preparation [ ] can result in a depression of dissolution performance and increased variability, probably due to the [ ]

During this period the 500mg tablet was developed which was [ ] with the 250mg tablet. The dissolution profiles for 250mg and 500mg tablets are shown in Figure 3. Note that some batches of 500mg tablets are similar to 250mg tablets, but other have a slower dissolution in this medium which may be caused by the solubility limitation of the medium.

FIGURE 3
Dissolution of crushed 250mg and 500mg Fosrenol tablets in [ ] rpm paddle



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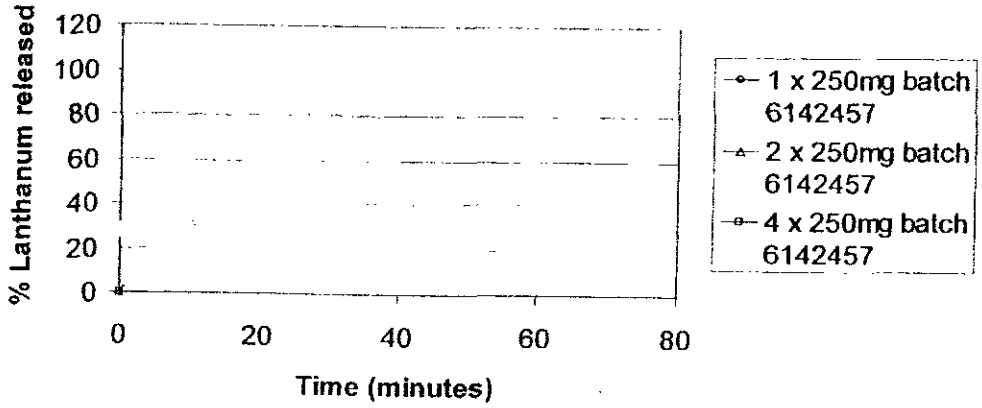
5 shows the release profiles of 1, 2 and 4 tablets per vessel using the current formulation 250mg tablet. This figure shows that the higher the drug concentration in the vessel, the slower the drug release. This is likely to be caused by limited drug solubility in the medium [ ] are not quite met for the 500mg strength. In [ ] the solubility is [ ] therefore [ ] to be met, the dose per tablet should be [ ]. It is apparent from the dissolution behavior of the multiples of the 250mg tablets and [ ] that solubility in the [ ] medium is rate limiting to the dissolution performance in vitro for the 500mg and higher tablet strengths.

FIGURE 5

Dissolution of crushed 250mg Fosrenol tablets current formula in [ ] at —rpm paddle



Development of a whole tablet dissolution method:

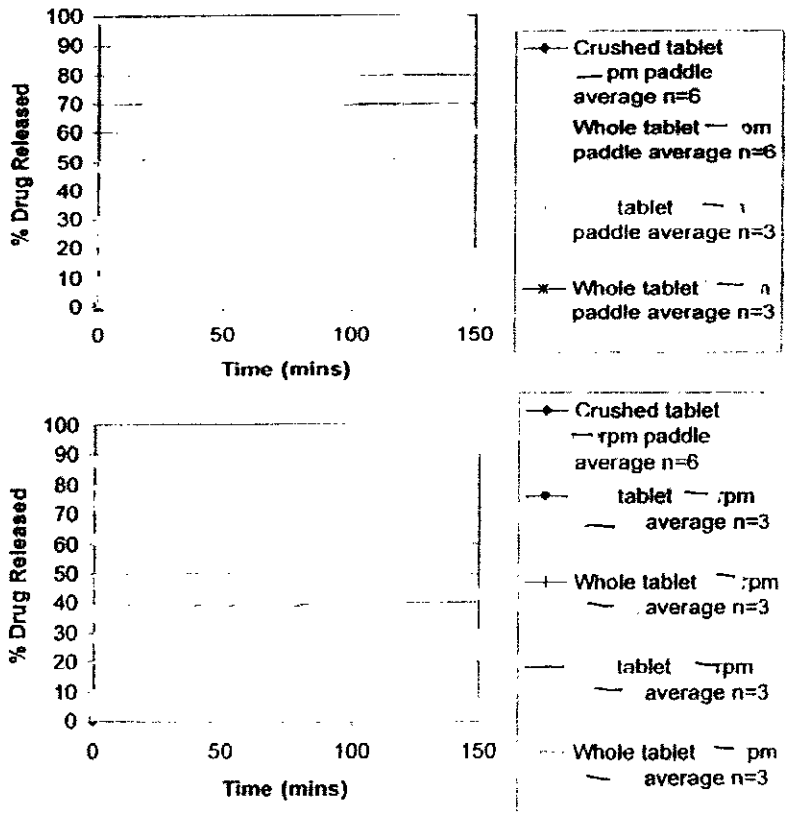
The FDA encouraged Shire to develop a whole tablet dissolution method due to the following concerns: **1)** in case patients do not follow the instruction to chew the tablet and swallow it whole , **2)** based on the fact that the crushed tablet technique is vulnerable to sample preparation [ ] can result in a depression of dissolution performance and increased variability, and **3)** the lot release testing is based on the release of whole tablets, not crushed tablets.

A whole range of approaches were used to develop this method including apparatus type, speed of rotation and type of medium. The one selected for the dissolution testing of whole tablets was [ ] using ~ ɔm paddle speed. This medium presented better solubility capacity for the drug than [ ] which is particularly important for the [ ] tablets in order to achieve Stressed tablets (including those with high levels of [ ] tablets) were used to test the discriminatory power of the method. After completing the development program the sponsor proposed a whole tablet-Apparatus 2 in [ ] for the [ ] dissolution test and if tablets fail to meet the Q value specification , — in 45 minutes), a [ ] test is carried out on crushed tablets-Apparatus 2 in [ ] (with the same Q value). A summary of the method development is presented next.

Apparatus: A number of traditional approaches were considered, first by investigating the use of paddle and by modifying the rates of stirring. [ ] Figure 6 shows that even using higher speeds of

paddle rotation, whole — tablets give release profiles which are unable to achieve a Q value of — ; in a reasonable timeframe.

FIGURE 6
Dissolution of current 250mg Fosrenol tablets under differing conditions in [ ] Batch 0H2772 paddles



The use of was somewhat more successful, yet figure 7 still shows that even using a tablet at — pm in a , the — of drug released is at or beyond 2 hours.

Media: Using USP Apparatus 2, the dissolution studies included a further evaluation of the media used, since the tablets do not contain disintegrants and the drug has limited solubility in 'traditional' media. The effect of adding a [ ] was evaluated, and using [ ] it was found that disintegration of the unit was considerably slower than without.

It was shown from earlier work that the drug has pH-dependent solubility and that — conditions of — — are not sufficient to [ ] for all strengths. Therefore , — strengths were investigated. It was found that disintegration of the unit in the dissolution medium using paddles was dependent upon the — concentration (Table 3). Additionally table 3 shows the effect of adding a [ ] to the medium which did not improve disintegration rate in the dissolution environment.

TABLE 3. Disintegration behavior of whole 250mg Fosrenol tablets in USP Apparatus 2, — pm.

Normality of HCl	pH	Media	Outcome
			No disintegration >2hrs
			ow, some disintegration >2 hrs
			Very slow, no disintegration >2 hrs
			Partial disintegration at 1 hr
			Rapid total disintegration 7 mins
			Rapid total disintegration 4 mins

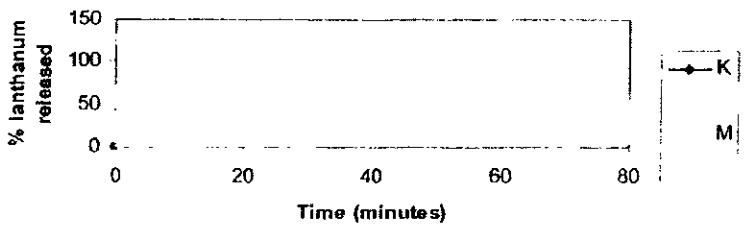
The improved disintegration in — media is likely to be related to the increased drug solubility in the [ ] conditions (Table 4) which shows [ ] (assuming — of the saturated solubility) for the [ ] at — molarities — or greater.

TABLE 4. Solubility of lanthanum in HCl solutions

Nominal Normality of HCl	pH	Elemental lanthanum solubility mg/ml n=3

Dissolution studies were carried out on whole 250mg current [ ] formulations in and [ ] using paddles at — pm (Figure 7) and showed that both media gave fast and complete dissolution sufficient to achieve — in a reasonable timeframe.

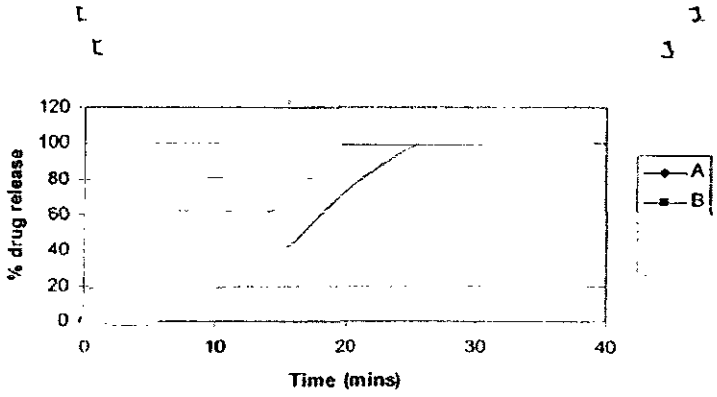
FIGURE 7
Dissolution profiles in % whole Fosrenol tablets using paddles at — pm n=3 trial
K = 250mg current — batch 6142457
[ ]
M = 250mg current — I batch 6142457
[ ]



The — medium was selected for further development due to its superior solubility capacity for lanthanum and paddle stir rate conditions were established. The normal speeds of rotation (— — , were investigated and Figure 8 shows that both gave acceptable profiles but the —pm speed was selected as it is likely to be more discriminatory.

FIGURE 8

Dissolution profiles whole Fosrenol tablets in nominal — at different paddle rpm
A= — pm current form 250mg batch 6142457
B= — pm current form 250mg 6142457



The discriminatory ability was evaluated by comparing the dissolution profiles of current 250mg tablets manufactured with the standard amount of [ ] with tablets containing [ ] this level of [ ] . Additionally the standard tablets were [ ]

Figure 9 shows that the dissolution method using nominal [ ] with —pm paddle is discriminatory.

FIGURE 9

Dissolution profiles whole Fosrenol tablets in [ ] using — paddle
a = 250mg current formula batch 6142457
b =
c =
d =

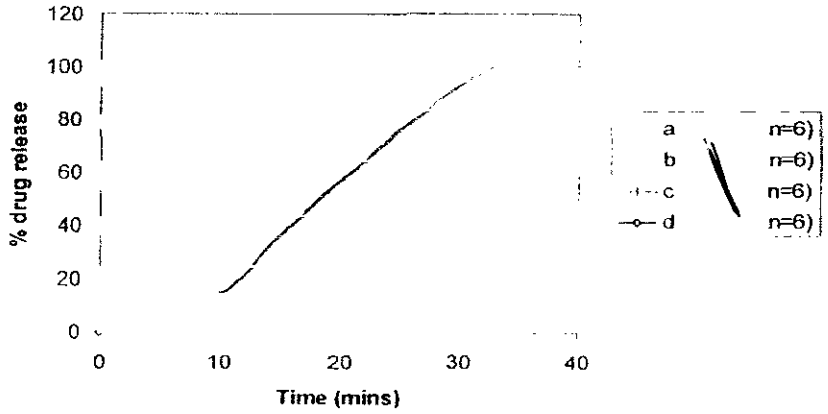


Figure 10 shows that in the medium [illegible] up to four 250mg tablets [illegible] can be present without affecting the release profile indicating that [illegible] are being met.

FIGURE 10

Dissolution profiles whole Fosrenol tablets in nominal [illegible] rpm paddle Current Formula 250mg batch 6142457 tablets

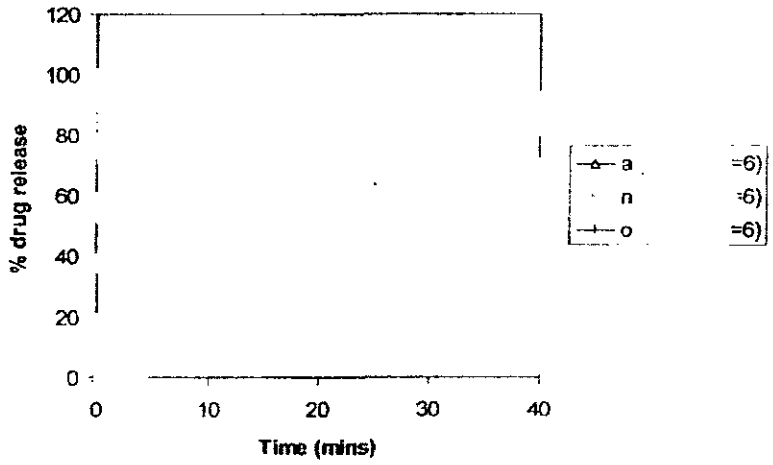


Figure 11 shows the release profiles of the 500mg tablets compared to two 250mg tablets of the current formulation. One of the 500mg batches has a slower dissolution than the 250mg profile, this may be related to the surface area being smaller and disintegration being slower for the larger tablet compared to two smaller tablets. Further 500mg batch analysis using this method is required, but based on the available data, a specification of Q[illegible] in 45 minutes seems achievable for the current formulation tablets tested whole.

FIGURE 11

Dissolution profiles whole lanthanum tablets in nominal [illegible] rpm paddle Current Formula 250mg and 500mg tablets

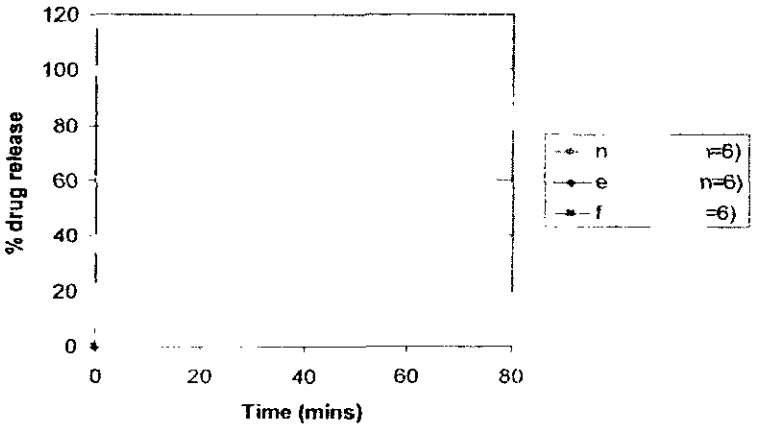
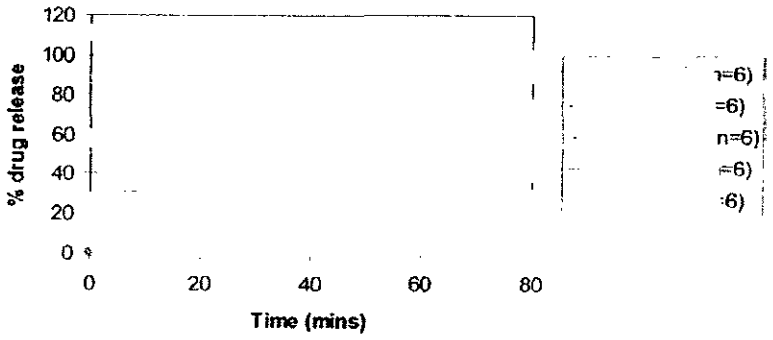


Figure 12 shows the release profiles for the current [ ]tablets using the whole tablet method and indicates [ ] the current formulation tablets, — can achieve ~ drug release by 45 minutes when using [ ]

]

FIGURE 12
Dissolution profiles whole Fosrenol tablets
in [ ] rpm paddle
a = 250mg current formula batch 8142457



Proposed Dissolution Specification:

The dissolution specification proposed by the sponsor for FOSRENOL Tablets is:

| % in 45 minutes whole tablets, Apparatus 2 , [ ] rpm paddle
| % in 45 minutes crushed tablets, Apparatus 2 [ ] rpm paddle

A [ ] dissolution specification is being proposed for a tablet formulation which is intended to be chewed before swallowing. A [ ] whole tablet test is applied and, should this fails, a crushed tablet test is followed. Both methods have been validated and the specification Q values have been set based upon dissolution experience on many samples and batches of product

REVIEWER COMMENTS:

1. With respect to the proposed [ ] dissolution testing submitted in the resubmission dated January 26, 2003, OCPB considered that the sponsor's proposal of having two tests for the same product was not appropriate. Therefore, on March 10, 2004, OCPB informed the sponsor that their resubmission proposal of using two consecutive different methods for the evaluation of Fosrenol tablets was not acceptable.

   Specifically, the proposed [ ] **dissolution test on whole tablets** in [ ] using Apparatus paddle 2 at — rpm, was properly validated and appears to be appropriate for the testing of FOSRENOL Tablets, with the exception that the test is referred to as [ ] dissolution test" and this "notation" is not acceptable. If a lot fails [ ] the testing should be continued to [ ] if needed. Only a lot that fails [ ] is called a **"FAILED"** lot. The proposed specification of Q=—% in 45 minutes for the whole tablets is not acceptable. For the "Current Formulation, the provided overall data showed that more than — is dissolved in 45

minutes (except for lot 2D6710; 500 mg). Thus, a dissolution specification of Q= — at 45 minutes would be more appropriate for the 250 and 500 mg current formulation tablets.

The following table summarizes the stability data for the "Current Formulation; 250 and 500 mg tablets".

WHOLE TABLET DISSOLUTION DATA FOR THE"CURRENT FORMULATION - 500 MG TABLET"				
		Available Dissolution at Stability Condition and Time Point		
Batch No.	Manufacturer	25°C/60%RH	30°C/60%RH	40°C/75%RH
2C6000				
*2D6710 (250cc)				
*2D6710 (300cc)				
3994377 (250cc)				
3994377 (300cc)				
6142523				
3B3018				
3B3019				
3B3020				
DISSOLUTION RANGE				
WHOLE TABLET DISSOLUTION DATA FOR THE"CURRENT FORMULATION - 250 MG TABLET"				
		Available Dissolution at Stability Condition and Time Point		
Batch No.	Manufacturer	25°C/60%RH	30°C/60%RH	40°C/75%RH
6142457 (bulk)				
6142457				
DISSOLUTION RANGE				

*The dissolution method was able to detect that Lot 2D6710 might be a bad performance lot

2. The sponsor's proposal to continue with a [ ] **dissolution test on crushed tablets**, if any tablet fails to meet the Q value requirement for [ ] (i.e., all 6 tablets must be — % in 45 min), was not acceptable to OCPB. Note that for the [ ] -crushed tablets test, the sponsor is proposing to have a different dissolution medium (i.e., [ ] using Apparatus paddles 2 at — pm. Q= — in 45 minutes for the crushed tablets).

3. Based on the review of the submitted data, OCPB is of the opinion that the sponsor may consider as an option the use of the already validated whole tablets method (USP Apparatus 2, [ ] and — rpm) with a specification of Q= — at 45 minutes, for the dissolution testing of the "Current Formulation; 250 and 500 mg tablets".

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BIOWAIVER REQUEST

LANTHANUM CARBONATE CHEWABLE TABLET FORMULATIONS

In this submission the sponsor requested **1)** a biowaiver for the 500 mg tablets using the current formulation [ ].

Current Formulations: The original formula was presented as 250 mg and 500 mg tablets, made from a common blend but compressed to different weights. These are known as the 'Current' formulation. The 250 mg 'Current' formulation has been used in all clinical studies to date. The sponsor provided the following information to support their request for a biowaiver for the 500 mg 'Current' formulation.

- ***Dosing Range:*** The 500 mg tablet is within the dosing range that was studied in the clinical trials.

- ***Linear Kinetics:*** It should be noted that the absorption of lanthanum is very low. The data provided in the original NDA showed within the limitations of the assay, that there is an increase in lanthanum plasma levels with increased dose, but not in a linearly proportional manner.

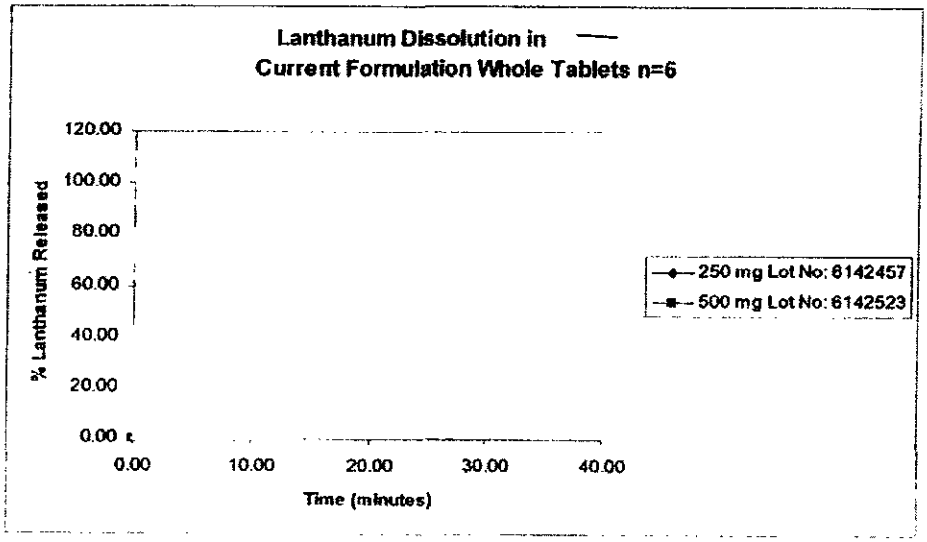
- ***Compositionally Proportional:*** The formulations of the 250 mg and 500 mg 'Current' tablets are compositionally proportional. These tablets are made from a common blend but compressed to different weights.

Formulation Comparison

	Current 250mg Tablet	Current 500mg Tablet
Dosage form	Chewable Tablet	Chewable Tablet
Tablet diameter	16mm	22mm
Formulation		
Lanthanum (elemental)	250mg	500mg
Lanthanum carbonate hydrate	477mg	954mg
Dextrates		
Colloidal silicon dioxide		
Talc		
Magnesium Stearate		
Total weight	1800mg	3600mg

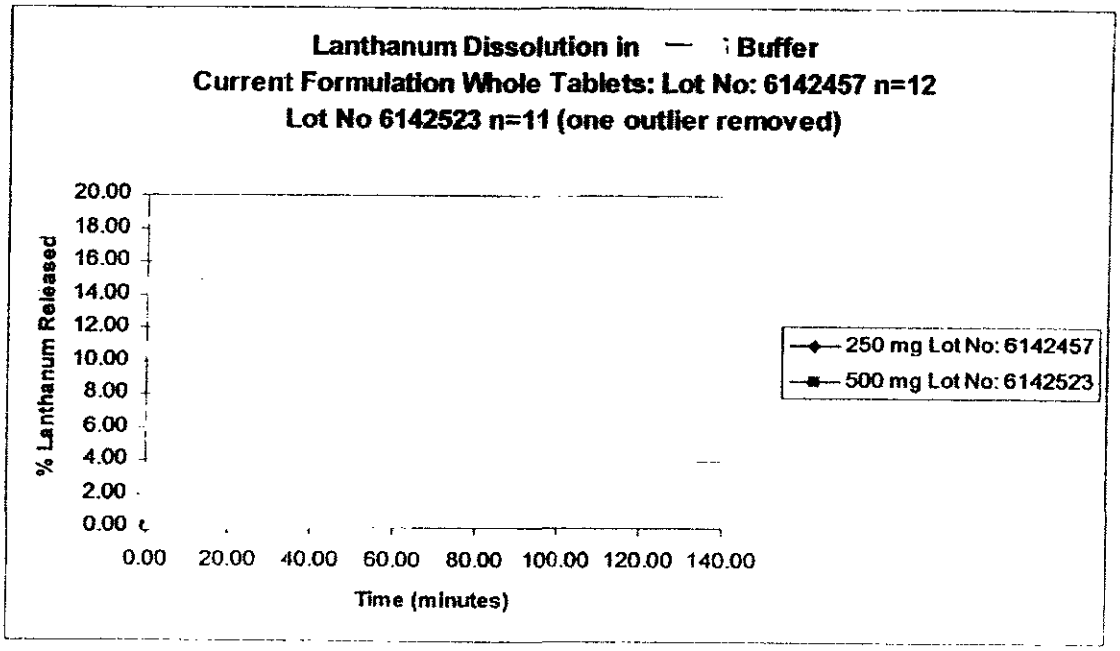
- ***Dissolution Data:*** The comparative dissolution data for the current 250 mg and current 500 mg formulations as whole tablets in [ ] are shown in the following graphics and tables.

Dissolution profiles of the whole 'Current ' 250 mg tablets compared to the 'Current' 500 mg tablets in 0.25N HCl



WHOLE TABLET- APPARATUS 2, CURRENT 250 MG, LOT 6142457												
Time	1*	2*	3*	4*	5*	6*	7**	8**	9**	10**	11**	12**
10							-	-	-	-	-	-
15	-	-	-	-	-	-						
20							-	-	-	-	-	-
30												
45	-	-	-	-	-	-						
60	-	-	-	-	-	-						
WHOLE TABLET- APPARATUS 2, CURRENT 500 MG, LOT 6142523												
Time	1*	2*	3*	4*	5*	6*	7**	8**	9**	10**	11**	12**
10							-	-	-	-	-	-
15	-	-	-	-	-	-						
20							-	-	-	-	-	-
30												
45	-	-	-	-	-	-						
60	-	-	-	-	-	-						
* First 6 tablets tested at [ ]							**Second 6 tablets tested at [ ]					

Dissolution profiles of the whole 'Current' 250 mg tablets compared to the 'Current' 500 mg tablets in — ; Buffer



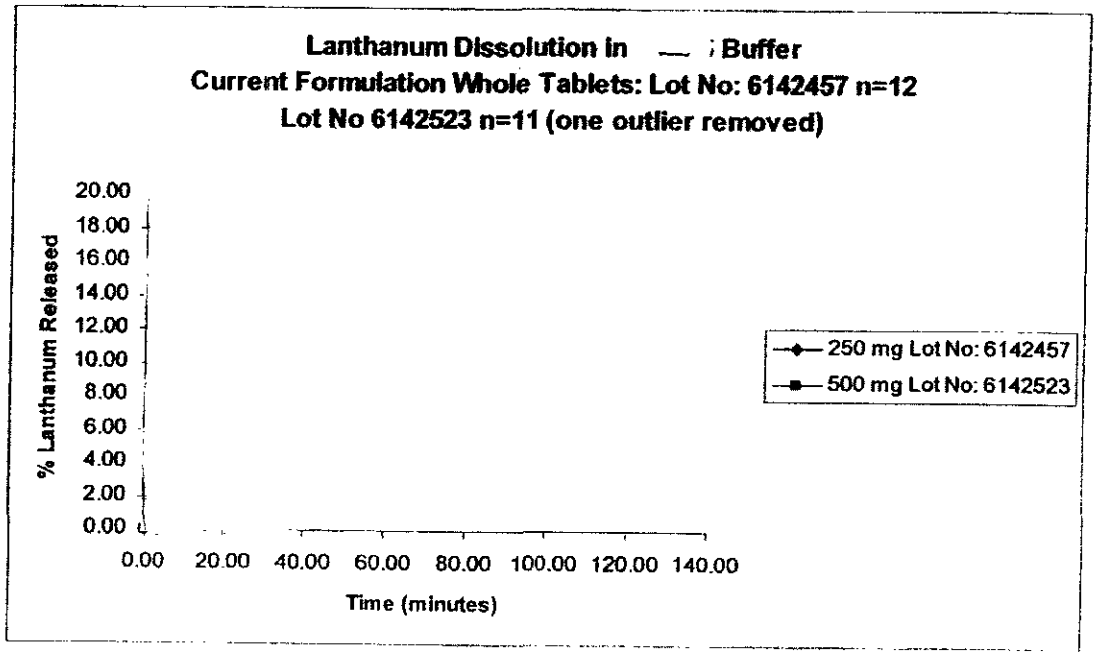
WHOLE TABLET- APPARATUS 2, BUFFER — ; CURRENT 250 MG, LOT 6142457

Time	1	2	3	4	5	6	7	8	9	10	11	12
15												
30												
45												
60												
120												

WHOLE TABLET- APPARATUS 2, BUFFER — CURRENT 250 MG, LOT 6142523

Time	1	2	3	4	5	6	7	8	9	10	11	12
15												
30												
45												
60												
120												

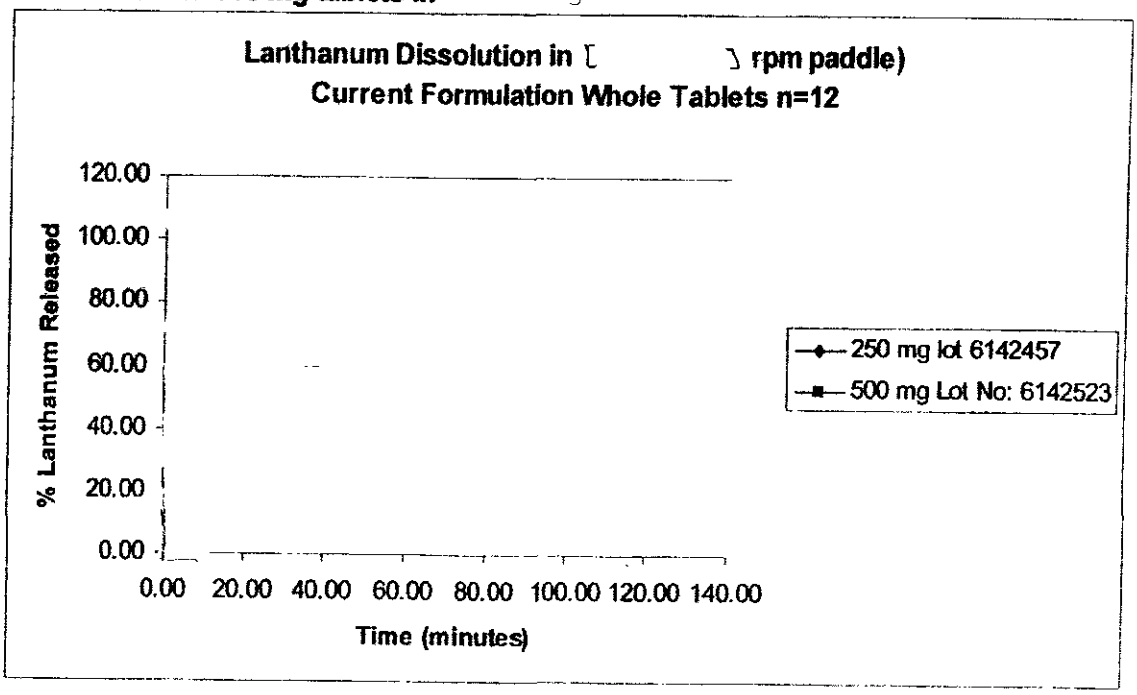
Dissolution profiles of the whole 'Current' 250 mg tablets compared to the 'Current' 500 mg tablets in — Buffer



WHOLE TABLET- APPARATUS 2, BUFFER — CURRENT 250 MG, LOT 6142457												
Time	1	2	3	4	5	6	7	8	9	10	11	12
15												
30												
45												
60												
120												

WHOLE TABLET- APPARATUS 2, BUFFER — CURRENT 250 MG, LOT 6142523												
Time	1	2	3	4	5	6	7	8	9	10	11	12
15												
30												
45												
60												
120												

Dissolution profiles of the whole 'Current ' 250 mg tablets compared to the 'Current' 500 mg tablets in [ ]



WHOLE TABLET- APPARATUS 2, [ ] ; CURRENT 250 MG, LOT 6142457												
Time	1	2	3	4	5	6	7	8	9	10	11	12
15												
30												
45												
60												
120												

WHOLE TABLET- APPARATUS 2, [ ] CURRENT 500 MG, LOT 6142523												
Time	1	2	3	4	5	6	7	8	9	10	11	12
15												
30												
45												
60												
120												

Similarity Factor:

The next table shows the similarity factor results for the current 500 mg formulation compared to the current 250 mg formulation as whole tablets in [ ] and [ ] buffer and as whole and crushed tablets in [ ]

SIMILARITY FACTOR F2 FOR THE CURRENT 250 VS. CURRENT 500 MG TABLETS				
FORMULATION	**BATCH No.**	**MEDIUM (Whole tablets)**	**APPARATUS**	**F2 % (Similarity Factor)**
Current 250 mg Vs. Current 500 mg	6142457 vs. 6142523	—	2 — rpm)	50 (n=6)* 59 (n=6)**
		—	2 — rpm)	45 (n=12)
		—	2 — rpm)	88 (n=11)#

* First 6 tablets tested at — **Second 6 tablets tested at — # One high value was removed

Similarity factor f2 is defined as showing similarity when the test value is between 50-100%. The results for the whole current 500 mg tablet showed similarity to the current 250mg using Apparatus 2 under this definition in [ ] buffer. The whole tablet f2 test for the 250 mg and 500 mg 'Current' formulations did not show similarity for the [ ] The sponsor claims that the tablets failed the f2 test because the medium is [ ] for one formulation but not the other (i.e. 250 mg 'Current' vs. 500mg 'Current' whole tablets in [ ]

REVIEWER COMMENTS:

1. To support the biowaiver request for the 500 mg current formulation the sponsor provided: **1)** formulation data showing that the 250 mg and the 500 mg tablets are compositional proportional, **2)** clinical data showing that the 500 mg dose is within the clinical range, and **3)** comparative dissolution data showing that the dissolution profiles of the 500 mg vs. the 250 mg current formulations are similar at the following testing conditions: whole tablets-Apparatus 2, [ ] rpm; Apparatus 2, Buffer [ ] rpm, and crushed tablets-Apparatus 2, [ ] rpm.

2. Note that the testing of whole tablets-Apparatus 2, [ ] rpm did not pass the F2 test. The sponsor mentioned that the F2 test failed because the dissolution test for the 500 mg tablets [ ] OCPB considers that the sponsor could test their hypothesis by repeating the F2 test in this medium by using [ ]

3. Overall, OCPB considers that the sponsor has provided appropriate supportive data and their request for a biowaiver of the requirement for a biostudy for the "Current 500 mg tablets" is granted.

ATTACHMENT 3

Includes:

- **Summary of BA and BE studies:**

  [ ]

  Study No. SPD405-117

Study No. SPD405-117

Title:

An Open Label, Parallel Group, Randomized Single Oral Dose Study of Lanthanum Following Intravenous and Oral Dosing in Healthy Male Subjects

Principal Investigator: [ ]

Study Center: [ ]

Study Objectives:

- To investigate the non-renal elimination of lanthanum.
- To investigate the absolute bioavailability of lanthanum.

Study Population:

Twenty-four subjects were randomized into the study. All 24 subjects completed the study and provided data for safety and pharmacokinetic analyses.

Main Criteria for Inclusion:

Healthy male volunteers aged between 18 and 35 years, with body weight range of 60-80kg and weighed within 10% of ideal weight according to height and frame size. Subjects did not have any clinically significant abnormal findings on physical examination, vital signs, ECG, medical history or clinical laboratory results during screening.

Summary of Demographic Data by Treatment Group

PARAMETERS	TREATMENT GROUP			TOTAL
	A	B	C	
Ethnic Origin (%)				
Caucasian	8 (100%)	8 (100%)	7 (87.5%)	23(95.8%)
Black	0 (0%)	0(0%)	1(12.6%)	1(4.2%)
Age in years	25.40±5.100	24.10±4.390	25.30±3.650	24.90±4.260
Weight in kg	73.60±1.666	69.98±4.347	72.75±6.132	72.11±4.531
Height in m	1.81±0.0676	1.75±0.0537	1.78±0.0441	1.78±0.0591

All subjects were male
Treatment Group A: A 10ml lanthanum chloride infusion over 4 hours
Treatment Group B: A single oral h of lanthanum carbonate chewable tablets (4 x 250 mg)
Treatment Group C: Control, no treatment administered

Study Design:

This was a Phase I single dose, open label, parallel group study in healthy male subjects to assess the pharmacokinetics of lanthanum following oral and intravenous dosing with a non-dosed control group of subjects. Subjects were admitted to the Unit during the evening of Day -4 before the start of dosing. On Day 1, subjects were dosed with their assigned study medications, and remained in the Unit for 7 days after dosing. All feces and urine were collected and pooled into collection periods to determine the excretion of lanthanum. A series of safety and pharmacokinetic assessments were also made throughout the treatment

period. Subjects were required to return to the Unit for a follow-up assessment between 5 and 9 days after discharge. The detailed scheduled of assessments is presented in the next table.

Detailed Study Period Schedule

Day	Protocol Time (h)	Informed Consent	In/Exclusion + Restrictions	Physical Examination	Vital Signs	12-Lead ECG	Clinical lab tests	Urinalysis	Drugs of Abuse Screen	Admission to Unit	Randomisation	Standardised Meals	Lanthanum Infusion[1]	Oral lanthanum[2]	Faecal collection[3]	24-hr urine collection[4]	Plasma Sample Treatment Group A	Plasma Sample Treatment Group B	Plasma Sample Treatment Group C	AE Monitoring	Concomitant Medications	Discharge from Unit
Check-in		X	X	X	X	X	X	X	X	X										X	X	
-3	-72h										X	X			X	X				X	X	
-2	-48h											X			X	X				X	X	
-1	-24h											X			X	X				X	X	
1	Predose			X	X	X						X			X	X	X	X	X	X	X	
	0h												X	X	X	X				X	X	
	1h				X								X		X	X	X	X		X	X	
	1.5h				X								X		X	X				X	X	
	2h				X								X		X	X	X	X		X	X	
	2.5h				X								X		X	X		X		X	X	
	3h				X								X		X	X	X	X		X	X	
	3.5h				X								X		X	X		X		X	X	
	4h		X	X	X								X		X	X	X	X	X	X	X	
	4h 5m														X	X	X			X	X	
	4h 10m														X	X	X			X	X	
	4h 15m														X	X	X			X	X	
	4h 30m				X										X	X	X	X		X	X	
	4h 45m														X	X	X			X	X	
	5h				X										X	X	X	X		X	X	
	5h 30m														X	X	X	X		X	X	
	6h			X	X	X	X					X			X	X	X	X		X	X	
	7h														X	X	X	X		X	X	
	8h														X	X	X	X		X	X	
	9h														X	X	X	X		X	X	
	10h														X	X	X	X		X	X	
	12h			X	X	X	X	X				X			X	X	X	X		X	X	
	14h														X	X	X	X		X	X	
	16h														X	X	X	X		X	X	
	18h														X	X	X	X		X	X	
2	24h			X	X	X	X	X				X			X	X	X	X	X	X	X	
	36h				X	X						X			X	X	X	X		X	X	
3	48h			X	X	X	X	X				X			X	X	X	X	X	X	X	
4	72h			X	X	X	X	X				X			X	X	X	X	X	X	X	
5	96h			X	X	X						X			X	X	X	X	X	X	X	
6	120h			X	X	X	X	X				X			X	X	X	X	X	X	X	
7	144h			X	X	X						X			X	X	X	X	X	X	X	
8	168h			X	X	X	X	X				X			X	X	X	X	X	X	X	X

[1] Subjects randomised to Treatment Group A,continuous infusion from 0h to 4h
[2] Subjects randomised to Treatment Group B, single oral dose of lanthanum carbonate
[3] Subjects randomised to Treatment Groups A and C. Faecal collections pooled during the following time intervals. -72 to -48h, -48 to -24h, -24 to 0h, 0 to 24h, 24 to 48h, 48 to 72h, 72 to 96h, 96 to 120h, 120 to 144h, 144 to 168h
[4] All subjects. 24-hour urine collections during the following time intervals: -72 to -48h, -48 to -24h, -24 to 0h, 0 to 4h, 4 to 8h, 8 to 12h, 12 to 16h, 16 to 24h, 24 to 48h, 48 to 72h, 72 to 96h, 96 to 120h, 120 to 144h, 144 to 168h

An untreated control (Treatment Group C) was included in the study to assess background levels of lanthanum. As lanthanum is an element that occurs naturally in many foods, it was expected that there would be detectable levels of lanthanum in the feces of control subjects. By collecting feces from the control subjects, a daily background level could be determined. This could then be subtracted from the amount of lanthanum in feces of treated subjects to determine the proportion of excreted lanthanum relating to the dose. However, since there was considerable inter subject variability in background fecal lanthanum levels, the mean daily pre-dose levels for each individual (collected over 3 days prior to dosing) were used instead. Plasma and urine samples were also collected from control subjects to assess background lanthanum levels.

Treatments and Mode of Administration:

Treatment Group A: A single lanthanum chloride 10mL IV infusion over 4 hours containing 120pg elemental lanthanum (212 mcg lanthanum chloride). Batch No.: PR-030604/P02903 Expiry Date: 06/08/03

Treatment Group B: A single oral dose of lanthanum carbonate chewable tablets (4 x 250mg) each containing 250mg elemental lanthanum (477mg lanthanum carbonate). Batch No.: PR-030604/6142457, Expiry Date: 01/04/05

Treatment Group C: Control group, no study medication.

Duration of Treatment:

Subjects were randomized to receive a single dose of lanthanum either as a 4-hour constant rate IV infusion or as orally administered chewable tablets. They were assessed for a total of 12 days (4 days before and 7 days after dose administration). A follow-up visit was attended by all subjects 5 to 9 days after completion of the 12 day assessment period.

Assessments:

- ***Pharmacokinetics:***
  The following parameters were assessed: Cmax, tmax, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, λz, $T_{1/2}$, CL_r, CL_t, V_z, and F.

- ***Elimination of lanthanum:***
  The percentage of the administered IV dose excreted in feces and urine (corrected for baseline lanthanum levels) during the 7 days following dosing.

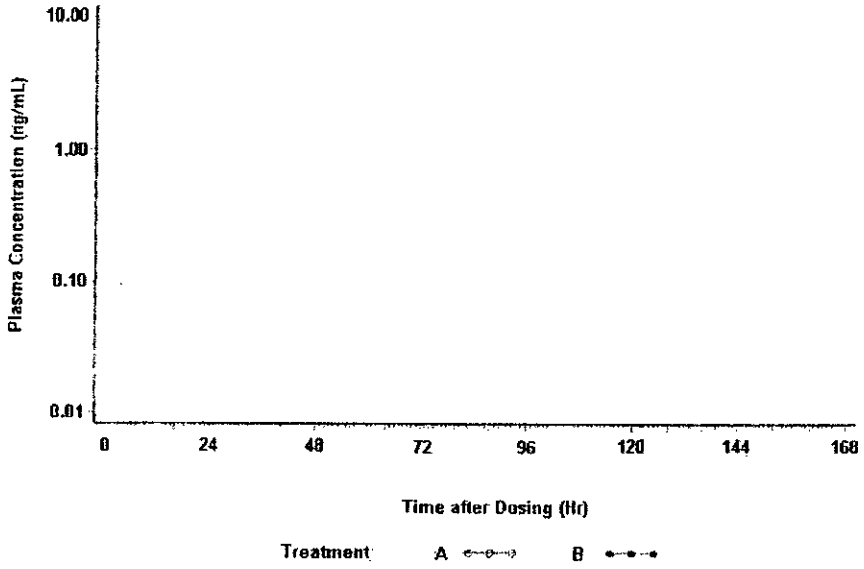
- ***Safety:***
  Adverse events were coded using the MedDRA 6.0 adverse event dictionary. The frequency of treatment emergent adverse events were calculated for each body system, by preferred term, by treatment group, for number of subjects and proportion reporting the event. The severity of the adverse events and the relationship to study treatment was summarized for each body system and preferred term by treatment.

  Descriptive statistics (number of observations, mean, standard deviation, minimum, median and maximum values) were calculated for vital signs, physical examination and clinical laboratory tests (hematology, biochemistry, urinalysis) at applicable visits. Categorical values were summarized using number of observations and percentages.

  Electrocardiograms were categorized and analyzed by number and percent per category. Categories consisted of normal, abnormal not clinically significant, and abnormal clinically significant values.

Results:

- ***Pharmacokinetics***



A summary of the plasma lanthanum pharmacokinetic parameters (mean ±SD (range)) after a single intravenous dose of lanthanum chloride and after a single oral dose of lanthanum carbonate are illustrated in the next Figure and presented in the next Table.

Summary of Lanthanum Pharmacokinetic Parameters

PARAMETER	INTRAVENOUS DOSE (N=8)	ORAL DOSE (N=8)
Cmax (ng/ml)	5.07±0.946	0.32±0.133
Tmax (h)	3.30±0.774	4.50±0.756
$AUC_{0\text{-}LAST}$ (h.ng/ml)	36.85±9.849	3.90±2.453
$AUC_{0\text{-}INF}$ (h.ng/ml)	38.88±10.463	4.79±3.452
$T_{1/2}$ (h)	37.36±22.014	34.451±11.993
CL_T (ml/h)	3297±927	-
Vz (L)	164.440±83.827	-
Ae (ng)	2104.977±1295.2714	357.4±338.3489
CLr (ml/h)	56.98±36.219	93.27±85.613 **
F (%)		0.00127 ± 0.00080

*n = 3 for $AUC_{0\text{-}inf}$ as the extrapolated tail area was more than 20% of the total area for most subjects indicating the extrapolation was not reliable.

**n = 7 for Ae and CLr.

- ***Absolute Bioavailability:***

The absolute bioavailability of lanthanum after an oral dose of 1000 mg lanthanum carbonate was 0.00127 ± 0.00080% (mean ± sd)

- ***Urinary Elimination of Lanthanum***

A summary of the excretion of lanthanum in urine (mean±SD) after intravenous and oral dosing is given below.

Excretion of Lanthanum in the Urine After Oral and Intravenous Dosing

POST-DOSE INTERVAL (HR)	INTRAVENOUS NG	DOSE (N=8) % DOSE	ORAL NG	DOSE (N=8) % DOSE
0-4	730.0 ± 518.4	0.61 ± 0.432	35.8 ± 27.8	0.000004 ± 0.000003
4-8	483.1± 180.9	0.40 ± 0.151	64.5 ± 71.6	0.000006 ± 0.000007
8-12	247.8 ± 137.1	0.21 ± 0.113	48.4 ± 35.3	0.000005 ± 0.000004
12-16	138.3 ± 143.2	0.12 ± 0.119	32.9 ± 40.7	0.000003 ± 0.000004
16-24	109.0 ± 142.1	0.09 ± 0.118	34.4 ± 61.2	0.000003 ± 0.000006
24-48	172.9 ± 155.6	0.14 ± 0.130	96.8 ± 157.1	0.000010 ± 0.000016
48-72	88.8 ± 127.1	0.07 ± 0.106	0 0 ± 0.0	0.000000 ± 0.000000
72-96	61.4 ± 94.9	0.05 ± 0.079	0.0 ± 0.0	0.000000 ± 0.000000
96-120	30.4 ± 56.4	0.03 ± 0.047	0.0 ± 0.0	0.000000 ± 0.000000
120-144	32.9 ± 60.9	0.03 ± 0.051	0.0 ± 0.0	0.000000 ± 0.000000
144-168	27.7 ± 54.2	0.02 ± 0.045	0.0 ± 0.0	0.000000 ± 0.000000
Total 0-168	**2105.0 ± 1295.3**	**1.75 ± 1.079393**	**312.7 ± 337.8**	**0.000031 ± 0.000034**

- ***Fecal Elimination of Lanthanum***

The cumulative amount of lanthanum excreted in the subjects following intravenous dosing was 5.55 ± 5.276%. By comparison the amount of lanthanum present in feces of the control subjects was equivalent to 2.79 ± 2.655% of the intravenous dose.

Excretion of Lanthanum in Feces After Intravenous Infusion of 120 mg of Lanthanum Chloride

	INTRAVENOUS DOSE				CONTROL SUBJECTS			
Post Dose Interval (hr)	n*	%Dose	n**	Cumulative %Dose	n*	%Dose	n**	Cumulative %Dose
0 to 24	7	1.11± 1.446	8	0.97:t 1.394	8	0.28 t 0 527	8	0.28 ± 0.527
24 to 48	7	1.53 ± 1.693	8	2.31 ± 1.773	8	0.34 ± 0.506	8	0.62 ± 0.850
48 to 72	6	0.02 ± 0.043	8	2.32 ± 1.782	8	1.13 ±1.265	8	1.76 ± 1.813
72 to 96	8	0.76 ± 1.451	8	3.08 ± 2.728	7	0.09 ± 0.141	8	1.83 ± 1.796
96 to 120	7	0.68 ± 1.141		3.68 ± 3.388	7	0.30 ± 0.529	8	2.09 ± 2.012
120 to 144	6	1.26± 2.071	8	4.62 ±4.505	7	0.72 ±1.239	8	2.72 ± 2.718
144 to 168	6	1.24 ± 2.023		5.55 ± 5.276	6	0.94±0.198	8	2 79 ± 2.655

* The average total amount excreted was based on the actual number of samples presented for analysis.
The average cumulative amount excreted was based on the entire sample size, regardless of sample availability

- ***Safety Results:***

Eight mild to moderate adverse events (AEs) were reported by five subjects during the study. Four of these events were considered possibly related to treatment and the other four were unrelated. Possibly related AEs included an episode of mild dizziness after Treatment A, mild and

moderate headaches and moderate nausea/vomiting after Treatment B. Unrelated AEs included moderate application site rash, dizziness and headache after Treatment A, and mild dizziness after Treatment B.

Transient, non-clinically significant changes occurred in biochemistry, hematology and urinalysis parameters. No significant findings were observed in vital sign, electrocardiogram or physical examination assessments during the study.

Sponsor's Conclusions:

- Lanthanum was very poorly absorbed after oral administration of lanthanum carbonate, with an absolute bioavailability of 0.00127 ± 0.00080%.
- Cumulative excretion in urine and feces during the 7 day period after intravenous administration were 1.75 ± 1.08% and 5.55 ± 5.28%, respectively.
- Renal clearance of lanthanum (mean of 0.95 ml/min) amounted to <2% of total plasma clearance. These results indicate that only a small fraction of systemic lanthanum is renally cleared.
- There was evidence that systemic lanthanum was excreted via the feces. However, due to the presence of significant quantities of environmental lanthanum in the feces, together with the limitations imposed by the strength of the intravenous dose, it proved difficult to quantify the component arising from systemic elimination.
- Both intravenous lanthanum chloride and orally administered lanthanum carbonate tablets appeared to be well tolerated in these healthy male volunteers. No serious adverse events occurred during this study and no safety concerns were raised with respect to clinical laboratory evaluations, vital signs, electrocardiograms or physical examination assessments.

Reviewer Comments:

1. It should be noted that a mass balance study for lanthanum carbonate in humans was not conducted as the use of radioactive isotopes of lanthanum in man is problematic. However the excretion of lanthanum after intravenous administration of lanthanum chloride to healthy subjects was investigated in this study.
2. The results showed that the excretion of lanthanum in urine and feces during the 7 day period after intravenous administration was 1.75 ± 1.08% and 5.55 ± 5.28%, respectively. It is a potential safety concern to know than more than 90% of the given IV-lanthanum is not excreted and remains in the body (possible in tissues/bone) for a long length of time.
3. Knowing that lanthanum accumulates in bone, it is therefore possible to consider that in man, deposition of lanthanum into the skeleton could be a significant plasma clearance mechanism.
4. It should be noted that although the sponsor measured the amount of lanthanum excreted in feces after IV administration, they did not measure the amount of lanthanum excreted in feces after oral administration. No justification was provided on why such a decision was taken. Therefore, OCPB's concern for mass-balance information for lanthanum carbonate following oral administration was not addressed in this study.
5. As previous studies, this study also confirmed the low bioavailability of lanthanum following oral administration (<0.002%). However, knowing that systemic levels of lanthanum do not correlate with total body exposure, the bioavailability of lanthanum is not a relevant/useful parameter in terms of assessing lanthanum's exposure.

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commercial information

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ATTACHMENT 5

Includes:

Proposed Labeling

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

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

/s/

Angelica Dorantes
8/19/04 05:04:16 PM
BIOPHARMACEUTICS

Patrick Marroum
8/19/04 05:09:12 PM
BIOPHARMACEUTICS

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