CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204734Orig1s000

OTHER REVIEW(S)

Project Manager Overview

NDA 204734

Fosrenol (lanthanum carbonate) oral powder, 750 and 1000 mg

Background:

On February 28, 2013, NDA 204734 was submitted by Shire Development LLC under Section 505(b)(1) of the FD&C Act for lanthanum carbonate, oral powder for the reduce serum phosphate in patients with end stage renal disease (ESRD). The Review priority for this application was determined to be STANDARD and a PDUFA goal date of December 28, 2013 was assigned. This application provides for a new dosage form of Fosrenol, which was first approved as a chewable tablet on October 26, 2004 under NDA 021468.

This NDA was discussed at the Pediatric Review Committee on October 9, 2013 and subsequently with Dr. Lynne Yao. The Division decided to grant a full waiver of pediatric studies required under PREA.

This NDA was the subject of a Pre-NDA meeting request under this NDA. The meeting was cancelled after the Division provided the applicant with preliminary comments to their questions on November 6, 2012.

A complete response letter was issued for this application on December 24, 2013. The Division met with the applicant on May 15, 2014 in a post-Action meeting.

The NDA was resubmitted on July 31, 2014 and determined by the Division to be a Class I resubmission with a September 30, 2014 PDUFA Goal Date.

The applicant submitted a Post Marketing Commitment on September 4, 2014. The PMC Development Template and Action letter were cleared by the Safety Requirements Team on September 23, 2014.

NDA Reviews and Memos

Division Director's Memo
Dr. Norman Stockbridge; December 24, 2013; September 24, 2014

In his memo of September 24, 2014, Dr. Stockbridge describes that the biopharmacutics issues have been satisfactorily resolved and conveys the Division's decision to approve the NDA.

In his memo dated December 24, 2013, Dr. Stockbridge outlines that the sole issue preventing approval is the biopharmaceutics issue.

CDTL Memo
Dr. Divya Menon-Andersen; December 21, 2013
Recommended Action: Complete Response

In her memo of December 21, 2013, Dr. Menon-Andersen recommends a complete response action based on unresolved biopharmaceutics issues.

Clinical/Clinical Pharmacology Review
Drs. Divya Menon-Andersen, Melanie Blank; October 28, 2013
Recommended Action: Approval

In a joint Clinical/ Clinical Pharmacology review, the reviewers conclude that the data support approval of Fosrenol oral powder for the indication to reduce serum phosphate in patients with ESRD.

Chemistry Review
Dr. Lydumila Soldatova; October 10, 2013; December 23, 2013; Sepember 11, 2014
Recommended Action: Approval

In her review of September 11, 2014, Dr. Soldatova recommends the application be approved from a CMC standpoint. Dr. Soldatova outlines that the Biopharmaceutics issue has been satisfactorily resolved.

In her review of December 23, 2013, Dr. Soldatova concludes that the NDA cannot be approved until there is a satisfactory resolution of the dissolution method and acceptance criteria raised by the biopharmaceutics reviewer.

Biopharmaceutics Review
Dr. Okpo Eradiri; October 25, 2013; December 20, 2013; September 8, 2014
Recommended Action: Complete Response

In his review of September 8, 2014, Dr. Eradiri recommends the application be approved based on the applicants interim dissolution method and acceptance criteria, and agreed to Post-Marketing Commitment.

In his review of December 20, 2013, Dr. Eradiri concludes that the proposed dissolution method is unacceptable.

Consult/Other Reviews:

OPDP
2013-11-27 – Labeling Review

DMEPA
2014-08-29 – Labeling Review
2013-10-07 – Labeling Review

SEALD
2013-12-20 – SRPI Review

Action Items:

An Approval letter will be drafted for Dr. Stockbridge's signature.

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/s/

MICHAEL V MONTELEONE
09/24/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	204734	
Product Name:	LANTHANUM CARBONATE POWDER, 750 & 1000 mg	
PMR/PMC Description:	Development of a new, more sensitive dissolution method and a proposal for a dissolution acceptance criterion. Submission of data supporting the newly proposed dissolution method and acceptance limit.	
PMR/PMC Schedule Milestones:	Preliminary Report Submission (high level update/overview of work):	11/29/2014
	Final Report Submission (PMC Supplement):	05/29/2014

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other (Dissolution method development)

The development of a new (more suitable) dissolution method and the collection of dissolution profile data using the new method on a sufficient number of batches to support a proposed dissolution acceptance criterion cannot be completed within the current review cycle.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The current dissolution method is not sufficiently discriminating. The testing parameters are not also adequately evaluated. The goal of the PMC is to develop and validate a more robust dissolution method.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**
     - ☐ Accelerated Approval (subpart H/E)
     - ☐ Animal Efficacy Rule
     - ☐ Pediatric Research Equity Act
     - ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - ☐ Assess a known serious risk related to the use of the drug?
     - ☐ Assess signals of serious risk related to the use of the drug?
     - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - ☐ Analysis of spontaneous postmarketing adverse events?
       Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     - ☐ Analysis using pharmacovigilance system?
       Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

1. The Applicant should develop a more sensitive and robust dissolution method for Lanthanum Carbonate Powder that will demonstrate adequate discriminating power.
2. As part of the new dissolution method development and validation, experiments to investigate the discriminating power of the method should be conducted. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the target formulation and the variant formulations 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).
3. The Applicant should propose a dissolution acceptance criterion that is adequate for the product based on adequate number of commercial batches. The *in-vitro* dissolution profile (e.g., 10, 15, 20, 30, 45, 60 min) 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. The selection of the specification time point should be where Q= (b) (4) % dissolution occurs.
4. The Applicant should provide in three months 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 will provide FDA with a status update but will not include data/conclusions.
   Targeted Submission date: November 2014.
5. The Applicant should submit the entire data package (including, but not limited to, dissolution method development report, proposed dissolution acceptance criterion, supporting dissolution data from the agreed upon number of commercial batches) as a Prior Approval Supplement (PAS). Prior Approval Supplement to include a complete report supporting the revised/new dissolution method (e.g., USP Apparatus 4) and corresponding final dissolution specification.
   Targeted Submission date: May 29, 2015.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☒ Other (Dissolution method development)

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)

☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☐ Does the study/clinical trial meet criteria for PMRs or PMCs?
☐ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

---

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(Signature line for BLAs)

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/s/

OKPONANABOFA ERADIRI
09/08/2014

ELSBETH G CHIKHALE
09/08/2014

Lori A WACHTER
09/09/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	August 28, 2014
Requesting Office or Division:	Division of Cardiovascular & Renal Products (DCRP)
Application Type and Number:	NDA 204734
Product Name and Strength:	Fosrenol (lanthanum carbonate) Oral Powder 750 mg and 1000 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Shire Development LLC
Submission Date:	July 31, 2014
OSE RCM #:	2014-1526
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

This review evaluates the revised container labels, carton labeling, and Prescribing Information for Fosrenol (lanthanum carbonate) Oral Powder for areas of vulnerability that could lead to medication errors.

2 REGULATORY HISTORY

Fosrenol (lanthanum carbonate) Chewable Tablet was approved on October 26, 2004 under NDA 021468. In an effort to aid compliance and offer more choice for patients, the Applicant submitted NDA 204734 for Fosrenol (lanthanum carbonate) Oral Powder, a new formulation, on February 28, 2013.

DMEPA first reviewed the proposed Fosrenol Oral Powder labels and labeling in OSE Review # 2013-1454 dated October 7, 2013[1]. The Applicant submitted revised labels and labeling on December 20, 2013. The application subsequently received a complete response (CR) and DMEPA's recommendations for the revised labels and labeling were sent to the Applicant in the CR letter issued on December 24, 2013[2].

On July 31, 2014, as part of the Class 1 Resubmission, the Applicant submitted revised container labels and carton labeling, the subject of this review.

[1] DeFronzo, K. Label and Labeling Review for Fosrenol Oral Powder (NDA 204734). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 OCT 07. 10 p. OSE RCM No.: 2013-1454.

[2] Stockbridge, N. Complete Response Letter (NDA 204734). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Drug Evaluation 1, Division of Cardiovascular and Renal Products (US); 2013 DEC 24. 16 p. Reference ID No.: 3427645.

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D- N/A
ISMP Newsletters	E – N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The revised container labels and carton labeling submitted on July 31, 2014 incorporated recommendations that we made during a previous label and labeling review[1] and in the CR Letter[2].

5 CONCLUSION

Shire Development LLC incorporated all of our recommendations so the revised labels and labeling adequately address our concerns from a medication error perspective. We have no additional comments at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager: Karen Bengtson, at 301-796-3338.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Fosrenol Oral Powder that Shire Development LLC submitted on July 31, 2014.

Table 2. Relevant Product Information for Fosrenol Oral Powder	
Initial Approval Date	N/A
Active Ingredient	Lanthanum Carbonate
Indication	To reduce serum phosphate in patients with end stage renal disease (ESRD)
Route of Administration	Oral
Dosage Form	Oral Powder
Strength	750 mg and 1000 mg
Dose and Frequency	Divide the total daily dose of Fosrenol and take with or immediately after meals. The recommended initial total daily dose of Fosrenol is 1500 mg. Titrate the dose every 2-3 weeks until an acceptable serum phosphate level is reached. Monitor serum phosphate levels as needed during dose titration and on a regular basis thereafter. In clinical studies of ESRD patients, Fosrenol doses up to 4500 mg were evaluated. Most patients required a total daily dose between 1500 mg and 3000 mg to reduce plasma phosphate levels to less than 6.0 mg/dL. Doses were generally titrated in increments of 750 mg/day.
How Supplied	Stick packs that contain 2.1 g (750 mg) or 2.8 g (1000 mg) oral powder packed in a polyethylene terephthalate/aluminum/polyethylene laminate. • 750 mg Patient pack (1 patient pack contains 9 cartons, each carton contains 10 stick packs (NDC 54092-256-01)) NDC 54092-256-02 • 1000 mg Patient Pack (1 patient pack contains 9 cartons, each carton contains 10 stick packs (NDC 54092-257-01)) NDC 54092-257-02
Storage	Store at 25°C (77°F): excursions permitted to 15° to 30°C (59° to 86°F).

Container Closure	The primary packaging material is an aluminum foil laminate comprised of polyethylene terephthalate/ aluminum/ polyethylene ((b) (4) . The dosage strength will be printed on the stick packs and color will be used to differentiate the two dosage strengths. Stick packs have a notch cut into the seal area at one end to facilitate opening.

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on August 14, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter[3].

Table 3: FAERS Search Strategy	
Date Range	**September 13, 2013 to August 14, 2014**
Product	**Lanthanum** [active ingredient] **Fosrenol** [product name]
Event (MedDRA Terms)	**Medication Errors** [HLGT] **Product Packaging Issues** [HLT] **Product Label Issues** [HLT] **Product Quality Issues** (NEC)[HLT]

B.2 Results

Our search identified 19 cases, of which 9 described errors relevant for this review. Each of the 9 cases reported wrong technique of administration errors where patients failed to chew Fosrenol Chewable Tablets adequately. Of the 9 cases, there were two cases that reported an outcome of bowel perforation; including one reported death resulting from bowel occlusion, which led to bowel perforation. These findings were consistent with our previous review and further support a place in the market for an alternative formulation that does not require chewing.

[3] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

We excluded 10 cases from the final analysis for the following reasons:

- Adverse event unrelated to medication error (n=1)
- Product Quality Complaint (n=2)
- Wrong dose errors unrelated to labels and labeling (n=7)

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

10057834	10195823	9681947
10062038	9665743	9739215
10172240	9678300	9812603

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L: Drive on August 4, 2014 using the terms, Fosrenol to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified one previous review[4], and we confirmed that our previous recommendations were implemented or considered.

[4] DeFronzo, K. Label and Labeling Review for Fosrenol Oral Powder (NDA 204734). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 OCT 07. 10 p. OSE RCM No.: 2013-1454.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[5] along with postmarket medication error data, we reviewed the following Fosrenol Oral Powder labels and labeling submitted by Shire Development LLC on July 31, 2014.

- Container label
- Carton labeling
- Prescribing Information

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[5] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI: 2004.

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/s/

JANINE A STEWART
08/28/2014

CHI-MING TU
08/29/2014

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title[1]	**FOSRENOL (lanthanum carbonate) Chewable Tablets, for oral use** **FOSRENOL (lanthanum carbonate) Oral Powder, for oral use**
Applicant	Shire US Inc.
Application/Supplement Number	NDA 204734
Type of Application	Original
Indication(s)	indicated to reduce serum phosphate in patients with end stage renal disease
Office/Division	ODE I/DCRP
Division Project Manager	Mike Monteleone
Date FDA Received Application	February 28, 2013
Goal Date	December 28, 2013
Date PI Received by SEALD	December 19, 2013
SEALD Review Date	December 20, 2013
SEALD Labeling Reviewer	Elizabeth Donohoe
Acting SEALD Division Director	Sandra Kweder

1 Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word "must" denotes that the item is a regulatory requirement, while the word "should" denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item **(deficiency)**.
- **YES:** The PI meets the requirement for this item **(not a deficiency)**.
- **N/A**: This item does not apply to the specific PI under review (**not applicable**).

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

NO 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *The top margin is > 1/2 inch.*

YES 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES"** in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

Selected Requirements of Prescribing Information

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

YES 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

YES 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

YES 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Selected Requirements of Prescribing Information

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

NO 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "*[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment: *The cross-references in subsections 7.2 and 7.3 include the subsection heading "Pharmacokinetics" where the section heading "Clinical Pharmacology (7.3)" is preferred.*

NO 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: *The corresponding text in Section 2 does not have a vertical line on the left edge.*

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

NO 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *Section 17 currently does not reference FDA-approved patient labeling. The draft Patient Counseling Information guidance recommends: "Advise the patient to read the FDA-approved patient labeling (Medication Guide)."*

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]
1 INDICATIONS AND USAGE
1.1 [text]
1.2 [text]
2 DOSAGE AND ADMINISTRATION
2.1 [text]
2.2 [text]
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 [text]
5.2 [text]
6 ADVERSE REACTIONS
6.1 [text]
6.2 [text]
7 DRUG INTERACTIONS
7.1 [text]
7.2 [text]
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
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9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
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12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 [text]
14.2 [text]
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

ELIZABETH A DONOHOE
12/20/2013

ERIC R BRODSKY
12/20/2013
I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 27, 2013

To: Michael Monteleone, Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Emily Baker, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 204734**
OPDP Labeling Comments for Fosrenol (lanthanum carbonate) oral powder

---

OPDP has reviewed the proposed carton and container labeling submitted for consult on November 26, 2013, for Fosrenol (lanthanum carbonate) oral powder (Fosrenol). Our comments are based on the proposed labeling emailed to us on November 13, 2013.

OPDP has no comments on the proposed carton and container labeling at this time.

Thank you for the opportunity to comment on the proposed materials.

If you have any questions, please contact Emily Baker at 301.796.7524 or emily.baker@fda.hhs.gov.

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

/s/

EMILY K BAKER
11/27/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	October 7, 2013
Reviewer(s):	Kimberly DeFronzo, RPh, MS, MBA Division of Medication Error Prevention and Analysis
Team Leader	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Drug Name(s) and Strength(s):	Fosrenol (Lanthanum Carbonate) Oral Powder 750 mg and 1000 mg
Application Type/Number:	NDA 204734
Applicant/sponsor:	Shire Inc.
OSE RCM #:	2013-1454

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION 1
1.1 Regulatory History ..... **Error! Bookmark not defined.**
1.2 Product Information 1
2 METHODS AND MATERIALS REVIEWED 2
2.1 Selection of Medication Error Cases 2
2.2 Labels and Labeling 3
3 MEDICATION ERROR RISK ASSESSMENT 3
3.1 Medication Error Cases 3
3.2 Integrated Summary of Medication Error Risk Assesment 3
4 CONCLUSIONS AND RECOMMENDATIONS ..... **Error! Bookmark not defined.**
4.1 Comments to the Division 4
4.2 Comments to the Applicant 4
Appendices 6

1 INTRODUCTION

This review evaluates the proposed label and labeling for Fosrenol (Lanthanum Carbonate) Oral Powder for areas of vulnerability that could lead to medication errors. The Applicant submitted this new application for a new oral powder dosage formulation of Fosrenol.

1.1 REGULATORY HISTORY

Fosrenol (Lanthanum Carbonate) Chewable Tablet was approved on October 26, 2004 under NDA 021468. The chewable tablets are available in 500 mg, 750 mg, and 1000 mg strengths.

1.2 PRODUCT INFORMATION

The May 15, 2013 submission provides the following product information:

- Active Ingredient: Lanthanum Carbonate[1]
- Indication of Use: To reduce serum phosphate in patients with end stage renal disease (ESRD)
- Route of Administration: Oral
- Dosage Form: Oral Powder
- Strength: 750 mg and 1000 mg
- Dose and Frequency: Divide the total daily dose of Fosrenol and take with or immediately after meals. The recommended initial total daily dose of Fosrenol is 1500 mg. Titrate the dose every 2-3 weeks until an acceptable serum phosphate level is reached. Monitor serum phosphate levels as needed during dose titration and on a regular basis thereafter. In clinical studies of ESRD patients, Fosrenol doses up to 4500 mg were evaluated. Most patients required a total daily dose between 1500 mg and 3000 mg to reduce plasma phosphate levels to less than 6.0 mg/dL. Doses were generally titrated in increments of 750 mg/day.
- How Supplied: Stick packs that contain 2.1 g (750 mg) or 2.8 g (1000 mg) oral powder packed in a polyethylene terephthalate/aluminum/polyethylene laminate.
    - 750 mg Patient pack (1 patient pack contains 9 cartons, each carton contains 10 stick packs (NDC 54092-256-01)) NDC 54092-256-02
    - 1000 mg Patient Pack (1 patient pack contains 9 cartons, each carton contains 10 stick packs (NDC 54092-257-01)) NDC 54092-257-02
- Storage: Store at 25°C (77°F): excursions permitted to 15° to 30°C (59° to 86°F).

[1] Per email correspondence from ONDQA on August 22, 2013, this application will be an exception to the USP salt nomenclature policy

- Container Closure System: The primary packaging material is an aluminum foil laminate comprised of polyethylene terephthalate/aluminum/polyethylene ((b) (4)). The dosage strength will be printed on the stick packs and color will be used to differentiate the two dosage strengths. Stick packs have a notch cut into the seal area at one end to facilitate opening, as shown below in Figure 1.

Figure 1: Schematic Drawing of Lanthanum Carbonate Oral Powder Stick Pack

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Fosrenol (Lanthanum Carbonate) medication error reports (See Appendix A for a description of the FAERS database). We also reviewed the Fosrenol labels, labeling and packaging submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS databases using the strategy listed in Table 1.

Table 1: FAERS Search Strategy	
Date	Search conducted on September 13,2013*
Drug Names	Active Ingredient: Lanthanum Trade Name: Fosrenol Verbatim term: Fosrenol
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

* Limited from last date of search conducted under OSE review #2011-1799 (TSI # 1011) on June 2, 2011 to Present

The FAERS database search identified 47 cases. Each case was reviewed for relevancy and duplication. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by

the reporter.[2] After individual review, 45 cases were not included in the final analysis for the following reasons:

- Adverse Events unrelated to medication Error
- Foreign cases excluded because uncertain if the product has the same dosing as in United States or if the product marketed in these countries is in same packaging configuration
- Use of expired drug
- Product Quality Complaint
- Wrong dose unrelated to labels and labeling

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[3] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Foil Container Labels submitted February 28, 2013 (Appendix B)
- Carton Labeling submitted February 28, 2013 (Appendix C)
- Insert Labeling submitted May 15, 2013 (no image)

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the Fosrenol Oral Powder packaging design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, two Fosrenol medication error cases remained for our detailed analysis (see Appendix D for case numbers). Both cases reported "wrong technique" errors where patients swallowed the chewable tablets whole instead of chewing.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

This new dosage form offers an alternative for patients with poor dentition that may encounter difficulty using the currently approved Fosrenol chewable tablets. We identified wrong technique errors with the chewable tablet formulation. This product must be mixed with a small quantity of soft food for administration. In order to ensure proper technique, we recommend the inclusion of an administration statement on the principal display panel of the carton labeling. Due to the limited size of the container labels, we do not recommend adding any additional statements to the container labels.

---

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www nccmerp.org/pdf/taxo2001-07-31.pdf.

[3] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Our review of the labels and labeling determined they can be improved for clarity and to increase the readability and prominence of important information on the label to promote the safe use of the product. We provide recommendations in Section 4.1 below.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA finds the addition of the oral powder dosage form acceptable from a medication error perspective. We conclude that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. DMEPA recommends the following be implemented prior to approval of this NDA supplement:

4.1 COMMENTS TO THE DIVISION

A. Full Prescribing Information

1) For clarity, we recommend revising the end of Section 16.2 to read:

   750 mg Patient pack (1 patient pack contains 9 cartons, each carton contains 10 stick packs (NDC 54092-256-01)) NDC 54092-256-02

   1000 mg Patient Pack (1 patient pack contains 9 cartons, each carton contains 10 stick packs (NDC 54092-257-01)) NDC 54092-257-02

2) In Section 17, include an instruction for patients to consume the entire dose after mixing with soft food.

4.2 COMMENTS TO THE APPLICANT

A. General comments on all container labels and carton labeling

3) Revise the presentation of the proprietary name from all caps (i.e. FOSRENOL) to title case (i.e. Fosrenol) to improve readability of the name.

4) Remove or minimize and move away the graphic in front of the proprietary name since it is distracting, competes with the prominence of the name, and may be mistaken as the letter 'O'.

5) Ensure that the established name (including the dosage formulation) is at least half the size of the proprietary name. Ensure the established name has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2). Additionally, the entire established name, including the active ingredient and the dosage form, should be presented in the same font.

6) Relocate the strength statement to appear below the established name statement on the principal display panel (PDP). Additionally, increase the font size of this statement for increased prominence.

7) Add the statement "Mix with food prior to ingestion" (or similar language) below the strength statement on the principal display panel (PDP).

B. Foil Container Labels

1. Remove the (b) (4) statement to reduce clutter on the small label. This statement should be retained for the carton labeling only.
2. The blue font utilized for the proprietary name, established name, and strength is difficult to read on the foil background. We recommend using a darker color font to ensure adequate contrast.

C. Carton Labeling (750 mg, 1000 mg, all net quantities)

3. Ensure the proprietary name, established name, and strength are the most prominent statements on the PDP.
4. The back panel looks too similar to the PDP, which can lead to the wrong panel displayed on a shelf during stocking. Revise the back panel to ensure adequate differentiation from the PDP.
5. Add a statement similar to "Mix with small quantity of soft food and take immediately" to ensure proper administration technique. This statement should be located beneath the statement of strength on the PDP.
6. To minimize clutter on the PDP, move the statement "Please follow your doctor's…" and the manufacturer information to the side or back panel.
7. Relocate the net quantity statement away from the statement of strength to avoid confusion of the information. Consider placing in the lower right corner of the PDP.
8. Debold the "Rx Only" statement and ensure the font size is smaller than the proprietary name, established name, and strength.
9. Minimize the "Shire" logo on the PDP for decreased prominence.

D. Carton Labeling (all strengths, patient pack)

1. Revise the net quantity to read similar to "9 cartons, each carton contains 10 stick packs" for clarity.

If you have further questions or need clarifications, please contact Cherye Milburn, OSE Project Manager, at 301-796-2084.

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KIMBERLY A DE FRONZO
10/07/2013

IRENE Z CHAN
10/07/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 204734 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Fosrenol Established/Proper Name: lanthanum carbonate Dosage Form: oral powder Strengths: 750 mg, 1000 mg		
Applicant: Shire Development LLC Agent for Applicant (if applicable):		
Date of Application: 02/28/2013 Date of Receipt: 02/28/2013 Date clock started after UN:		
PDUFA Goal Date: 12/28/2013	Action Goal Date (if different):	
Filing Date: 04/29/2013	Date of Filing Meeting: 04/17/2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3		
Proposed indication(s)/Proposed change(s): reduce serum phosphate in patients with end stage renal disease (ESRD)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): 055054

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***				
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***		X		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	X			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	X			

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:			X	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***		X		
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide)			

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined?				

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***			X	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***			X	
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** Cancelled (Preliminary Comments 11/06/2012) ***If yes, distribute minutes before filing meeting***			X	
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***			X	

ATTACHMENT

MEMO OF FILING MEETING

DATE: 04/17/2013

BLA/NDA/Supp #: 204734

PROPRIETARY NAME: Fosrenol

ESTABLISHED/PROPER NAME: Lanthanum Carbonate

DOSAGE FORM/STRENGTH: Oral Powder 750 mg, 1000 mg

APPLICANT: Shire

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): reduce serum phosphate in patients with end stage renal disease (ESRD)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Michael Monteleone	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Divya Menon-Andersen		Y
Clinical	Reviewer:	Melanie Blank	Y
	TL:	Aliza Thompson	Y
Clinical Pharmacology	Reviewer:	Divya Menon-Andersen	Y
	TL:	Rajnikanth Madabushi	N
Biostatistics	Reviewer:	Ququan Liu	Y
	TL:	James Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Xavier Joseph	Y
	TL:	Thomas Papoian	Y

Product Quality (CMC)	Reviewer:	Lyudmila Soldatova	Y
	TL:	Kasturi Srinivasachar	Y

Other attendees	Rebecca McKnight (ONDQA PM)	Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

reason. For example: o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☒ N/A
• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?	☐ YES ☐ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Division of Cardiovascular and Renal Products **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): NA **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional):	

Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

MICHAEL V MONTELEONE
04/29/2013