

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-116

CHEMISTRY REVIEW(S)

NDA 22-116

Lexiva (fosamprenavir calcium) Oral Suspension

GlaxoSmithKline

**George Lunn, Ph.D.
Division of Anti-Viral Products**

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Chemistry Review Data Sheet

1. NDA 22-116
2. REVIEW #: 1
3. REVIEW DATE: 31-MAY-2007
4. REVIEWER: George Lunn, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original
Amendment-006

Document Date

13-DEC-2006
31-MAY-2007

7. NAME & ADDRESS OF APPLICANT:

Name: GlaxoSmithKline
Address: P.O. Box 13398
Five Moore Drive
Research Triangle Park, NC 27709
Representative: Eric B. Benson
Senior Director, U.S. Regulatory Affairs

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Chemistry Review Data Sheet

Telephone:

(919) 483-3627

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Lexiva Oral Suspension
- b) Non-Proprietary Name (USAN): fosamprenavir calcium oral suspension
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 2
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION:

10. PHARMACOL. CATEGORY: Antiviral

11. DOSAGE FORM: Oral Suspension

12. STRENGTH/POTENCY: 50 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

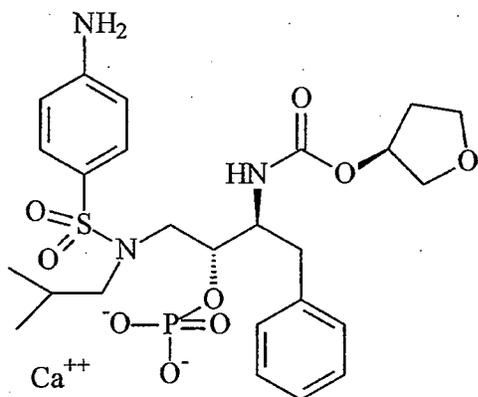
Not a SPOTS product

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

(3S)-tetrahydrofuran-3-yl (1S,2R)-3-[[[4-aminophenyl)sulfonyl]](isobutyl)amino]-1-benzyl-2-(phosphonoxy)propylcarbamate monocalcium salt

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CAS Registry number: 226700-81-8

Molecular Formula: C₂₅H₃₄CaN₃O₉PS

Molecular Weight: 623.7

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
—	IV	┌	—	4	N/A		See review of approved NDA 21-548
—	III	┌	┌	1	Adequate	5/24/99 2/4/00 1/7/04	Reviews by N. Ya, M. Adams, and M.D. Cooper
—	III	┌	┌	1	Adequate	3/1/07	Reviewed by G. Lunn
—	III	┌	┌	4	N/A		

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

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Chemistry Review Data Sheet

- 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
NDA for Lexiva (fosamprenavir calcium) 700 mg tablets	NDA 21-548	Approved 20-OCT-2003

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	30-Jan-2007	J. D'Ambrogio, OC
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Not required		
OPDRA	N/A		
EA	Categorical exclusion requested. This is acceptable.	19-JAN-2007	G.Lunn
Microbiology	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-116

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from the CMC perspective. All CMC issues have been satisfactorily resolved and an overall recommendation of Acceptable has been made by the Office of Compliance.

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

None

II. Summary of Chemistry Assessments

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

Drug substance information is found in the approved NDA 21-548 for Lexiva (fosamprenavir calcium) Tablets and it is incorporated by reference. The drug substance specification is acceptable for this product. †

b(4)

The drug product is a white to off-white suspension that has a characteristic bubblegum odor. It contains 50 mg/mL fosamprenavir as fosamprenavir calcium. The suspension is packaged in white, round — bottles with † — CRCs containing 225 mL.

b(4)

Inactive ingredients are propylene glycol, hypromellose — sucralose, methylparaben, propylparaben, polysorbate 80, calcium chloride dihydrate, artificial grape bubblegum flavor — natural peppermint flavor — and purified water. All excipients, except for the flavors, are compendial. The flavors are covered by DMFs and Letters of Authorization to refer to these DMFs are provided. The components of each flavor are either generally recognized as safe (GRAS) or are permitted synthetic flavorings listed in 21 CFR. The suspension contains — — propylene glycol. This is not a concern.

b(4)

The formulation development process is described. †

† For the clinical, stability, and commercial batches the internal volume of the bottle is 277 mL and the fill volume is 225 mL.

b(4)

Executive Summary Section

Adequate specifications are provided for appearance, identity, impurities, methylparaben, propylparaben, content uniformity, pH, dissolution, deliverable volume, redispersibility, and microbial limits. Inter-bottle uniformity is controlled by the content uniformity test which relies on sampling 10 bottles selected at random during the filling process. Intra-bottle uniformity is controlled by the redispersibility specification which relies on sampling the top and bottom of two shaken bottles. The analytical methods are well described and have been validated.

A justification of the specifications is provided. A slight decrease in pH is observed during storage. The pH specification allows for this decrease. Antimicrobial effectiveness testing was carried out using formulations containing of the specification preservative level and at the extremes of the specification pH. All four formulations passed the test. This supports the pH and preservative specifications. The impurity specification is the same as that for fosamprenavir tablets in approved NDA 21-548.

Satisfactory batch analyses are provided for 3 consecutive commercial-scale batches. Satisfactory batch analyses are also provided for 18 batches used in clinical trials. All batches used for clinical trials were manufactured using the proposed commercial formulation and using the proposed commercial process at the proposed commercial site.

The suspension is packaged in an bottle and a child-resistant closure. The is not covered by a DMF but all components of the conform to the relevant 21 CFR regulations so reference to a DMF is not necessary. The bottle, bottle resin, and closure are covered by DMFs and Letters of Authorization to refer to these DMFs are provided. These DMFs have been reviewed and found to be adequate. The dimensions, with tolerances, are given in a drawing for the bottle. These dimensions assure appropriate control of the internal volume of the bottle which is required for satisfactory redispersibility.

Thirty six months of satisfactory stability data are supplied for 3 batches stored at 25°C/40% RH and 30°C/60% RH and one batch stored at 5°C. Six months of satisfactory data are supplied for 3 batches stored at 40°C/25% RH. All bottles were stored horizontally. The only marked trend observed is a decline in pH. There are minor trends to a decrease in preservatives and an increase in impurities with time and temperature. Storage in the light cabinet and at 50°C for 3 months showed no out of specification results. However, storage under freeze/thaw conditions showed out of specification results for assay and redispersibility. Additionally, dissolution required S2 testing. The stability data support a shelf life of 36 months and the following storage statement "Store at 5°C to 30°C (41°F to 86°F). Shake vigorously before using. Do not freeze."

Executive Summary Section

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

Lexiva (fosamprenavir calcium) oral suspension is a protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV infection. The recommended dose is calculated based on age, weight, previous treatment experience, and whether ritonavir is co-administered as described in Table 1 of the package insert. The dose should not exceed 2800 mg per day. The suspension is supplied in _____ bottles with child-resistant closures containing 225 mL suspension. The storage statement is as follows "Store at 5° to 30°C (40°F to 86°F). Shake vigorously before using. Do not freeze." The expiration dating period is 36 months.

b(4)

C. Basis for Approvability or Not-Approval Recommendation

The chemistry, manufacturing, and controls for fosamprenavir calcium drug substance are incorporated by reference from approved NDA 21-548 for fosamprenavir calcium tablets. The composition, manufacturing process, and specifications for the oral suspension are appropriate. The expiration dating period of 36 months when stored at 5-30°C is supported by adequate data. The container-closure system and labeling are appropriate. All manufacturing sites have been found to be acceptable. This NDA is therefore recommended for approval from a CMC perspective.

III. Administrative

A. Reviewer's Signature

George Lunn, Ph.D. {Signed Electronically in DFS}

B. Endorsement Block

Norman R. Schmuff, Ph.D. {Signed Electronically in DFS}

C. CC Block

Stephen P. Miller, Ph.D.
Pharmaceutical Assessment Lead

37 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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

/s/

George Lunn
6/13/2007 05:11:14 PM
CHEMIST

Set for approval on Thurs 6/14/07

Norman Schmuff
6/15/2007 12:40:20 PM
CHEMIST