CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-468

Chemistry Review(s)

NDA 21-468

Lanthanum Carbonate

Shire Pharmaceutical Development Inc.

Kris Raman, Ph.D.
Cardio-Renal Drug Products (HFD-110)

CHEMISTRY REVIEW

1. **NDA:** 21-468

2. **REVIEW:** # 4 (resubmssion)

3. **REVIEW DATE:** 9/14/04

4. **REVIEWER:** Kris Raman

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Date
Original	4/30/02
N000 (C)	6/07/02
N000 (BC)	8/29/02
N000 (C)	9/16/02
N000 (BC)	11/4/02
N000 (BC)	11/27/02
N000 (BC)	11/27/02
N000 (BL)	11/27/02
N000 (BC)	12/13/02
N000 (BC)	4/24/03

6. **SUBMISSION(S) BEING REVIEWED:**

Submissions(s) Reviewed	Date
N000 (BC)	3/31/03
N000 (BC)	4/11/03
N000 (BC)	5/2/03
N000 (C)	9/5/03
N000 (AZ)	1/26/04
N000 (BZ)	4/1/04
N000 (BC)	5/28/04
N000 (BC)	7/12/04
N000 (BZ)	7/23/04
N000 (BC)	7/26/04
N000 (BC)	8/6/04
N000 (BC)	8/18/04
N000 (BC)	9/7/04

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Shire Pharmaceutical Development Inc.
Address:	1801 Research Boulevard Suite 600
	Rockville, MD 20850
Representative:	Lisa Wittmer, Ph.D.
Telephone:	240-453-2032

8. **DRUG PRODUCT NAME/CODE/TYPE**

   a) **Proprietary Name: Fosrenol**
   b) **Non-Proprietary Name (USAN): Lanthanum carbonate**
   c) **Code Name/# (ONDC only):**
      - **Chem. Type: 1**
      - **Submission Priority:** S

9. **LEGAL BASIS FOR SUBMISSION:** N/A

10. **PHARMACOL. CATEGORY:** Used in the treatment of hyperphosphatemia

11. **DOSAGE FORM:** Chewable Tablets

12. **STRENGTH/POTENCY:** 250 mg and 500 mg

13. **ROUTE OF ADMINISTRATION:** Oral

14. **Rx/OTC DISPENSED:** _X_ **Rx** ____ **OTC**

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note 28]:** No

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

    Lanthanum carbonate hydrate, $La_2(CO_3)_3 \cdot 4H_2O$, Relative molecular weight —
    (Average 3-5 moles of H_2O)

RELATED/SUPPORTING DOCUMENT:

A. DMFS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	III			3	Adequate	Sept. 26/00	
	III			3	Adequate	Sept. 17/01	
	III			3	Adequate	April 5/02	
	III			3	Adequate	Nov. 1/99	
	III			3	Adequate	Review is not needed with reference to "Policy on the Review of Container Closure Systems for Solid Oral Drug Products"	
	III			3	Adequate	Aug. 9/01	
	III			3	Adequate	Sept. 28/00	
	III			3	Adequate	Jan. 7/04	

[redacted]	III	—	\	3	Adequate	Oct. 7/03	(/

[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
IND	55,054	Lanthanum carbonate hydrate

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Overall acceptance recommendation	2/18/04	J. D. Ambrogio
Pharm/Tox	The issue with respect to metal impurities limits in the drug substance was consulted with Pharm/Tox reviewer and the final specification limits agreed between the Agency and the firm is presented in **Table 10**. There was no formal Toxicology review for the Pahrm/Tox consult.	6/10/04	Xavier Joseph,D.V.M.
Biopharm	OCPB considers that the already validated whole tablet method (USP Apparatus 2, [redacted] is an appropriate method to be used for the dissolution testing of 250 and 500 mg 'Current' formulation tablets. A dissolution specification of Q= — at 45	8/19/04	Angelica Dorantes, Ph.D.

	minutes would be more appropriate for the stability and lot release testing. Therefore, OCPB recommends that the sponsor consider the option of using the above method and specification for testing the 250 and 500 mg 'Current' formulation Fosrenol tablets.		
LNC	N/A	N/A	N/A
Methods Validation	Pending	Pending	Kris Raman, Ph.D.
DMETS	USAN Council adopted lanthanum carbonate as their United States Adopted Name for Fosrenol™, Foznol™, —— , Shire's phosphate binder . ~	6/17/04	Linda M. Wisniewski, RN
EA	Categorical exclusion has been submitted under 21CFR § 25.31 (c). Acceptable	2/23/04	Kris Raman, Ph.D.
Microbiology	N/A	N/A	N/A

N/A = Not Applicable

The Chemistry Review for NDA 21-468

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Compliance has issued an overall acceptable recommendation for all establishments on 2/18/04 (see attachment).

This application may be '**APPROVED**', only for 250 and 500 mg tablets of 'Current' formulation, from a chemistry, manufacturing and controls standpoint. The action letter should state the expiration date will be **24 months** for both 250 and 500 mg tablets of 'Current' formulation when stored at 25°C (77°F), with excursion permitted to 15 – 30°C (59 – 86°F). All CMC issues in the action letter dated 2/28/03 have been satisfactorily resolved.

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)

Lanthanum carbonate chewable tablets 250 and 500 mg strength of 'Current' formulation are composed of the active ingredient, lanthanum carbonate hydrate and the inactive components - dextrates, colloidal silicon dioxide, magnesium stearate, and talc. Because patients with hyperphosphataemia have a very limited daily liquid intake allowance, lanthanum carbonate has been formulated as chewable tablets.

The formulation was initially developed by Shire as a tablet weighing 1800 mg, which delivered 250 mg of elemental lanthanum. This is known as 'Current' formulation and was used in Phase 2 and 3 clinical trials. Subsequently 500 mg tablet was made from a common blend for 250 mg tablet.

[

]

Based on the review of the overall information, OCPB considers that the sponsor has provided appropriate supportive data and their biowaiver request for the 500 mg 'Current' formulation is granted.

The applicant has proposed a shelf life of **24 months** for both strengths 250 mg and 500 mg tablets 'Current' formulation stored at 25°C (77°F), based on stability data generated under long term (25°C/60%RH), intermediate (30°C/60%RH), and accelerated (40°C/75%RH) conditions.

The originally proposed dissolution method for the crushed tablets (USP Apparatus 2, was acceptable on an interim basis. as per the action letter of 2/28/03, with the understanding that the sponsor will continue with the development of a more adequate dissolution methodology for the whole tablets.

The proposed dissolution testing submitted in the resubmission (1/26/04) was dissolution test on whole tablets' (USP 2, paddles rpm, and Q = , in 45 minutes) and dissolution test on crushed tablets' (USP 2, The proposed dissolution method is not acceptable to OCPB, since two different dissolution medium are used. This was communicated to the applicant in March 10, 2004 meeting. Shire proposed that they may consider using for dissolution studies.

The dissolution method in USP 2 (rpm) has been validated by Shire; therefore OCPB considers this method an appropriate method to be used for dissolution testing of the 250 mg and 500 mg 'Current' formulation tablets. The overall data showed that more than is dissolved in 45 minutes (amendment of 5/28/04), therefore a dissolution specification of Q= % at 45 minutes would be more appropriate for the stability lot release testing. OCPB has recommended (review dated 8/19/04) that the applicant consider the option of using the above method and specification for testing of the 250 and 500 mg 'Current' formulation.

In the stability update of 5/28/04, Shire presented preliminary dissolution data on 'Current' formulation of Fosrenol chewable tablets of various time points using Apparatus 2 and) and showed that the batches which have slow drug release using Apparatus 2, release drug fast and efficiently using technique. In

7/8/04 amendment, Shire has reported that a whole tablet dissolution test using [ ] has been developed. The test uses [ ] speed. Shire was told by the OCPB that the proposed use of dissolution [ ] may be acceptable. However, additional work to establish the discriminatory nature of the method needs to be done before this can become a regular method.

The active pharmaceutical ingredient lanthanum carbonate is a white to almost white powder and contains 3-5 moles of bound water. Although there are [ ] for lanthanum carbonate associated with the [ ] there is no evidence for [ ] of lanthanum carbonate. Lanthanum carbonate [ ] [ ] It has poor aqueous solubility at [ ] It is insoluble in [ ]

The drug substance will be manufactured by [ ]. Shire has withdrawn [ ] from NDA 21-468 as manufacturer of lanthanum carbonate drug substance (amendment 4/1/2004). The drug substance is manufactured by [

]

Inspection of drug substance manufacturer [ ] by the Office of Compliance revealed the presence of a degradant, [ ] in the drug substance, which was not documented in the NDA. According to the applicant the extent and impact of the impurity [ ] was not fully understood at the time of original NDA submission. Subsequently, it was established that [ ] is a degradant caused by [ ] such as those [ ]

There were some critical issues related to the metal impurities in the drug substance because of its manufacture from [ ] and hence lack of consistency batch to batch. Originally metal impurities [ ] were listed in the specification, as these were regularly found at levels significantly above detection limits in development batches. Later [ ] was added to the list in response to agency's concern regarding [ ] to be a carcinogen. In the NDA resubmission (1/26/2004), the applicant added [ ] impurities to the list of including [ ] impurities proposed earlier (11/4/2002).

Based on Agency's recommendation to include all possible metal impurities, on April 1, 2004 Shire submitted an amendment to included [ ] impurities (except [ ] since it is as internal standard). The proposed specification limits for [ ] impurities had acceptable limits according to Pharm/Tox reviewer Dr. Xavier Joseph,

based on justification provided by the applicant. The FDA raised two points with Shire in relation to the metal impurity for [ ] The first to tighten Shire's proposed specification limits for metal impurities (see **Table** 7), and the second relates

to other [ ] (see **Table 8**) not covered by Shire's specifications. After several negotiations, the applicant submitted a revised specification limits for [ ] metal impurities, which were agreeable to both the FDA and Shire. Shire also provided a justification for including/not including the metal impurities [ ] not covered by the specifications. Shire agreed to include [ ] as well, although they are used as internal standard.

The primary stability data on total — batches of drug substance manufactured at [ ] includes [ ] stability at 5°C and 25°C/60%RH, [ ] stability at 30°C/60%RH, and [ ] stability at 40°C/75%RH.

The proposed retest date is [ ] when stored at refrigerated (5°C) condition to prevent formation of the [ ]

B. Description of How the Drug Product is intended to be used

Lanthanum carbonate will be available as chewable tablets containing 250 mg and 500 mg elemental lanthanum ([ ] for oral administration. The maximum recommended daily dosage is 3.0 g/day elemental lanthanum, equivalent to 114.5 mg (salt)/kg/day for a 50 kg person.

The primary packaging for 250 and 500 mg lanthanum carbonate chewable tablet of 'Current' formulation is a trade pack containing 100 of the 250 mg in a round white [ ] bottle with a child resistant, tamper evident [ ] closure that includes [ ] The 250 mg will also be supplied in [ ]

[ ] The 500 mg tablets trade pack contains 100 tablets in a around [ ] bottle with a child resistant, [ ] closure and an induction seal (for tamper evidence) and includes —
— Based on the given stability data the proposed expiration date of 24 months for 250 and 500 mg 'Current' formulation tablet is acceptable.

Lanthanum carbonate is intended for the control of hyperphosphatemia in patients with chronic renal failure. In vitro phosphate-binding studies confirmed that lanthanum carbonate has a relatively high phosphate-binding capacity compared with calcium carbonate. Lanthanum carbonate becomes ionized in the stomach acid following oral administration. As phosphate (PO_4^{3-}) is liberated during digestion, the free phosphate ions can react with lanthanum ions (La^{2+}) forming highly insoluble lanthanum phosphate.

C. Basis for Approvability or Not-Approval Recommendation

The Office of Compliance has issued an overall acceptable recommendation for all establishments (see attachment).

This application may be '**APPROVED**', only for 250 and 500 mg lanthanum carbonate

chewable tablets of 'Current' formulation, from a chemistry, manufacturing and controls standpoint.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Kris Raman/9/14/4
ChemistryTeamLeader: Kasturi Srinivasachar/9/14/04
Project Manager: Denise Hinton

C. CC Block

Original NDA 21-468
HFD-110/Division File
HFD-110/Team Leader/Kasturi Srinivasachar
HFD-810/Chemistry Division Director/John Simmons

APPEARS THIS WAY
ON ORIGINAL

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

(b4)

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

/s/

Kris Raman
9/14/04 04:43:16 PM
CHEMIST

Kasturi Srinivasachar
9/14/04 05:36:39 PM
CHEMIST

NDA 21-468

Lanthanum Carbonate

Shire Pharmaceutical Development Inc.

Kris Raman, Ph.D.
Division of Cardio-Renal Drug Products

Table of Contents

Chemistry Review Cover Sheet

NDA 21-468

Lanthanum Carbonate

Shire Pharmaceutical Development Inc.

Kris Raman, Ph.D.
Cardio-Renal Drug Products (HFD-110)

CHEMISTRY REVIEW

1. **NDA:** 21-468

2. **REVIEW:** # 3

3. **REVIEW DATE:** 2/27/03

4. **REVIEWER:** Kris Raman

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
Original	4/30/02
N000 (C)	6/07/02
N000 (BC)	8/29/02
N000 (C)	9/16/02
N000 (BC)	11/4/02
N000 (BC)	11/27/02
N000 (BC)	11/27/02
N000 (BL)	11/27/02
Amendment	12/20/02

6. **SUBMISSION(S) BEING REVIEWED:**

Submissions(s) Reviewed	Document Date

This is a final review of overall approval recommendation of all establishments from the Office of Compliance (2/25/03) and some issues uncovered during the cGMP inspections (1/31/03) that needed clarification.

7. **NAME & ADDRESS OF APPLICANT:**

Name: Shire Pharmaceutical Development Inc.

Address: 1901 Research Boulevard Suite 500
Rockville, MD 20850

Representative: Rick Lilley, Ph.D.

Telephone: 240-453-6400

8. **DRUG PRODUCT NAME/CODE/TYPE**

a) **Proprietary Name: Fosrenol**
b) **Non-Proprietary Name (USAN): Not Available**
c) **Code Name/# (ONDC only):**

- **Chem. Type: 1**
- **Submission Priority:** S

9. **LAGAL BASIS FOR SUBMISSION:** N/A

10. **PHARMACOL. CATEGORY:** Used in the treatment of hyperphosphatemia

11. **DOSAGE FORM:** Chewable Tablets

12. **STRENGTH/POTENCY:** 250 mg and 500 mg

13. **ROUTE OF ADMINISTRATION:** Oral

14. **Rx/OTC DISPENSED:** _X_ **Rx** ___ **OTC**

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note 28]:** No

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

Lanthanum carbonate hydrate, $La_2(CO_3)_3 \cdot 4H_2O$, Relative molecular weight (Average 3-5 moles of H_2O)

APPEARS THIS WAY
ON ORIGINAL

RELATED/SUPPORTING DOCUMENT:

A. DMFS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	III			3	Adequate	Sept. 26/00	
	III			3	Adequate	Sept. 17/01	
	III			3	Adequate	Nov. 1/99	
	III			3	Adequate	Sept. 28/00	
	III			3	Adequate	July 28/99	

[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
IND	55,054	Lanthanum carbonate hydrate

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Overall approval recommendation	2/25/03	S. Adams
Pharm/Tox	Pharm/Tox has requested for more recent references to evaluate the toxicology and biological monitoring of [ ] impurities in humans	1/16/03	John Koerner, Ph.D.
Biopharm	The originally proposed dissolution method for the crushed tablets (USP Apparatus 2, [ ] is acceptable on an interim basis, with the understanding that the sponsor will continue with the development of a more adequate dissolution methodology for the whole tablet	2/25/03	Angelica Dorantes, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Pending	Pending	Kris Raman, Ph.D.
DMETS	DMETS has no objection to the use of the proposed proprietary name Fosrenol. However, DMETS recommends that the Division request that the sponsor apply to the United States Adopted Names (USAN) Council for a different established name as the current established name, Lanthanum Carbonate, has potential for confusion with Lithium Carbonate.	1/2/03	Nora Roselle, PharmD The applicant said that they were submitting the application to the USAN Council on January 14, 2003 for the approval of the established name.
EA	Categorical exclusion has been sub mitted under 21CFR § 25.31 (c). Accepted	12/31/02	Kris Raman, Ph.D.
Microbiology	N/A	N/A	N/A

N/A = Not Applicable

The Chemistry Review for NDA 21-468

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is APPROVABLE from a chemistry, manufacturing and controls standpoint, pending satisfactory resolution of the issues identified at the end of this review (Page 14).

A retest date of — for the drug substance and an expiration dating of 24 months for 250 mg tablets is acceptable. However, for 500 mg tablets additional stability data is needed to support the proposed 24 months expiry dating.

The Office of Compliance has issued an overall approval recommendation for all establishments (see attachment).

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)

Lanthanum carbonate chewable tablets, 250 mg and 500 mg strength are composed of the active ingredient, lanthanum carbonate hydrate and the inactive components - dextrates, colloidal silicon dioxide, talc and magnesium stearate.

The 250 mg tablet is white to off-white, round, convex tablets embossed on one side with S405 above a cosmetic score line and 250 below the line. The 500 mg tablet is white to off-white, flat bevelled edge tablets embossed on one side with S405 above a cosmetic score line and 500 below the line.

The stability report contains — primary stability data on — batches of 250 mg lanthanum carbonate chewable tablets and — supportive stability data on — batches of 250 mg lanthanum carbonate chewable tablets. For 500 mg tablets the applicant has provided — stability data for — batches and — data for — batch at 25°C/60%RH and — data for — batches at 40°C/75%RH. Based on the given stability data an expiration date of 24 month for 250 mg tablets and — — for 500 mg tablet is acceptable. The applicant's proposed expiry date of 24 month for 500 mg tablets is not acceptable.

The originally proposed dissolution specification of Q — minutes for both 250 mg and 500 mg lanthanum carbonate tablets is not acceptable. The provided dissolution data for several clinical and stability lots using crushed tablets showed that a specification of — would be more appropriate for both, the 250 and 500 mg Forsenol chewable tablets. The originally proposed dissolution method for the crushed tablets (USP Apparatus 2, [ ] is acceptable on an interim basis, with the understanding that the sponsor will continue with the development of a more adequate dissolution methodology for the whole tablets. After the Division has approved the new dissolution method and new acceptance criteria the sponsor should revise the drug product release and stability specifications accordingly. In addition, the sponsor should demonstrate that the stability of the 250 mg tablets, using the new dissolution specifications, is comparable to the stability documented in the original submission. For the 500 mg tablets, because of limited stability data available, we recommend that the sponsor initiate stability studies using the new dissolution specifications and generate sufficient data to assign a meaningful expiration date.

The active pharmaceutical ingredient lanthanum carbonate is a known chemical substance described in the scientific literature. It is a white to almost white powder and contains 3-5 moles of bound water. Although there are — for lanthanum carbonate associated with the — there is no evidence for — — of lanthanum carbonate. Lanthanum carbonate [ ] [ ] It has poor aqueous solubility at [ ] It is insoluble in [ ] [ ]

No impurities from degradation of the lanthanum carbonate are anticipated. However, the presence of [ ] impurities is likely in the drug substance. The applicant states that only [ ] impurities were regularly found at levels significantly above detection limits in development batches. The proposed metal impurities in the specification are [ ] In the original submission, the applicant had excluded [ ] the list of specified metal impurities in lanthanum carbonate, although it is proven carcinogen. In response to agency's concern the sponsor provided a toxicological justification for excluding [ ] from the list of specified metal impurities in the drug substance. However, the applicant has proposed in the recent amendment N00 (BC), Nov 4/02 to include [ ] in the drug substance specification, despite their toxicological arguments regarding the relatively low potential exposure to [ ]

Recent inspections of [ ] have revealed the presence of a degradant, [ ] in the drug substance. However, this was not documented in the NDA.

The drug substance is manufactured by [

]

The primary stability data on — batches of drug substance, used in the drug product, manufactured at —, includes — stability at 25°C/60%RH and — stability at 40°C/75%RH.

The secondary stability data on — batches of drug substance manufactured at — includes — stability at 25°C/60%RH and — stability at 40°C/75%RH.

Based on the provided stability data on the drug substance lanthanum carbonate a — retest period has been assigned.

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

Lanthanum carbonate will be available as chewable tablets containing 250 or 500 mg elemental lanthanum ([ ] for oral administration. The maximum recommended daily dosage is 3.0 g/day elemental lanthanum, equivalent to 114.5 mg (salt)/kg/day for a 50 kg person.

Lanthanum carbonate chewable tablets 250 mg and 500-mg strength will be packaged in [ ] containers fitted with a non-child resistant white , [ ] caps and induction seal in configuration of 100 — counts respectively. The applicant has proposed a two-year expiry date for 250 mg and 500 mg strength drug product in these containers. Based on the given stability data an expiration date of 24 month for 250 mg tablet and — for 500 mg tablet is acceptable.

Lanthanum carbonate is intended for the control of hyperphosphatemia in patients with chronic renal failure. In vitro phosphate-binding studies confirmed that lanthanum carbonate has a relatively high phosphate-binding capacity compared with calcium carbonate. Lanthanum carbonate becomes ionized in the stomach acid following oral administration. As phosphate (PO_4^{2-}) is liberated during digestion, the free phosphate can react ionically with lanthanum ions (La^{3+}) forming highly insoluble lanthanum phosphate.

C. Basis for Approvability or Not-Approval Recommendation

This application is APPROVABLE from a chemistry, manufacturing and controls standpoint. A list of chemistry related issues attached at the end of this review (Page 14) should be addressed by the sponsor. Some of these issues arise from discrepancies noted between what was submitted in the NDA and what was discovered during the cGMP inspection. Clarification of these issues is important but should be relatively straightforward. Hence the CMC recommendation is "Approvable" rather than "Not Approvable".

A retest date of [ ] for the drug substance and an expiration dating of 24 months for 250 mg tablets is acceptable. However, for 500 mg tablets additional stability data is needed to support the proposed 24 months expiry dating.

The Office of Compliance has issued an overall approval recommendation for all establishments (see attachment).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Kris Raman/2/27/03
ChemistryTeamLeader: Kasturi Srinivasachar/2/27/03
Project Manager: Denise Hinton

C. CC Block

Original NDA 21-468
HFD-110/Division File
HFD-110/Team Leader/Kasturi Srinivasachar
HFD-810/Chemistry Division Director/John Simmons

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ON ORIGINAL

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

NDA 21-468
FOSRENOL (lanthanum carbonate) Chewable Tablets
Shire Pharmaceuticals Development Inc.

Methods Validation

The Division has not completed validation of the regulatory methods. However, we expect their continued cooperation to resolve any problems that may be identified.

Chemistry Review Cover Sheet

NDA 21-468

Lanthanum Carbonate

Shire Pharmaceutical Development Inc.

Kris Raman, Ph.D.
Cardio-Renal Drug Products (HFD-110)

CHEMISTRY REVIEW

1. **NDA:** 21-468

2. **REVIEW:** # 2

3. **REVIEW DATE:** 1/16/03

4. **REVIEWER:** Kris Raman

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
Original	4/30/02
N000 (C)	6/07/02
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N000 (C)	9/16/02
N000 (BC)	11/4/02
N000 (BC)	11/27/02
N000 (BC)	11/27/02
N000 (BL)	11/27/02

6. **SUBMISSION(S) BEING REVIEWED:**

Submissions(s) Reviewed	Document Date
Amendment	12/20/02

7. **NAME & ADDRESS OF APPLICANT:**

Name: Shire Pharmaceutical Development Inc.

Address: 1901 Research Boulevard Suite 500
Rockville, MD 20850

Representative: Rick Lilley, Ph.D.

Telephone: 240-453-6400

8. **DRUG PRODUCT NAME/CODE/TYPE**

a) **Proprietary Name: Fosrenol**
b) **Non-Proprietary Name (USAN): Not Available**
c) **Code Name/# (ONDC only):**
   - **Chem. Type: 1**
   - **Submission Priority:** S

9. **LAGAL BASIS FOR SUBMISSION:** N/A

10. **PHARMACOL. CATEGORY:** Used in the treatment of hyperphosphatemia

11. **DOSAGE FORM:** Chewable Tablets

12. **STRENGTH/POTENCY:** 250 mg and 500 mg

13. **ROUTE OF ADMINISTRATION:** Oral

14. **Rx/OTC DISPENSED:** _X_ **Rx** ___ **OTC**

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note 28]:** No

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

    Lanthanum carbonate hydrate, $La_2(CO_3)_3 \cdot 4H_2O$, Relative molecular weight (Average 3-5 moles of H_2O)

RELATED/SUPPORTING DOCUMENT:

A. DMFS:

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	III			3	Adequate	Nov. 1/99	
	III			3	Adequate	Sept. 28/00	
	III			3	Adequate	July 28/99	

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B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	55,054	Lanthanum carbonate hydrate

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	Under review	Valeria Freidlin, Ph.D.
EES	Pending	1/16/03	Kris Raman
Pharm/Tox	Pharm/Tox has been consulted for safety level of metal impurities in drug substance	Under review	Joseph Xavier, Ph.D.
Biopharm	Dissolution method and specification has been revised	Under review	Angelica Dorantes, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Pending	Pending	Kris Raman, Ph.D.
DMETS	DMETS has no objection to the use of the proposed proprietary name Fosrenol. However, DMETS recommends that the Division request that the sponsor apply to the United States Adopted Names (USAN) Council for a different established name as the current established name, Lanthanum Carbonate, has potential for confusion with Lithium Carbonate.	1/2/03	Nora Roselle, PharmD The applicant said that they were submitting the application to the USAN Council on January 14, 2003 for the approval of the established name.
EA	Categorical exclusion has been submitted under 21CFR § 25.31 (c). Accepted	12/31/02	Kris Raman, Ph.D.
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 21-468

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is NOT APPROVABLE from a chemistry, manufacturing and controls standpoint because overall establishment evaluation by the Office of Compliance is still pending.

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)

Lanthanum carbonate chewable tablets, 250 mg and 500 mg strength are composed of the active ingredient, lanthanum carbonate hydrate and the inactive components - dextrates, colloidal silicon dioxide, talc and magnesium stearate.

The 250 mg tablet is white to off-white, round, convex tablets embossed on one side with S405 above a cosmetic score line and 250 below the line. The 500 mg tablet is white to off-white, flat bevelled edge tablets embossed on one side with S405 above a cosmetic score line and 500 below the line.

The stability report contains — primary stability data on — batches of 250 mg marketed lanthanum carbonate chewable tablets and — supportive stability data on — batches of 250 mg lanthanum carbonate chewable tablets. For 500 mg tablets the applicant has provided — stability data for — batches and — data for — batch at 25°C/60%RH and — data for — batches at 40°C/75%RH. Based on the given stability data an expiration date of 24 month for 250 mg tablets — — for 500 mg tablet is acceptable. The applicant's proposed expiry date of 24 month for 500 mg tablets is not acceptable.

The proposed dissolution specification for both 250 mg and 500 mg lanthanum carbonate tablet is Q =( )at ———————— using USP method <711>. The applicant states that the proposed Q (Q =( )) value and —minutes time point is supported by the data obtained in the stability study and validation data for the method [ ] The proposed dissolution specification and the method are not acceptable to the Agency. The applicant

has been advised by Agency to produce dissolution study data using crushed tablets, USP II apparatus [ ] rpm, and [ ] The applicant has agreed to use the method and will submit the data to FDA for review. The Biopharm will propose a dissolution specification for the drug product after the review of the data. The active lanthanum carbonate is a stable mineral. As such degradation of the active is probably not likely but that dissolution will be critical to monitor on the stability of the drug product.

The active pharmaceutical ingredient lanthanum carbonate is a known chemical substance described in the scientific literature. It is a white to almost white powder and contains 3-5 moles of bound water. Although there are [ ] for lanthanum carbonate associated with [ ], there is no evidence for [ ] of lanthanum carbonate. Lanthanum carbonate [ ] It has poor aqueous solubility at [ ] It is insoluble in [ ]

No impurities from degradation of the lanthanum carbonate are anticipated. However, the presence of [ ] metal impurities is likely in the drug substance. The applicant states that only [ ] metal impurities were regularly found at levels significantly above detection limits in development batches. The proposed metal impurities in the specification are [ ]. In the original submission, the applicant had excluded [ ] form the list of specified metal impurities in lanthanum carbonate, although it is proven carcinogen. In response to agency's concern the sponsor provided a toxicological justification for excluding [ ] from the list of specified — impurities in the drug substance. However, the applicant has proposed in the recent amendment N00 (BC), Nov 4/02 to include [ ] in the drug substance specification, despite their toxicological arguments regarding the relatively low potential exposure to [ ].

The drug substance is manufactured by [ ]

The primary stability data on — batches of drug substance, used in the drug product, manufactured at — includes — stability at 25°C/60%RH and — stability at 40°C/75%RH.

The secondary stability data on — batches of drug substance manufactured at — includes — stability at 25°C/60%RH and — stability at 40°C/75%RH.

Based on the provided stability data on the drug substance lanthanum carbonate a — retest period has been assigned.

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

Lanthanum carbonate will be available as chewable tablets containing 250 or 500 mg elemental lanthanum (e.g. 477 mg or 954 mg lanthanum carbonate) for oral administration. The maximum recommended daily dosage is 3.0 g/day elemental lanthanum, equivalent to 114.5 mg (salt)/kg/day for a 50 kg person.

Lanthanum carbonate chewable tablets 250 mg and 500-mg strength will be packaged in [redacted] containers fitted with a non-child resistant white [redacted] caps and induction seal in configuration of 100 [redacted] counts respectively. The applicant has proposed a two-year expiry date for 250 mg and 500 mg strength drug product in these containers. Based on the given stability data an expiration date of 24 month for 250 mg tablet [redacted] for 500 mg tablet is acceptable.

Lanthanum carbonate is intended for the control of hyperphosphatemia in patients with chronic renal failure. In vitro phosphate-binding studies confirmed that lanthanum carbonate has a relatively high phosphate-binding capacity compared with calcium carbonate. Lanthanum carbonate becomes ionized in the stomach acid following oral administration. As phosphate (PO_4^{2-}) is liberated during digestion, the free phosphate can react ionically with lanthanum ions (La^{3+}) forming highly insoluble lanthanum phosphate.

C. Basis for Approvability or Not-Approval Recommendation

The application is NOT APPROVABLE from a chemistry, manufacturing and controls standpoint because overall establishment evaluation by the Office of Compliance is still pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Kris Raman/1/16/03
ChemistryTeamLeader: Kasturi Srinivasachar/1/16/03
Project Manager: Denise Hinton

C. CC Block

Original NDA 21-468 — HFD-110/team Leader/Kasturi Srinivasachar
HFD-110/Division File — HFD-810/Chemistry Division Director/John Simmons

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and/or confidential

commercial information

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

/s/

Kris Raman
1/16/03 03:01:13 PM
CHEMIST

Ramsharan Mittal
1/16/03 05:09:30 PM
CHEMIST
For Kasturi Srinivasachar

NDA 21-468

Lanthanum Carbonate

Shire Pharmaceutical Development Inc.

Kris Raman, Ph.D.
Division of Cardio-Renal Drug Products

NDA 21-468 Chemistry Assessment Section
Chemistry Review # 1

Chemistry Review Data Sheet

1. NDA 21-468

2. REVIEW #: 1

3. REVIEW DATE: December 31, 2002

4. REVIEWER: Kris Raman, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 55,054	September 28, 2000

6. SUBMISSION (S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N000C	6/07/02
N000 (BC)	8/29/02
N000 (C)	9/16/02
N000 (BC)	11/4/02
N(000) BC	11/27/02
N(000) BC	11/27/02
N000 (BL)	11/27/02

7. NAME & ADDRESS OF APPLICANT:

Name:	Shire Pharmaceutical Development Inc.
Address:	1901 Research Boulevard Suite 500 Rockville, MD 20850
Representative:	Rick Lilley, Ph.D.
Telephone:	240-453-6400

8. DRUG PRODUCT NAME/CODE/TYPE:

CHEMISTRY REVIEW

NDA 21-468 Chemistry Assessment Section
Chemistry Review # 1

a) Proprietary Name: FOSRENOL™
b) Non-Proprietary Name (USAN): Not available

c) Code Name/# (ONDC only): SPD 405
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Used in the treatment of hyperphosphatamia

11. DOSAGE FORM: Chewable Tablets

12. STRENGTH/POTENCY: 250 mg and 500 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note28]:
_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Lanthanum carbonate hydrate, $La_2(CO_3)_3 \cdot 4H_2O$, Relative molecular weight (Average 3-5 moles of H_2O)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

NDA 21-468 Chemistry Assessment Section
Chemistry Review # 1

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	III			3	Adequate	Sept. 26/00	
	III			3	Adequate	Sept. 17/01	
	III			3	Adequate	Nov. 1/99	
	III			3	Adequate	Sept. 28/00	
	III			3	Adequate	July 28/99	

[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
IND	55,054	Lanthanum carbonate hydrate

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		Valeria Freidlin, Ph.D.
EES	Pending	12/31/02	
Pharm/Tox	Pharm/Tox has been consulted for safety level of metal impurities in drug substance	Under review	Joseph Xavier, Ph.D.
Biopharm	Dissolution method and specification has been revised	Under review	Angelica Dorantes, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Pending	Pending	Kris Raman, Ph.D.
DMETS	Pending		
EA	Categorical exclusion has been submitted under 21CFR § 25.31 (c). Accepted	N/A	Kris Raman, Ph.D.
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 21-468

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Numerous deficiencies were identified in the chemistry, manufacturing and controls section. A list of deficiencies that have been communicated to the applicant by email on 12/6/02 is attached at the end of this review. In addition to the CMC deficiencies, the inspections of three establishments are still pending. From standpoint of CMC review, this application is not approvable until satisfactory responses to all deficiencies are received from the applicant.

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)

Lanthanum carbonate chewable tablets, 250 mg and 500 mg strength are composed of the active ingredient, lanthanum carbonate hydrate and the inactive components – dextrates, colloidal silicon dioxide, talc and magnesium stearate.

The 250 mg tablet is white to off-white, round, convex tablets embossed on one side with S405 above a cosmetic score line and 250 below the line. The 500 mg tablet is white to off-white, flat bevelled edge tablets embossed on one side with S405 above a cosmetic score line and 500 below the line. The stability report contains [ ] primary stability data on [ ] batches of 250 mg marketed lanthanum carbonate chewable tablets and [ ] supportive stability data on [ ] batches of 250 mg lanthanum carbonate chewable tablets. The stability data is very limited for 500 mg lanthanum carbonate chewable tablets and more stability data is needed to assign a meaningful expiration date.

The proposed dissolution specification for both 250 mg and 500 mg lanthanum carbonate tablet is Q = — at [ ] using USP method <711>. The applicant states that the proposed Q (Q = — %) value and — minutes time point is supported by the data obtained in the stability study and validation data for the method [ ] The proposed dissolution specification and the method are not acceptable to the Agency. The applicant has been advised by Agency to produce dissolution study data using crushed tablets, USP II apparatus, — rpm, and [ ] The applicant has agreed to use the method and will submit the data to FDA for review. The Biopharm will propose a dissolution specification for the drug product after the review of the data. The active lanthanum carbonate is a stable mineral. As such degradation of the active is probably not likely but that dissolution will be critical to monitor on the stability of the drug product.

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No impurities from degradation of the lanthanum carbonate are anticipated. However, the presence of — metal impurities is likely in the drug substance. The applicant states that only — metal impurities were regularly found at levels significantly above detection limits in development batches. The proposed metal impurities in the specification are — In the original submission, the applicant had excluded — form the list of specified metal impurities in lanthanum carbonate, although it is proven

carcinogen. In response to agency's concern the sponsor provided a toxicological justification for excluding — from the list of specified metal impurities in the drug substance. However, the applicant has proposed in the recent amendment N00 (BC), Nov 4/02 to include — in the drug substance specification, despite their toxicological arguments regarding the relatively low potential exposure to —

The drug substance is manufactured by [redacted]

The primary stability data on [redacted] batches of drug substance, used in the drug product, manufactured at — includes — stability at 25°C/60%RH and — stability at 40°C/75%RH.

The secondary stability data on — batches of drug substance manufactured at — includes — stability at 25°C/60%RH and — stability at 40°C/75%RH.

Based on the drug substance stability data a [redacted] retest period has been assigned.

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

Lanthanum carbonate will be available as chewable tablets containing 250 or 500 mg elemental lanthanum ([redacted]) for oral administration. The maximum recommended daily dosage is 3.0 g/day elemental lanthanum, equivalent to 114.5 mg (salt)/kg/day for a 50 kg person.

Lanthanum carbonate chewable tablets 250 mg and 500-mg strength will be packaged in [redacted] containers fitted with [redacted] caps and induction seal. The applicant has proposed a two-year expiry date for drug product in these containers. However, additional stability data are needed before a decision can be made. Lanthanum carbonate is intended for the control of hyperphosphatemia in patients with chronic renal failure. In vitro phosphate-binding studies confirmed that lanthanum carbonate has a relatively high phosphate-binding capacity compared with calcium carbonate. Lanthanum carbonate becomes ionized in the stomach acid following oral administration. As phosphate (PO_4^{2-}) is liberated during digestion, the free phosphate can react ionically with lanthanum ions (La^{3+}) forming highly insoluble lanthanum phosphate.

C. Basis for Approvability or Not-Approval Recommendation

A copy of the deficiencies list has be sent to the sponsor by email on 12/6/02. From standpoint of CMC review, this application is not approvable until satisfactory responses to all deficiencies are received from the applicant.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Kris Raman/12/31/02
ChemistryTeamLeader: Kasturi Srinivasachar/12/31/02
ProjectManager: Denise Hinton

C. CC Block

Original NDA 21-468
HFD-110/Division File
HFD-110/team Leader/Kasturi Srinivasachar
HFD-810/Chemistry Division Director/John Simmons

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

/s/

Kris Raman
12/31/02 01:48:12 PM
CHEMIST

Nallaperumal Chidambaram
12/31/02 02:16:14 PM
CHEMIST
This review is being signed off on behalf of
Kasturi Srinivasachar, Chemistry Team leader.