

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204734Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

NDA # 204-734 (Division of Cardiovascular and Renal Products)
Date: 31-Jul-2014, Resubmission
Product Name: Fosrenol® (lanthanum carbonate) Oral Powder
Company Name: Shire Development LLC
Subject: Approval of the NDA 204-734 (Amendments 28-Jul-2014, 31-Jul-2014, 08-Aug-2014, 26-Aug-2014, and 04-Sep-2014)

The following updated information is included in this Memorandum:

1. The issue on dissolution method and acceptance criteria that was a subject of CR recommendation for this NDA, has been resolved by ONDQA Biopharmacology Reviewer based on the provided data and information as well as the PMC agreed-to by the Applicant (refer to the Review dated 08-Sep-2014). The interim dissolution method and acceptance criterion for Fosrenol (lanthanum carbonate) powder is found to be acceptable.
2. The applicant has provided the updated drug product specifications that include dissolution method and acceptance criteria for Fosrenol Oral Powder, 750 mg and 1000 mg, the Section 3.2.P.5.1 of the NDA (refer to the Attachment 1).
3. The applicant has addressed CMC comment to include the equivalence statement for dosage strengths in the carton and container labels (refer to the final carton and container labels in the DMEPA Review dated 29-Aug-2014).
4. Regarding the inclusion of the statement "Product of Italy" as country of origin in the drug product carton labels, the Agency confirms that product's country of origin is governed by the regulations set forth by the U.S. Customs and Border Protection. The Agency has no further comment on this statement in the proposed label.
5. The updated overall Acceptable OC recommendation for drug substance and drug product manufacturing facilities is issued on 21-Aug-2014 (refer to the Attachment 2).

Evaluation: The provided information is Adequate.

Recommendation and Conclusion on Approvability

NDA 204-734 for Fosrenol® (lanthanum carbonate) Oral Powder, 750 mg and 1000 mg, is recommended for **APPROVAL** from a Chemistry, Manufacturing and Controls standpoint. The issue on dissolution method and acceptance criteria has been resolved by ONDQA Biopharmacology Reviewer (refer to the Review dated 08-Sep-2014). Based on the drug product stability data, and based on the acceptance of the dissolution stability data by ONDQA Biopharm reviewer, the following expiration dating period is recommended: 24 months expiry for Fosrenol® (lanthanum carbonate) Oral Powder, 750 mg and 1000 mg, packaged in commercial stick packs made of aluminum foil laminate (80 mm x 23 mm). The updated overall Acceptable OC recommendation for drug substance and drug product manufacturing facilities is issued on 21-Aug-2014.

Attachment 1

Table 1: Specifications for Lanthanum Carbonate 1000mg Oral Powder

Parameter	Test Method	Specification (Acceptance Criteria Applied)
Appearance ^a	Visual	White to off-white powder
Lanthanum Identity	ICP	Positive
Carbonate Identity	USP	Positive
Lanthanum Assay ^a	Titration	90.0 to 110.0% of label claim
(b) (4) Determination ^a	USP/Ph. Eur.	NMT (b) (4)%
Mean Weight	Determine average weight of the contents of 20 stick packs.	(b) (4)% of target fill weight (1000mg: 2660–2940mg)
Uniformity of Dosage Units	USP	Complies with USP
Dissolution ^a	USP Apparatus 2 and Titration	Q= (b) (4)% at (b) (4) minutes Meets USP <711>
Lanthanum Hydroxycarbonate Impurity (b) (4)	(b) (4)	NMT (b) (4)%
Lanthanum Hydroxycarbonate Impurity (b) (4)	(b) (4)	NMT %

^a Tested on stability.
NMT – Not More Than.

Table 1: Specifications for Lanthanum Carbonate 750mg Oral Powder

Parameter	Test Method	Specification (acceptance criteria applied)
Appearance ^a	Visual	White to off-white powder
Lanthanum Identity	ICP	Positive
Carbonate Identity	USP	Positive
Lanthanum Assay ^a	Titration	90.0 to 110.0% of label claim
(b) (4) Determination ^a	USP/Ph. Eur.	NMT (b) (4)%
Mean Weight	Determine average weight of the contents of 20 stick packs.	(b) (4)% of target fill weight (750mg: 1995–2205mg)
Uniformity of Dosage Units	USP	Complies with USP
Dissolution ^a	USP Apparatus 2 and Titration	Q= (b) (4)% at (b) (4) minutes Meets USP <711>
Lanthanum Hydroxycarbonate Impurity (b) (4)	(b) (4)	NMT (b) (4)%
Lanthanum Hydroxycarbonate Impurity (b) (4)	(b) (4)	NMT %

^a Tested on stability.
NMT – Not More Than.

Attachment 2

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 204734/000	Sponsor:	SHIRE LLC
Org. Code:	110		725 CHESTERBROOK BLVD
Priority:	3		WAYNE, PA 19087
Stamp Date:	28-FEB-2013	Brand Name:	FOSRENOL
PDUGA Date:	30-SEP-2014	Ectab. Name:	
Action Goal:		Generic Name:	LANTHANUM CARBONATE
Distriet Goal:	20-OCT-2013	Product Number: Dosage Form: Ingredient: Strengths:	001; POWDER; LANTHANUM CARBONATE; 750MG 002; POWDER; LANTHANUM CARBONATE; 1000MG
FDA Contacts:	L. SOLDATOVA	Prod Qual Reviewer	3017961758
	T. BOUIE	Product Quality PM	3017901049
	M. MONTELEONE	Regulatory Project Mgr	(HPD-110) 3017061052

Overall Recommendation:	ACCEPTABLE	on 21-AUG-2014	by T. WILSON	()	2404024226
	PENDING	on 07-AUG-2014	by EES_PROD		
	PENDING	on 07-AUG-2014	by EES_PROD		
	ACCEPTABLE	on 29-APR-2013	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 11-APR-2013	by EES_PROD		
	PENDING	on 11-APR-2013	by EES_PROD		
	PENDING	on 11-APR-2013	by EES_PROD		
	PENDING	on 11-APR-2013	by EES_PROD		
	PENDING	on 11-APR-2013	by EES_PROD		

Establishment:	CFN: (b) (4)	FEI: (b) (4)
	(b) (4)	
DMF No:		
Responsibilities:	FINISHED DOSAGE RELEASE TESTER	AADA:
Profile:	CONTROL TESTING LABORATORY	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	14-AUG-2014	
Decision:	ACCEPTABLE	
Reason:	DISTRICT RECOMMENDATION	

Establishment:	CFN: (b) (4)	FEI: (b) (4)
	(b) (4)	
DMF No:		
Responsibilities:	FINISHED DOSAGE MANUFACTURER	AADA:
	FINISHED DOSAGE RELEASE TESTER	
	FINISHED DOSAGE STABILITY TESTER	
Profile:	POWDERS (INCLUDES ORAL AND TOPICAL)	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	21-AUG-2014	
Decision:	ACCEPTABLE	
Reason:	DISTRICT RECOMMENDATION	

Establishment:	CFN: (b) (4)	FEI: (b) (4)
	(b) (4)	
DMF No:		
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER	AADA:
Profile:	CONTROL TESTING LABORATORY	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	16-APR-2013	
Decision:	ACCEPTABLE	
Reason:	BASED ON PROFILE	

Establishment:	CFN: (b) (4)	FEI: (b) (4)
	(b) (4)	
DMF No:		
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER	AADA:
Profile:	CONTROL TESTING LABORATORY	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	07-AUG-2014	
Decision:	ACCEPTABLE	
Reason:	BASED ON PROFILE	

Attachment 2 (cont'd)

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE OTHER TESTER
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 07-AUG-2014
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 12-APR-2013
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE STABILITY TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 07-AUG-2014
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 12-APR-2013
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

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/s/

LYUDMILA SOLDATOVA
09/10/2014

OLEN M STEPHENS
09/11/2014

Memorandum

NDA # 204-734
 Date: 23-Dec-2013
 Product Name: NDA 204-734 for Fosrenol® (lanthanum carbonate) Oral Powder, 750 mg and 1000 mg
 Company Name: Shire Development LLC
 Subject: 1. Quality Amendment dated 18-Dec-2013
 2. Final Recommendation on Action for this NDA from the CMC Perspective

Recommendation and Conclusion on Approvability

A complete response is recommended for NDA 204-734's Fosrenol® (lanthanum carbonate) Oral Powder, 750 mg and 1000 mg, from a Chemistry, Manufacturing and Controls standpoint due to a complete response recommendation from the biopharmaceutics reviewer. The recommendation is based on the biopharmaceutical reviewer's evaluation of the dissolution method and acceptance criteria. The Office of Compliance issued an overall Acceptable recommendation for drug substance and drug product manufacturing facilities on (b) (4).

Background

The purpose of the NDA Amendment dated 18-Dec-2013 is to provide the Shire's full response to the Agency's request at the 4-Nov-2013 teleconference. Specifically, the Agency requested the following information/data:

1. 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.
2. 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.
3. 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.
4. 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.

The evaluation of the Shire's response to the requests #1, #2 (partial) and #3 has been provided in the ONDQA Biopharmaceutical Review dated 20-Dec-2013. The Biopharm reviewer (Okpo Eradiri, Ph.D.) has not accepted the proposed dissolution method.

Evaluation of the Firm's Response to the Request #2

Provided data

Table 1: Specifications for Lanthanum Carbonate 1000mg Oral Powder		
Parameter	Test Method	Specification (Acceptance Criteria Applied)
Appearance ^a	Visual	White to off-white powder
Lanthanum Identity	ICP	Positive
Carbonate Identity	USP	Positive
Lanthanum Assay ^a	Titration	90.0 to 110.0% of label claim
(b) (4) Determination ^a	USP/Ph. Eur.	NMT (b) (4)%
Mean Weight	Determine average weight of the contents of 20 stick packs.	(b) (4)% of target fill weight (1000mg: 2660–2940mg)
Uniformity of Dosage Units	USP	Complies with USP
Dissolution ^a	USP Apparatus 2 and Titration	Q= (b) (4)% at (b) (4) minutes Meets USP <711>
Lanthanum Hydroxycarbonate Impurity (b) (4)	(b) (4)	NMT (b) (4)%
Lanthanum Hydroxycarbonate Impurity (b) (4)	(b) (4)	NMT %

^a Tested on stability.
 NMT = Not More Than.

Table 1: Specifications for Lanthanum Carbonate 750mg Oral Powder

Parameter	Test Method	Specification (acceptance criteria applied)
Appearance ^a	Visual	White to off-white powder
Lanthanum Identity	ICP	Positive
Carbonate Identity	USP	Positive
Lanthanum Assay ^a	Titration	90.0 to 110.0% of label claim
Water Determination ^a	USP/Ph. Eur.	NMT (b)(4)%
Mean Weight	Determine average weight of the contents of 20 stick packs.	(b)(4)% of target fill weight (750mg: 1995–2205mg)
Uniformity of Dosage Units	USP	Complies with USP
Dissolution ^a	USP Apparatus 2 and Titration	Q= (b)(4)% at (b)(4) minutes Meets USP <711>
Lanthanum Hydroxycarbonate Impurity (b)(4)	(b)(4)	NMT (b)(4)%
Lanthanum Hydroxycarbonate Impurity (b)(4)	(b)(4)	NMT %

^a Tested on stability.
NMT = Not More Than.

Analytical Method

Determination of the lanthanum content is performed by the same method as that described for assay in the original submission. This analytical method was adequately validated as per Review #1 dated 10-Oct-2013 (reviewer Lyudmila Soldatova, Ph.D.).

Evaluation: Inadequate. The revised specification includes the proposed test and limits for dissolution. This analytical method for lanthanum content as a part of the dissolution method was adequately validated as per Review #1 dated 10-Oct-2013 (reviewer Lyudmila Soldatova, Ph.D.). Biopharm reviewer has not accepted the proposed dissolution method and acceptance criteria of Q= (b)(4)% at (b)(4) minutes.

Evaluation of the Firm’s Response to the Request #4

Provided data

Shire has provided the updated 18-month long-term stability data for the three commercial-scale batches of each dosage strength (750 mg and 1000 mg) that were manufactured in November/December 2011 and packaged in the commercial stick packs (b)(4) as compared to the 12-month data for the same batches in the original submission. This stability data includes the dissolution data collected using the proposed dissolution method and acceptance criterion of Q= (b)(4)% at (b)(4) minutes. The dissolution data for the developmental batches packaged in the non-commercial (b)(4) stick packs are provided at the final time points of 36-48 months.

Evaluation: The 18-month stability data for all tested conditions provided for the primary stability batches meet the proposed specifications but the dissolution data is incomplete. The dissolution data at the long term (25°C/60%RH) and intermediate (30°C/75%RH) storage conditions are provided for 9, 12 and 18 months time points; no dissolution data provided at the accelerated condition (40°C/75%RH). The data at the long-term and intermediate conditions meet the proposed Q= (b)(4)% at (b)(4) minutes; however, the conclusion on the trends in dissolution can not be made since the data at the initial time point are absent. Such conclusion can be made based on the 9-month long-term and 6-months accelerated dissolution data provided for batches manufactured later than the primary stability data. The conclusion is that the trend of decreasing of dissolution is observed for 1000 mg batches at the long-term conditions, and more prominent decreasing trend is observed at the accelerated condition; nonetheless, all dissolution data are within the proposed limits. The similar but less significant trend is observed for 750 mg batch. The single final point (36-48 months) supportive dissolution data from the batches packaged in the non-commercial packs meet the proposed Q= (b)(4)% at (b)(4) minutes. The applicant proposed the (b)(4)-month expiry for the drug product based on the 18-month stability data.

Comment for Carton and Container Labels

Revise the equivalency statement in the “Active Ingredient” section of back panel to read:
 750 mg carton: “Each stick pack contains 1431 mg lanthanum carbonate hydrate equivalent to 750 mg lanthanum”
 1000 mg carton: “Each stick pack contains 1908 mg lanthanum carbonate hydrate equivalent to 1000 mg lanthanum”.

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/s/

LYUDMILA SOLDATOVA
12/23/2013

OLEN M STEPHENS
12/23/2013

NDA 204-734

Fosrenol (lanthanum carbonate)

Shire Development LLC

Lyudmila N. Soldatova, Ph. D.
Office of New Drug Quality Assessment
for
Division of Cardiovascular and Renal Products

Review of Chemistry, Manufacturing, and Controls

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Chemistry Review Data Sheet

1. NDA 204-734
2. REVIEW #: 1
3. REVIEW DATE: 10-OCT-2013
4. REVIEWER: Lyudmila N. Soldatova

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

28-FEB-2013

Amendment

05-SEP-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Shire Development LLC
Address: 725 Chesterbrook Blvd.
Wayne, PA 19087
Representative: SabrinaR. Girty, J.D., Director,
Global Regulatory Affairs
Telephone: 484-595-5368

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Fosrenol
- b) Non-Proprietary Name (USAN): Lanthanum Carbonate
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

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

11. DOSAGE FORM: Oral Powder

12. STRENGTH/POTENCY: 750 mg and 1000 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Lanthanum carbonate

Molecular Formula: $\text{La}_2(\text{CO}_3)_3 \cdot \text{XH}_2\text{O}$ where X is an average 4-5 moles

Molecular Weight: Relative Molecular Mass: 457.8 (anhydrous)

Relative Molecular Mass: 529.9 (assuming 4 moles H_2O)

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	Packaging material for drug product

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Overall Acceptable	29-Apr-2013	Office of Compliance
Pharm/Tox	Pending		Xavier Joseph, Ph.D.
Biopharm	Pending		Okpo Eradiri, Ph.D.
DMEPA	Acceptable	07-Oct-2013	Kimberly Defronzo, Ph.D.
Methods Validation	Acceptable as per this Review	23-Sep-2013	Lyudmila Soldatova, Ph.D.
EA	Categorical exclusion is granted as per this Review	23-Sep-2013	Lyudmila Soldatova, Ph.D.

The Chemistry Review for NDA 204-734

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 204-734 for Fosrenol® (lanthanum carbonate) Oral Powder, 750 mg and 1000 mg, cannot be approved at this time from a Chemistry, Manufacturing and Controls standpoint. The approval is contingent upon satisfactory resolution of the issue on dissolution method and acceptance criteria raised by ONDQA Biopharm reviewer. The overall Acceptable OC recommendation for drug substance and drug product manufacturing facilities is issued on 29-Apr-2013.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The proposed dosage form for NDA 204-734 for Fosrenol® (lanthanum carbonate) Oral Powder, 750 mg and 1000 mg, is white to off-white oral powder with immediate release mechanism containing 1431 mg lanthanum carbonate hydrate equivalent to 750 mg lanthanum, and containing 1908 mg lanthanum carbonate hydrate equivalent to 1000 mg lanthanum, respectively. Fosrenol is a phosphate binder indicated to reduce serum phosphate in patients with end stage renal disease. The lanthanum carbonate oral powder has been developed as an alternative to the marketed Fosrenol® chewable tablets due to the patients complains on difficulties to chew the tablet. The drug product is packaged in a heat-sealed aluminum foil laminate stick pack (elongated sachet), ~ 80 mm x 23 mm. The excipients in the oral powder formulation, hydrated dextrates, magnesium stearate and colloidal silicon, are of compendial quality, USP/NF. The particle size of the drug substance and of all ingredients are controlled by the specification (b) (4), respectively. The manufacturing process consists of (b) (4)

(b) (4). The applicant has performed the Design of Experiment (DoE) study to evaluate the effects of key variables on product attributes and to establish operating ranges for both stages of the manufacturing process. Results of DoE demonstrated that the manufacturing process is (b) (4)

Executive Summary Section

(b) (4)

he product specification is similar to that for the chewable tablets but modified to fit the new dosage form: the dissolution test was removed based on the provided justification. The ONDQA biopharm reviewer has evaluated the applicant rationale for excluding the dissolution test and acceptance criteria. The specification limits for

(b) (4)

The NDA stability package was updated in the Amendment dated 05-Sep-2013 to include the 12-month stability data for the three commercial-scale batches of 750 mg and 1000 mg dosage strengths that were packaged in the commercial stick packs (23mm x 80mm), and stored at long-term (25°C/60%RH) and intermediate (30°C/75%RH) storage conditions. These data, including the previously provided 6-month accelerated stability data demonstrate no any specific trends in the levels of assay and (b) (4) or any other tested parameters. The same conclusion applies to the stability of the developmental batches packaged in non-commercial (b) (4) stick packs, and stored for 36 months and 48 months. Based on the provided updated 12-month stability data for the three commercial-scale batches of 750 mg and 1000 mg dosage strengths in the commercial packs, the 24-month expiry for drug product, 750 mg and 1000 mg, could have been granted providing the successful resolution of the issue with the dissolution method and acceptance criteria as per ONDQA biopharm reviewer. The necessity of the dissolution method and acceptance criteria remains under discretion of the ONDQA biopharm reviewer. The recommended storage condition for drug product is: “Store at 25°C (77°F). Excursions permitted to 15°C–30°C (59°F–86°F)”.

Drug Product Label Issue. The established name, lanthanum carbonate, does not match the dosage strength expressed as the amount of elemental lanthanum, 750 mg or 1000 mg (prohibited mismatch in labeling). Even though usage of the established name as a salt could be used in the labels as an exception for simple salts from USP Salt Policy (effective 1-May-2013), the mismatch had to be resolved. This issue was consulted with CDER Drug Nomenclature Policy Group, USP liaison for FDA, with DMEPA regarding potential medical error, with clinical reviewer, and the ONDQA Precedence Committee held on 20-Aug-2013 has granted the mismatch exception for this drug label. The applicant was advised to revise the labels by addition of the equivalence statement reflecting the quantity of lanthanum carbonate equals to the dosage strengths of 750 mg and 1000 mg; the suggested revision of the labels has been sent to the applicant.

The active ingredient, lanthanum carbonate, is a white to almost white powder consisting mostly of lanthanum carbonate tetrahydrate, $\text{La}_2(\text{CO}_3)_3 \cdot 4 \text{H}_2\text{O}$, although other lanthanum carbonate hydrates may be present with on average 4-5 moles of bound water. The structure is made up of layers containing lanthanum atoms and carbonate ions. (b) (4)

Executive Summary Section

Lanthanum carbonate has poor aqueous solubility at an alkaline pH with increasing solubility in an acid environment. It is insoluble in organic solvents. Particle size is a critical quality attribute and is controlled using (b) (4) specification. The applicant cross-referenced all relevant CMC drug substance information to the approved Fosrenol® chewable tablets, NDA 21-468. Shire provided copy of the approved regulatory release specifications for lanthanum carbonate drug substance and the batch analysis data for the batches of lanthanum carbonate drug substance that were used to formulate and manufacture the batches of Fosrenol Oral Powder. All batch results meet the approved drug substance specifications.

B. Description of How the Drug Product is Intended to be Used

The subject of the NDA is Fosrenol® (lanthanum carbonate) Oral Powder, 750 mg and 1000 mg, being developed by Shire Development LLC to reduce serum phosphate in patients with end stage renal disease (ESRD).

Proposed Fosrenol Administration

Storage - Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).
[See USP controlled room temperature].

C. Basis for Approvability or Not-Approval Recommendation

NDA 204-734 cannot be approved at this time from a Chemistry, Manufacturing and Controls standpoint. The outstanding issues that need to be resolved include the satisfactory resolution of the issue on dissolution method and acceptance criteria raised by ONDQA Biopharm reviewer, and subsequent submission of the dissolution data for primary stability batches. The drug substance information is cross-referenced to the approved NDA 21-468. The overall Acceptable OC recommendation for drug substance and drug product manufacturing facilities is issued on 29-Apr-2013.

Executive Summary Section

III. Administrative**A. Reviewer's Signature***Lyudmila N. Soldatova***B. Endorsement Block**

LSoldatova: October 10, 2013

KSrinivasachar: October 10, 2013

RSood: October 10, 2013

C. CC Block

TBowie

MMonteleone

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/s/

LYUDMILA SOLDATOVA
10/10/2013

RAMESH K SOOD
10/10/2013

Initial Quality Assessment
Branch I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	204734
Applicant:	Shire Development LLC
Letter Date:	28 Feb 2013
Status Date:	28 Feb 2013
PDUFA Date:	28 Dec 2013
Tradename:	FOSRENOL
Established Name:	Lanthanum Carbonate
Dosage Form:	Oral powder, 750 mg and 1000 mg
Route of Administration:	Oral
Indication:	Reduction of serum phosphate in patients with End Stage Renal Disease
Assessed by:	Kasturi Srinivasachar
ONDQA Fileability:	Yes

$\text{La}_2(\text{CO}_3)_3 \cdot \text{XH}_2\text{O}$ where X is on average 4-5 moles

Summary

This is a 505(b)(1) NDA for a new oral formulation of lanthanum carbonate, a phosphate binder. A chewable tablet dosage form of lanthanum carbonate has been marketed under the same tradename, Fosrenol, (NDA 21468) since 2004. The applicant states that they developed this new formulation, an oral powder which is intended to be mixed with soft food, to provide greater choice for patients who have difficulty chewing tablets. It is anticipated that this alternate treatment option will lead to greater patient compliance. The NDA contains a single biopharmaceutical study designed to demonstrate equivalence of the oral powder formulation with the currently marketed chewable tablet. A multidiscipline pre-NDA meeting was scheduled with the Agency for Nov.13, 2012 to discuss the planned NDA submission. CMC questions for which Shire sought responses included the acceptability of cross-reference to NDA 21468 for all drug substance information and the designation of the dosage form as "Oral Powder". They were told that cross-reference to the approved NDA, 21468 for drug substance information was acceptable. Regarding the dosage form designation, Shire was informed that Oral Powder was tentatively acceptable pending evaluation of all information to be submitted in the NDA. The agency also agreed that further in vivo or in vitro comparison testing to support the biowaiver for the 750 mg strength was not required.

Drug Substance

Lanthanum carbonate is a white to almost white powder consisting (b) (4) lanthanum carbonate hydrates may be present with on average 4-5 moles of bound water. Lanthanum carbonate dissolves in dilute mineral acids with effervescence. It is insoluble in organic solvents. It has poor aqueous solubility at alkaline pH with increasing solubility in an acidic environment. Particle size is a critical quality attribute and is controlled (b) (4) specification. All CMC information for the drug substance is cross-referenced to NDA 21468. The current NDA does contain the specification as well as batch analysis data for batches used in the manufacture of the oral powder formulation. The retest date is (b) (4) months.

Drug Product

The drug product is a white to off-white powder contained in an aluminum foil laminate stick pack, approximately 80 mm x 23 mm. Two strengths are available, 750 and 1000 mg. The strengths are based on elemental lanthanum. Standard compendial excipients, dextrates (hydrated), colloidal silicon dioxide, and magnesium stearate are used in the formulation. The same inactive ingredients are used in the approved chewable tablet formulation (b) (4). The composition (b) (4) both strengths but filled at different fill weights to achieve the required dose. It is stated that the main objectives of the formulation development program was to reduce the total weight of the formulation for a given dose of lanthanum carbonate, to maintain palatability and to have an efficient manufacturing process. The product is manufactured in Germany by Catalent. There (b) (4) to the manufacturing process:

(b) (4)

The product specification is similar to the chewable tablets except that dissolution testing is not included. The only degradation product identified is (b) (4) which can exist in (b) (4). Assay is performed by a complexometric titration procedure which is also used for Content Uniformity. Batch analysis data have been provided for clinical, registration and validation batches.

Long term, intermediate and accelerated stability data have been provided for 2 primary commercial scale batches of each dosage strength. The proposed expiration dating period of (b) (4) months is based on data from these batches. In addition, some stability data are available from multiple validation batches. The test attributes include appearance, assay, (b) (4) degradation products. Bulk powder stability has also been monitored for up to 6 months. An annual batch stability commitment has been provided.

Critical Review Issues

Drug Product

- The claim for a biowaiver for the lower dosage strength, 750 mg, as well as the rationale for not including a dissolution test in the product specification should be reviewed by the Biopharmaceutics reviewer.
- Has the manufacturing process been described in sufficient detail?
- Have the values or ranges for process parameters for routine manufacture of bulk powders and filling stick packs been adequately justified by the DoE results?
- Regarding the specification:
 - Has the omission of a microbial limits test been justified?
- Regarding stability:
 - Can an expiration dating period of (b) (4) months be granted based on the available data?
 - Is the annual batch stability commitment to place only one dosage strength of product at a batch size of (b) (4) on long term stability satisfactory? It is stated that the other strength and batch size will be rotated each year as applicable.

Labeling

- The established name, lanthanum carbonate, and strength do not match since the latter refers to the amount of lanthanum. It should be noted that Fosrenol Chewable Tablets is also mislabeled in the same way.
- The D & A section of the PI states that Fosrenol oral powder should be consumed within (b) (4) after mixing with soft food. What is the basis for this statement?

Comments and Recommendations: The NDA is fileable – see attached filing check list. Facilities will be entered into EES shortly. The reviewer should verify the completeness of the entries. Methods validation will not be requested at this time since this is not an NME and the other criteria are also not met. The reviewer has the option to initiate MV if the in-depth review reveals the need for one. A single reviewer is recommended since the drug substance information is cross-referenced to an approved NDA and the dosage form is very simple.

Kasturi Srinivasachar_____

CMC Lead

Ramesh Sood_____

Branch Chief

Mar. 22, 2013

Date

Mar. 22, 2013

Date

PRODUCT QUALITY -- CMC and BIOPHARMACEUTICS
FILING REVIEW FOR NDA

NDA Number: 204734 **NDA Type:** 3 **Established/Proper Name:** Lanthanum carbonate/Fosrenol
Original NDA, N-000

Applicant: Shire Development LLC **Letter Date:** Feb 28, 2013 **PDUFA Goal:** Dec 28, 2013
Stamp Date: Feb 28, 2013 **(Standard Review)**

CMC Reviewer: Lyudmila Soldatova

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		
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* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion requested

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Cross-reference to NDA 21468
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Cross-reference to NDA 21468
14.	Does the section contain information regarding the characterization of the DS?	X		Cross-reference to NDA 21468
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		Cross-reference to NDA 21468
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any Comparability Protocols been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	Some QbD elements provided
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		LoA to DMF for packaging material provided

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		Fileable for Product Quality. See Biopharmaceutics Filing Review for fileability of the Biopharm Section
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
36.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			See Biopharm filing review
37.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	

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/s/

KASTURI SRINIVASACHAR
03/22/2013

RAMESH K SOOD
03/25/2013