CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204734Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204-734 **Resubmission** (Class1)	**Reviewer:** Okpo Eradiri, Ph.D.	
Division:	DCRP		
Applicant:	Shire Development, LLC	**Acting Biopharmaceutics Team Leader:** Elsbeth Chikhale, Ph.D.	
Trade Name:	Fosrenol	**Acting Biopharmaceutics Supervisor:** Paul Seo, Ph.D.	
Generic Name:	Lanthanum Carbonate Powder	**Date Assigned:**	Mar 25, 2013.
Indication:	Reduction of phosphate in patients with end stage renal disease.	**Date of Review:**	Sep 8, 2014.
Formulation/strength	Powder/750 and 1000 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED/REFERENCED IN THIS DOCUMENT

Submission Dates	Date of informal/Formal Consult	PDUFA DATE
Feb 28, 2013 (Original NDA) Sept 5, 2013 (Amendment Sequence # 009) Nov 18, 2013 (Amendment, Sequence # 013) May 30, 2014 (Amendment, Sequence # 017) Jul 31, 2014 (Class 1 Resubmission, Sequence # 019) Aug 8, 2014 (Amendment, Sequence # 020) Aug 26, 2014 (Amendment, Sequence # 021) Sep 4, 2014 (Amendment, Sequence # 022)		N/A

Type of Submission:	NDA - Class 1 Resubmission
Key review points	- Applicant's proposed interim dissolution method and acceptance criterion; - PMC and associated timelines for development of a new dissolution method and acceptance criterion.

Link for Class I Resubmission: \\cdsesub1\evsprod\nda204734\0019\m1\us\quality-information-amendment.pdf.

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1 INTRODUCTION

Background: A Complete Response letter was issued for this NDA on December 24, 2013; dissolution-related deficiencies were the only CR issues. In an End-of-Review meeting between the Applicant and the FDA, which took place on May 15, 2014 via teleconference, the Applicant's strategy for a Class I resubmission was discussed. The Applicant also submitted a formal proposal for a (b) (4), interim dissolution acceptance criterion utilizing the current dissolution methodology. Minutes of the May 15th meeting were posted in DARRTS on 5/28/2014.

The Briefing Package for the May 15th 2014 meeting was submitted as an amendment to the NDA (Sequence # 0017) on 5/30/2014. The review of that data package by this Reviewer was posted in DARRTS on 6/27/2014.

Current submission: This Class I resubmission of NDA 204734 is essentially the same as the Applicant's Briefing Package submitted to the NDA on 5/30/2014 (Sequence # 0017). Another review of the same data package is therefore unnecessary.

2 REVIEW

The objectives of the Biopharmaceutics review for this NDA Class I resubmission are the same as those of the Amendment submitted by the Applicant on May 30, 2014:

- Evaluation of the revised proposed interim dissolution specification of Q = (b) (4) % at 20 min using the interim dissolution method submitted on 11/18/2013; and
- Assessment of a PMC for the development of a new dissolution method and the associated timelines.

As stated in section 1 above, a second review of the same data package will not be undertaken. However, the Applicant will be asked to explain the potential out-of-specification dissolution results for stability samples analyzed with the current method.

3 INFORMATION REQUEST SENT TO THE APPLICANT ON 8/25/2014

The following IR was sent to the Applicant on August 25, 2014:

Please refer to Module 1, section 1.11.1 of your July 31, 2014 Class I resubmission. The stability data for a number of the Lanthanum Carbonate Powder batches presented in tabular form on pages 8 – 14 seem to have S1 out-of-specification values at some

stability time points. Confirm if the affected batches were subjected to S2 testing; provide the S2 results for the affected batches.

3.1 *Applicant's Response to the IR*

The Applicant responded on 8/25/2014, the same date that the IR was sent. The Applicant's response is as follows:

> *The affected batches were not subjected to S2 testing. All submitted 20-minute dissolution data was collected for informational purposes and were not assessed against specification requirements at the time of the filing.*
>
> *Please note that at the time the dissolution data was generated, the proposed specification (Q= (b)(4)% in (b)(4) minutes) was based on a sampling time of (b)(4) minutes. Therefore, no additional testing for Stage 2 or Stage 3 was initiated based on the results at the 20 minute sampling time. The newly proposed (b)(4) interim specification at 20 minutes (Q= (b)(4)% in 20 minutes) was based upon a simulation analysis (using available stability data) which predicted that (b)(4)% of the Fosrenol Oral Powder batches would not meet the Stage 1 acceptance criteria and thus would proceed to Stage 2 (and that a further (b)(4)% of the batches would need to proceed to Stage 3 testing). Consequently, and in line with the simulation analysis, some of the stability dissolution results tabulated in the Class I resubmission do not meet the Stage 1 acceptance criteria at 20 minutes.*
>
> *Once the newly proposed interim specification (Q= (b)(4)% in 20 minutes) is approved, future results that do not meet the Stage 1 acceptance criteria at the 20 minute sampling time will undergo additional testing (Stage 2 or 3) in accordance with compendial requirements.*

3.2 *Reviewer's Assessment: SATISFACTORY*

The Applicant's response is acceptable.

4 POST-MARKETING COMMITMENT PROPOSAL

The Applicant has agreed to a PMC regarding the development of a new dissolution method and acceptance criterion; please see the Applicant's agreement to the PMC in DARRTS (posted 9/4/2014, eCTD Sequence # 0022).

5 RECOMMENDATION

The interim dissolution method and acceptance criterion for Fosrenol (lanthanum carbonate) powder agreed to by the Applicant are displayed below:

USP Apparatus	Paddle Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion*
					(b) (4)

ONDQA-Biopharmaceutics has reviewed the Applicant's Class I resubmission of NDA 204-734 for Lanthanum Carbonate Powder, 750 and 1000 mg. Based on the provided data and information as well as the PMC agreed-to by the Applicant, Biopharmaceutics recommends **APPROVAL** of NDA 204734.

Okpo Eradiri, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Paul Seo

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/s/

OKPONANABOFA ERADIRI
09/08/2014

ELSBETH G CHIKHALE
09/08/2014

BIOPHARMACEUTICS REVIEW - ADDENDUM Office of New Drug Quality Assessment			
Application No.:	NDA 204-734 (0017)	**Reviewer:** Okpo Eradiri, Ph.D.	
Division:	DCRP		
Applicant:	Shire	**Team Leader:** Angelica Dorantes, Ph.D.	
Trade Name:	Fosrenol	Acting Biopharmaceutics Supervisor: Richard Lostritto, Ph.D.	
Generic Name:	Lanthanum Carbonate Powder	**Date Assigned:**	Mar 25, 2013.
Indication:	Reduction of phosphate in patients with end stage renal disease.	**Date of Review:**	Jun 27, 2014.
Formulation/strength	Powder/750 and 1000 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED/REFERENCED IN THIS DOCUMENT		
Submission Dates Feb 28, 2013 (Original NDA) Sept 5, 2013 (Amendment Serial # 009) Nov 18, 2013 (Amendment, Serial # 013) **May 30, 2014 (Amendment, Serial # 017)**	**Date of informal/Formal Consult**	**PDUFA DATE**
		N/A

Type of Submission:	505(b)(1)
Key review points	- Applicant's proposed interim dissolution acceptance criterion; - PMC and associated timelines for development of new dissolution method and acceptance criterion.

Link for NDA Amendment: \\cdsesub1\evsprod\nda204734\0017\m1\us\quality-information-amendment.pdf

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1 INTRODUCTION

Following the Complete Response issued for this NDA on December 24, 2013, the Applicant requested an End-of-Review meeting with FDA. The meeting was held on May 15, 2014 via teleconference. The following HHS Intranet-link includes the document for the minutes of the May 15th meeting:
http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af8033564a

Per the minutes of that meeting, the Applicant has submitted the current amendment (serial # 0017) for review. In this amendment the Applicant is providing a formal proposal for a (b) (4), interim dissolution acceptance criterion utilizing the current dissolution methodology. Also, in this amendment the Applicant is requesting that FDA allow them to submit a Class I resubmission for their NDA 204734 on the basis of this interim specification and the timing of providing the new dissolution method data relative to a resubmission.

2 REVIEW

The objectives of the Biopharmaceutics review for this NDA Amendment are:

- Evaluation of the revised proposed interim dissolution specification of Q = (b) (4) % at 20 min using the interim dissolution method submitted on 11/18/2013; and
- Assessment of a PMC for the development of a new dissolution method and the associated timelines.

The outcome of review of the above issues will determine if the Applicant's proposal for a Class 1 labeling resubmission will be accepted by FDA.

3 INTERIM DISSOLUTION ACCEPTANCE CRITERION OF Q = (b) (4) % AT (b) (4) min

The current proposed dissolution method (PA (b) (4)) and acceptance criterion are displayed in Table 1.

Table 1: Proposed dissolution method and acceptance criterion for Lanthanum Carbonate Powder, 750 and 1000 mg.

USP Apparatus	Paddle Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion*
					(b) (4)

The Applicant states that a simulation analysis using stability data from 18 batches of the drug product was used to determine the interim specification.

3.1 *Reviewer's Assessment: SATISFACTORY*

The (b) (4) of the previously proposed dissolution specification of Q = (b) (4)% at (b) (4) min to Q = (b) (4)% at 20 min is acceptable. Based on the limited stability dissolution data on validation batches for which data at time zero were available, the proposed interim dissolution acceptance criterion is acceptable.

4 POST-MARKETING COMMITMENT PROPOSAL

The Applicant commits to develop a new dissolution method and generate sufficient stability dissolution data to permit setting of an acceptance criterion. The proposed timelines for the PMC are as follows:

i. Submit a formal proposal to the Agency regarding the (b) (4), interim dissolution specification: Submission date: May 30, 2014.
ii. Receive feedback from the Agency regarding the Applicant's proposal. Anticipated: June 30, 2014.
iii. Submit a Class I resubmission including the Applicant's response to the other requests (e.g. labeling and safety updates) outlined in the CR letter and include the interim dissolution specification (eCTD Section 3.2.P.5.1 only). Targeted Submission date: July 30, 2014.
iv. The Applicant will provide a high-level update/overview regarding the status of the requested dissolution work to the Agency via Module 1, Section 1.11.1. This update would be to provide the Agency with a status update but will not include data/conclusions. Targeted Submission date: November 2014.
v. The Applicant will submit a Prior Approval Supplement to include a revised/new dissolution method (e.g., USP Apparatus 4) and corresponding final specification.

Targeted Submission date: May 29, 2015.

4.1 *Reviewer's Assessment: SATISFACTORY*

The Applicant's PMC timelines are acceptable.

5 RECOMMENDATION

The ONDQA-Biopharmaceutics team has reviewed the Applicant's proposal submitted in Amendment-017 under NDA 204-734 for Lanthanum Carbonate Powder, 750 and 1000 mg. Based on the provided information, Biopharmaceutics agrees with the Applicant's proposal to use the current dissolution method with an acceptance criterion of Q = (b) (4)% at 20 minutes on an interim basis. The proposed PMC timelines for the submission of a PAS with a complete report supporting a revised/new dissolution method and corresponding acceptance criterion are also acceptable.

Okpo Eradiri, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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/s/

OKPONANABOFA ERADIRI
06/27/2014

ANGELICA DORANTES
06/27/2014

The Biopharmaceutics Assessment of this Amendment was performed, and the recommendation was provided in the Biopharmaceutics Review dated 27-Jun-2014 (refer to this review).

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/s/

LYUDMILA SOLDATOVA
06/27/2014

ONDQA - BIOPHARMACEUTICS
INITIAL PRODUCT QUALITY ASSESSMENT AND FILING REVIEW

NDA Number	204-734
Submission Date	2/28/2013
Product name, generic of active(s)	Lanthanum Carbonate Oral Powder
Dosage form and strengths	750, 1000 mg
Indication	Reduction of phosphate in patients with end stage renal disease.
Applicant	Shire Development LLC
Clinical Division	DCRP
Type of Submission	505(b)(1) New Drug Application
Biopharmaceutics Reviewer	Okpo Eradiri, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.
Acting Biopharmaceutics Supervisor	Richard Lostritto, Ph.D.

SUBMISSION

The Applicant is the holder of approved NDA # 021-468, Lanthanum Carbonate Chewable Tablets, which is the RLD for generics of the drug. This NDA provides for an alternative formulation to the chewable tablets in cases when a patient may have difficulty in chewing the tablets due to tablet hardness, tooth injury, aspiration, etc. This proposed (powder) drug product is intended to be mixed with soft food and then ingested.

In the November 6, 2012Written Request comments sent to the Applicant in lieu of a pre-NDA meeting, it was agreed that *in-vivo* PK or *in-vitro* dissolution comparison testing is not required to support biowaiver for the lower (750 mg) strength of the product. In this NDA submission, the Applicant has included their justification for not developing a dissolution test for the powder dosage form of the drug. This Reviewer will therefore evaluate the merit of the Applicant's assertion that their scientific rationale for not proposing *in-vitro* dissolution as a release test for their drug product is valid.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 204-734 for Lanthanum Carbonate Oral Powder is fileable.

{See appended electronic signature page}

Okpo Eradiri, Ph.D. Date
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}

Angelica Dorantes, Ph.D. Date
Biopharmaceutics Team Leader
The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary

in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS A. INITIAL OVERVIEW OF THE APPLICATION FOR FILING				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the dissolution test part of the DP specifications?		X	Rationale is provided in Module 3, section 3.2.P.5.6, page 2.
2.	Does the application contain the dissolution method development report?			N/A; see 1 above.
3.	Is there a validation package for the analytical method and dissolution methodology?			N/A; see 1 above.
4.	Does the application include a biowaiver request?	X		A waiver for in-vivo study on the lower strength, 750 mg is being requested (Regional Information, section 1.12).
5.	Is there information provided to support the biowaiver request?	X		The biowaiver request and rationale are presented in section 1.12.13 (Regional Information).
6.	Is there information provided to assess dose dumping in the presence of alcohol?		X	Not needed. The proposed drug product is not a modified-release dosage form.
7.	Is discriminating power of the dissolution test demonstrated?			N/A
8.	Does the application include an IVIVC model?			N/A
9.	Is information such as BCS classification mentioned, and supportive data provided?		X	NDA 021-468 is referenced for DS.
10.	Is information on mixing the product with foods or liquids included?			N/A. Mixing with soft food is the mode of administration.
11.	Is there any in *vivo* BA or BE information in the submission?	X		One in-vivo PK study with PD endpoint is included in the Application.
B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
12.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		Absence of biopharmaceutics data/information is a review issue.
13.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	-	-	The NDA is fileable from a Biopharmaceutics perspective.
14.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		X	

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/s/

OKPONANABOFA ERADIRI
04/24/2013
Biopharmaceutics Filing Review

ANGELICA DORANTES
04/25/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

Lanthanum carbonate (FOSRENOL®) formulated as a chewable tablet is a phosphate binder indicated to reduce serum phosphate in patients with ESRD (NDA 21468). In this NDA the sponsor is seeking approval of FOSRENOL® formulated as an oral powder. Lanthanum carbonate oral powder will be available in two strengths – 750 and 1000 mg.

	Information		Information
NDA/BLA Number	204734	Brand Name	Fosrenol
OCP Division (I, II, III, IV, V)	I	Generic Name	Lanthanum carbonate
Medical Division	DCRP	Drug Class	Phosphate binder
OCP Reviewer	Divya Menon-Andersen	Indication(s)	ESRD
OCP Team Leader	Raj Madabushi	Dosage Form	Powder
Pharmacometrics Reviewer Pharmacogenomics Reviewer	-	Dosing Regimen	Divided doses to be taken with meals
Date of Submission	02/28/2013	Route of Administration	Oral
Estimated Due Date of OCP Review	07/28/2013	Sponsor	Shire LLC
Medical Division Due Date		Priority Classification	Standard
PDUFA Due Date	12/28/2013		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed (tentative)	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	X			
Healthy Volunteers-	X			
single dose:				
multiple dose:	X	1	1	PK/PD study (SPD405-127)
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	X	1	1	PK/PD study (SPD405-127)
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1	1	PK/PD study (SPD405-127)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			√	
2	Has the applicant provided metabolism and drug-drug interaction information?			√	Previously evaluated under NDA 21468
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	√			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	√			
5	Has a rationale for dose selection been submitted?	√			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	√			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	√			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	√			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	√			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			√	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	√			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			√	Previously evaluated under NDA 21468
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			√	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			√	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			√	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			√	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	√			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	√			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			√	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Divya Menon-Andersen	04/17/2013
Reviewing Clinical Pharmacologist	Date
Raj Madabushi	04/17/2013
Team Leader/Supervisor	Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

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/s/

DIVYA MENON ANDERSEN
04/18/2013

RAJANIKANTH MADABUSHI
04/18/2013

BIOPHARMACEUTICS REVIEW - ADDENDUM Office of New Drug Quality Assessment			
Application No.:	NDA 204-734 (000)	**Reviewer:** Okpo Eradiri, Ph.D.	
Division:	DCRP		
Applicant:	Shire	**Team Leader:** Angelica Dorantes, Ph.D.	
Trade Name:	Fosrenol	Acting Biopharmaceutics Supervisor: Richard Lostritto, Ph.D.	
Generic Name:	Lanthanum Carbonate Powder	**Date Assigned:**	Mar 25, 2013.
Indication:	Reduction of phosphate in patients with end stage renal disease.	**Date of Review:**	Dec 19, 2013.
Formulation/strength	Powder/750 and 1000 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT		
Submission Dates Feb 28, 2013 (Original NDA) Sept 5, 2013 (Amendment Serial # 009) Nov 18, 2013 (Amendment, Serial # 013)	**Date of informal/Formal Consult**	**PDUFA DATE**
	March 25, 2013	Feb 3, 2014

Type of Submission:	505(b)(1)
Key review points	Applicant's responses to IR comments clarified in a teleconference on Nov 4, 2013.

This document is an addendum to the original Biopharmaceutics review by Dr. Okpo Eradiri, dated October 25, 2013 in DARRTS.

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I) SUMMARY OF BIOPHARMACEUTICS FINDINGS

This addendum is a review of the Applicant's dissolution data package submitted on November 18, 2013. In a teleconference between the Agency and the Applicant held on November 4, 2013, the Agency requested the following data/information:

- A dissolution method development report. The report should contain experimental data to demonstrate the robustness of the dissolution method, its discriminating power and optimization of testing conditions.
- Proposed dissolution acceptance criterion, including an updated specification table for the drug product, including the proposed dissolution specification (method and acceptance criterion) along with validation report for the analytical method, if different from the one for assay, CU, etc.
- Comparative dissolution data for the 750 and 1000 mg strengths in 3 different dissolution media in support of the biowaiver; if solubility-pH issues do not allow for testing in all 3 media provide a justification for the lack of this information.
- Dissolution profile data using the proposed dissolution method for the primary registration stability batches that are currently on stability. These data should include dissolution data for drug product batches manufactured between November and December 2011, and packaged in the commercial stick packs.

Although the submitted data/information package provides the applicant's responses to the above requests, its content is quite large and approximates to that of a typical Biopharmaceutics section of an NDA. Therefore a Question based Review (QbR) format is being used for this review, omitting the questions for which adequate data and information have been summarized in the original review, and adding those that were initially excluded.

1) Dissolution Method and Acceptance Criterion:

The proposed dissolution method (PA (b) (4)) and acceptance criterion are displayed below.

USP Apparatus	Paddle Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
					(b) (4)

The Applicant's proposed dissolution method (PA (b) (4)) for Lanthanum Carbonate Powder, 750 and 1000 mg, was assessed and found to be unacceptable. Although the addition of the surfactant, Tween 80, (b) (4), the choice of a (b) (4)% concentration is very high and not supported by the provided data. The submitted dissolution profiles with lower Tween 80 concentrations (b) (4) appear to be

more appropriate and more likely to demonstrate higher discriminating power than the selected (b)(4)% surfactant concentration.

Using the proposed method, the proposed dissolution acceptance criterion of Q = (b)(4)% at (b)(4) min is adequate for the 750 mg strength, which exhibits a slower dissolution rate, but permissive for the 1000 mg strength.

2) Biowaiver Request for the 750 mg Strength

The Applicant provided the following data/information in support of the biowaiver request for the 750 mg strength:

i) In-vivo PD equivalence study on the higher (1000 mg) strength (21 CFR 320.22(d)(2)(iii). The Office of Clinical Pharmacology has reviewed the study and found the results to be acceptable;
ii) Compositional proportionality data of the 750 and 1000 mg strengths ((21 CFR 320.22(d)(2)(i); and
iii) Similar dissolution profiles between the 750 and 1000 mg strengths in the proposed regulatory dissolution test method (*f*2 = 84).

The Applicant's data and rationale for not conducting dissolution testing in two additional pH-media are acceptable. Therefore, the biowaiver request for the 750 mg is granted.

II) RECOMMENDATION

The ONDQA-Biopharmaceutics team has reviewed the additional data and information amendment submitted to NDA 204-734 for Lanthanum Carbonate Powder, 750 and 1000 mg. Based on the assessment of the overall data, the proposed dissolution method is found to be unacceptable and from the Biopharmaceutics perspective a COMPLETE RESPONSE (CR) is recommended for this NDA.

The following deficiencies, comments, and requests for information should be conveyed to the Applicant in the CR communication:

1. The provided dissolution method development data do not support the selection of (b)(4)% Tween 80 as surfactant concentration in the dissolution medium of proposed method PA (b)(4) and is not acceptable. The provided dissolution profiles with lower Tween 80 concentrations showed complete dissolution (e.g., (b)(4)% dissolution in (b)(4) minutes with (b)(4)% surfactant) and are more likely to demonstrate adequate discriminating power compared to the selected (b)(4)% surfactant concentration.

2. Adequacy of the (b) (4) rpm agitation speed for the proposed dissolution method PA (b) (4) has not been fully investigated. Data for the alternate paddle speed of (b) (4) rpm were only provided for the (b) (4)% surfactant concentration and the results indicate that (b) (4) rpm is the optimal paddle rotation speed for this concentration.

3. The formulation approach adopted in the investigation of the discriminating ability of the proposed dissolution method is not acceptable. The scenario investigated is unlikely to occur; i.e. (b) (4)

4. Provide additional data in support of your choice of surfactant concentration, paddle speed, and discriminating power; your experimental investigations should include (but not be limited to) the following:

   - Conduct further experiments with paddle speeds of 50 and 75 rpm (as needed) and surfactant concentrations of 0.25%, 0.5%, 0.75%, 1%, Tween 80. Provide the individual vessel data at 15, 20, 30, 45, and 60 minutes and the descriptive statistics. Also provide the individual dissolution plots, including the mean dissolution profiles for both 50 and 75 rpm/per surfactant concentration in each individual plot.
   - Based on the results from the above, revise (as appropriate) the dissolution method for your drug product;
   - Provide the complete dissolution profile data from the new experiments investigating the discriminating power of the revised dissolution method as recommended in comment 3 above.

5. Using the revised dissolution method, collect dissolution profile data (15, 20, 30, 45, and 60 minutes, n=12) from the registration and other available stability batches at the current stability time points. Provide the individual vessel data and the descriptive statistics. Based on the overall data, submit a proposal for the dissolution acceptance criterion of your drug product.

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/s/

OKPONANABOFA ERADIRI
12/20/2013

ANGELICA DORANTES
12/20/2013

QUALITY-BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 204-734 (000)	**Reviewer:** Okpo Eradiri, Ph.D.	
Division:	DCRP		
Applicant:	Shire	**Team Leader:** Angelica Dorantes, Ph.D.	
Trade Name:	Fosrenol	Acting Biopharmaceutics Supervisor: Richard Lostritto, Ph.D.	
Generic Name:	Lanthanum Carbonate Powder	**Date Assigned:**	Mar 25, 2013.
Indication:	Reduction of phosphate in patients with end stage renal disease.	**Date of Review:**	Oct 7, 2013.
Formulation/strength	Powder/750 and 1000 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates	**Date of informal/Formal Consult**	**PDUFA DATE**
Feb 28, 2013 (Original NDA) Sept 5, 2013 (Amendment Serial-009)	March 25, 2013	Feb 3, 2014

Type of Submission:	505(b)(1)
Key review points	1. Rationale for not including dissolution as a QC release test and for stability; 2. Acceptability of data supporting the biowaiver request for the lower (750 mg) strength.

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II) SUMMARY OF BIOPHARMACEUTICS FINDINGS

The Applicant is the holder of the approved NDA 21-468 for Lanthanum Carbonate Chewable Tablets, which is the Reference Listed Drug product for generics of the drug. This NDA provides for an alternative formulation to the chewable tablets in cases when a patient may have difficulty in chewing the tablets due to tablet hardness, tooth injury, aspiration, etc. This proposed (powder) drug product is intended to be mixed with soft food and then ingested.

In this NDA submission, the Applicant has included their justification for not developing a dissolution test for the powder dosage form of the drug

This review focuses on the evaluation of the following:

1) Acceptability of rationale for excluding dissolution testing from the QC release tests; (section 3.2.P.5.6, page 2)
2) Justification for not performing comparative dissolution testing in support of the biowaiver request for the 750 mg strength (section 1.12.13).

1) Rationale for Excluding Dissolution from QC Release Test Methods:

The Applicant's rationale submitted in Amendment Serial #-009 dated 9/5/2013, for excluding dissolution from QC release testing and generating dissolution data for information purposes only is not acceptable. Although the final dosage form is described as a powder, it actually comprises (b) (4) and packed into sachets of 750 and 1000 mg. Several factors affect the physicochemical properties of (b) (4) dissolution remains a crucial test to characterize their quality. Since in-vivo dissolution of lanthanum carbonate and binding of phosphate occur in only the acidic stomach environment, evaluation of in-vitro release of the drug becomes even more important and should be implemented as a QC release test and in the stability program.

The Applicant generated up to 24 months of dissolution data on the stability batches. Due to the (b) (4) paddle speed of (b) (4) rpm and since the method's robustness and discriminating ability were not confirmed/validated, the data were not rigorously reviewed. The use of surfactant in the dissolution medium in the most recent dissolution testing of one batch each of the 750 and 1000 mg strengths permitted the paddle speed to be (b) (4) rpm, a more standard rotation speed. The Applicant can therefore investigate and optimize the amount and type of surfactant needed to develop a robust dissolution method.

2) Acceptability of Biowaiver Request for the 750 mg Strength

The Applicant initially did not submit comparative in-vitro dissolution data for the two strengths of their proposed product in the NDA as stipulated in 21 CFR 320.22(d)(2)(ii). In a September 5, 2013 response to an IR dated August 8, 2013, the Applicant submitted mean dissolution data (n = 12) on the 750 and 1000 mg strengths; the calculated f_2

similarity factor was (b) (4) indicating that the two dissolution profiles are similar. Multi-point dissolution data in two additional dissolution media were not provided. The dissolution method used for the comparative dissolution test was not validated and the Applicant does not deem the method a regulatory method for use in the QC testing of the product. The utility and validity of the data generated are therefore questionable. In addition, the absence of data from two additional dissolution media as requested in the IR letter still makes the biowaiver supporting data incomplete. It is noted that compositional proportionality between the two strengths of the proposed product, as required by 21 CFR 320.22(d)(2)(i), has been met by the data presented in the NDA. The in-vivo pharmacodynamic equivalence study as required by 21 CFR 320.22(d)(2)(iii) was conducted by the Applicant. If OCP assesses the study results as acceptable, this requirement for the biowaiver will also be met. The similar comparative dissolution data requirement is pending and will be determined when a robust dissolution method is developed, validated and submitted for review.

II) RECOMMENDATION

The ONDQA-Biopharmaceutics team has reviewed NDA 204-734 for Lanthanum Carbonate Powder, 750 and 1000 mg. Due to the lack of a validated QC dissolution method for batch release and stability testing, from the Biopharmaceutics perspective a Complete Response (CR) is recommended for this NDA.

The following comments and requests for information should be conveyed to the Applicant in the CR communication:

1. Your response to our Information Request (IR) dated September 5, 2013, on the requirement for a QC release dissolution test method is not acceptable. As we stated in the IR, dissolution of lanthanum carbonate must take place for binding of phosphate to occur. In addition, the final "powder" formulation comprises (b) (4) not the drug substance. The dissolution of the drug substance (b) (4), is therefore critical in the quality control of your proposed drug product.

2. Below are general guidelines that should be taken into consideration in the development and validation of a QC dissolution method and on the setting of the dissolution acceptance criterion that is appropriate for your product and suitable for use in batch release and on stability testing:

   A. ***Dissolution Test:*** Include the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:
      i. Solubility data for the drug substance over the relevant physiologic pH range;
      ii. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution method as the optimal test for your product. If a surfactant is used, include the data supporting the selection of the type and amount of surfactant. The testing

conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least (b)(4)% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable;

iii. Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*);

iv. Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., (b)(4)% change to the specification-ranges of these variables);

v. Supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

B. ***Dissolution Acceptance Criterion:*** For the selection of the dissolution acceptance criterion of your product, the following points should be considered:

i. The dissolution profile data from commercial/validation batches should be used for the setting of the dissolution acceptance criterion of your product (i.e., specification-sampling time point and specification value).

ii. The in vitro dissolution profile should encompass the timeframe over which at least (b)(4)% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.

iii. For immediate release products the selection of the specification time point should be where Q= (b)(4) % dissolution occurs.

3. Your biowaiver request for the proposed 750 mg strength cannot be granted at this time due to the lack of complete/adequate supportive information. Although you submitted comparative dissolution data in support of your biowaiver request, these data were collected using a dissolution method that is not validated. The use of (b)(4)% Tween 80 as surfactant in the dissolution medium is extreme and should be re-examined as indicated in the comments above (A(ii)). In addition, you failed to submit multi-point dissolution data in two additional pH media as requested in the IR dated August 8, 2013. To support the approval of the biowaiver request for this strength, provide the requested data after developing and validating a dissolution method.

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III) QUESTION BASED REVIEW – BIOPHARMACEUTICS EVALUATION

A) GENERAL ATTRIBUTES

1. ***What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?***

Drug Substance

Lanthanum Carbonate is a white powder. The drug molecule exists as a hydrate with 4-5 moles of bound water. The molecular formula is $La_2(CO_3)_3.4H_2O$. (b) (4) [redacted]. Lanthanum carbonate is soluble in aqueous solvents at acidic pH but exhibits poor solubility at alkaline pH. Lanthanum carbonate is insoluble in organic solvents.

Drug Product

The intended drug product is an immediate-release, white to off-white powder in an elongated sachet. The manufacturing process (b) (4) [redacted] The components and composition of Lanthanum Carbonate Tablets are summarized in Tables 1 and 2 for the 750 and 1000 mg strengths, respectively.

Table 1. Composition of Lanthanum Carbonate Powder, 750 mg.

Ingredient	Amount (mg)	Function	Reference to Standards
Drug Substance(s)			
Lanthanum Carbonate Hydrate[a] (Equivalent to elemental Lanthanum)	1431 (750)	Active ingredient	Sponsor's specification 3.2.S.4.1
Excipient(s)			
Dextrates (Hydrated)[b]	(b) (4) [redacted]		USP-NF
Colloidal Silicon Dioxide			USP-NF
Magnesium Stearate			USP-NF
Total	2100		

a The lanthanum carbonate hydrate is adjusted for lanthanum assay.
b The dextrates level is adjusted to compensate for the lanthanum assay to maintain total dose weight.

Table 2. Composition of Lanthanum Carbonate Powder, 1000 mg.

Ingredient	Amount (mg)	Function	Reference to Standards
Drug Substance(s)			
Lanthanum Carbonate Hydrate [a] (Equivalent to elemental Lanthanum)	1908 (1000)	Active ingredient	Sponsor's specification 3.2.S.4.1
Excipient(s)			
Dextrates (Hydrated) [b]	(b) (4)		USP-NF
Colloidal Silicon Dioxide			USP-NF
Magnesium Stearate			USP-NF
Total	2800		

a The lanthanum carbonate hydrate is adjusted for lanthanum assay.
b The dextrates level is adjusted to compensate for the lanthanum assay to maintain total dose weight.

It is pertinent to mention that the Applicant asserts that all the excipients in the powder formulation are the same as those in the approved Fosrenol Chewable Tablets. However, the quantities, relative to the drug substance, were reduced in order to lessen the total weight of each unit dose. For example, the quantity of the diluent (Dextrates) was reduced by (b) (4)% in the proposed powder formulation relative to the chewable tablet.

B) DISSOLUTION INFORMATION

2. What is the proposed dissolution method?

The Applicant asserts in the NDA that "Lanthanum carbonate acts locally in the gastrointestinal tract to bind ingested phosphate, therefore, dissolution is not critical to performance".

No dissolution method is therefore proposed for the QC release testing of Lanthanum carbonate Powder. However, the Applicant has used the following method to perform dissolution testing of the clinical batch (1000 mg) 5 months after manufacture:

Table 3: Dissolution test method for Lanthanum Carbonate Powder used during formulation development

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium
(b) (4)				

The Applicant performed dissolution testing on the primary registration batches for both the 750 and 1000 mg strengths immediately after manufacture and in the stability program for up to 24 months.

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/s/

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