CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-548

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

NDA 21-548

LEXIVA™ (fosamprenavir calcium) Tablets

GlaxoSmithKline

George Lunn
Division of Anti-Viral Drug Products

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Chemistry Review Data Sheet

1. NDA 21-548

2. REVIEW #:1

3. REVIEW DATE: October 10, 2003

4. REVIEWER: George Lunn

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	19-Dec-2002
Amendment	24-Jan-2003
Amendment	11-Mar-2003
Amendment (BZ)	21-Mar-2003
Amendment (BC)	16-Apr-2003
Amendment	30-Apr-2003
Amendment	15-May-2003
Amendment	11-Jun-2003
Amendment	9-Jul-2003
Amendment	17-Jul-2003
Amendment	1-Aug-2003
Amendment (BC)	18-Sep-2003
Amendment (BZ)	29-Sep-2003
Amendment	13-Oct-2003
Amendment	16-Oct-2003

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	GlaxoSmithKline
Address:	P.O. Box 13398 Five Moore Drive Research Triangle Park, NC 27709
Representative:	Anne N. Stokley, M.S.P.H. Director, Antiviral/Antibacterial Regulatory Affairs
Telephone:	(919) 483-6405, Fax (919) 483-5756

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Lexiva
b) Non-Proprietary Name (USAN): fosamprenavir calcium
c) Code Name/# (ONDC only): GW433908G
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 2
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Anti-Viral

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 700 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note29]:
_____SPOTS product – Form Completed

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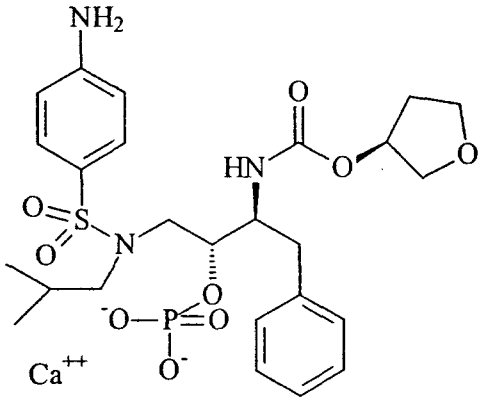
__X__Not a SPOTS product

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

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



CAS Registry number: 226700-81-8

Molecular Formula: $C_{25}H_{34}CaN_3O_9PS$

Molecular Weight: 623.7

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	3	Adequate	9/15/00	Reviewed by R. Frankewich
[redacted]	III	[redacted]	[redacted]	3	Adequate	2/14/03	Reviewed by J. Salemme
[redacted]	III	[redacted]	[redacted]	3	Adequate	5/7/99	Reviewed by R.S. Harapanhalli
[redacted]	III	[redacted]	[redacted]	3	Adequate	5/19/03	Reviewed by D. Klein

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[redacted]	III	[redacted]	4	Adequate		
[redacted]	III	[redacted]	3	Adequate	10/30/01	Reviewed by R. Frankewich
[redacted]	IV	[redacted]	4	Adequate		

[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
ND	58-627	Fosamprenavir calcium
NDA	21-007	Amprenavir Soft Gelatin Capsules
NDA	21-039	Amprenavir Oral solution

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	15-Oct-2003	S. Adams
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Pending		
OPDRA	N/A		
EA	N/A		
Microbiology	N/A		

)GD:

CONSULTS/ CMC	RECOMMENDATION	DATE	REVIEWER

Chemistry Review Data Sheet

RELATED REVIEWS			
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

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 21-548

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from the CMC perspective.

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

There are no specific CMC recommendations for a Phase 4 commitment. However, it is noted that there is a toxicology Phase 4 commitment that impurities [redacted] will be qualified at an appropriate level in a 90-day rat toxicity study as agreed in the Amendment of 7/9/03.

II. Summary of Chemistry Assessments

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

Drug Substance

Fosamprenavir is the calcium salt of the phosphate ester of amprenavir. It is a pro-drug for amprenavir. Fosamprenavir is a protease inhibitor for the treatment of HIV infection.

Fosamprenavir is a white to cream solid with some solubility in water (0.31 mg/mL) and 100 mM HCl ([redacted]). Fosamprenavir is a single enantiomer with 3 chiral centers. There is only one known crystalline form which is hydrated with 5 molecules of water.

The drug substance synthesis is very similar to the synthesis of amprenavir in the approved NDA 21-007. [redacted] The procedures are well described. This is obviously the [redacted] procedure that yields variant A. [redacted] this process produced the non-bioequivalent Variant C (see below).

The specifications for the [redacted] are adequate. They are very similar to those given in the approved NDA 21-007 for amprenavir.

The [redacted] are well controlled through tight specifications that are almost identical to those found in the approved NDA 21-007 for amprenavir.

The structure of fosamprenavir is established by [redacted] The structure is confirmed by a [redacted]

Generally the impurities are qualified. However, the qualification levels of some impurities are less than the proposed limits when the No Observed Adverse Event Levels (NOAEL) found in the non-clinical toxicity studies in rats and dogs are considered. After a recommendation from the Division these impurities will be qualified at an appropriate level in a 90-day rat toxicity study that will be conducted as a Phase 4 commitment.

The specifications are similar to those proposed during the IND process but there are many more specified impurities. In general, the specifications are reasonable. [redacted] Generally the acceptance criteria are based on production capabilities. At the request of the Division the sponsor agreed to reduce the acceptance criteria for [redacted] amprenavir, and total impurities. The residual solvents specification is in accord with ICH Q3C. The analytical methods are described in detail and have been validated by the applicant.

Early batches of drug substance were made on a [redacted] scale [redacted] (Variant A). Later the process was [redacted] to produce drug substance Variant B which was [redacted] to produce drug substance Variant C. It was then found that tablets made from variants B and C were not bioequivalent to tablets made from Variant A. Since tablets made from Variant A were most bioavailable the sponsor decided to go forward only with Variant A. The sponsor has not been able to develop a physical test to distinguish between Variant A and Variant C. In particular, there is no correlation between particle size and bioavailability. It is known that tablets manufactured from drug substance Variants A and C have different bioavailability yet they have almost identical particle size distributions. Therefore there is no particle size specification.

Satisfactory batch analysis data are provided for [redacted] production batches manufactured on a [redacted] scale (Variant A) at Dartford.

[redacted] of satisfactory stability data obtained at 30°C/60% RH and [redacted] of data obtained at 40°C/75% RH are provided for [redacted] batches of variant A drug substance manufactured at a [redacted] scale. [redacted] of supportive data are provided for [redacted] batches of variant C drug substance manufactured at a [redacted] scale. There are no obvious trends and the drug substance

appears quite stable. A retest period of [redacted] for the drug substance stored at up to 30°C is reasonable.

Drug Product

The drug product is a pink, film-coated, capsule shaped, biconvex 700 mg tablet debossed GX LL7 on one face. The tablet is fairly large ([redacted] nm, total weight of [redacted] mg. The inactive ingredients are microcrystalline cellulose, croscarmellose sodium, povidone K30, magnesium stearate, colloidal silicon dioxide, [redacted] The inactive ingredients are compendial except for the film coat. This is composed of compendial materials and is covered by a DMF.

The tablets are manufactured using a [redacted] The manufacturing process is described in detail and the in-process controls are appropriate. The process has been validated by the manufacture of [redacted] scale ([redacted] batches using Variant A ([redacted] scale) drug substance. In addition, Variant A tablets used to initiate pivotal Phase III studies were shown to be bioequivalent to commercial Variant A tablets. At the Pre-NDA meeting the Division stipulated that this demonstration of bioequivalence was a condition for filing the NDA.

The specification is appropriate and contains tests for appearance, identity, assay, impurities, content uniformity, and dissolution. In addition, a [redacted] test is included to [redacted] Justifications are provided for the specifications. Except for the [redacted] method the specifications are generally unremarkable for a solid oral dosage form. At the request of the FDA the sponsor lowered the limits for amprenavir, [redacted] and total impurities.

The [redacted] method was introduced to distinguish between tablets made from Variant A, Variant B, and Variant C drug substance which have been shown to be non-bioequivalent although identical in all other respects. Although initial data appears to show that the predictive ability of this test is poor the sponsor has stated that they believe that the test is discriminatory between tablets of different bioavailability. The test will remain in the drug product specification and more data will be gathered.

The analytical methods are described in detail and have been validated by the applicant.

Satisfactory batch analyses are provided for [redacted] batches using the proposed commercial process from Variant A drug substance.

The tablets are supplied in an HDPE bottle with a child-resistant closure. All packaging materials comply with the 21 CFR food contact regulations and have been reviewed and found acceptable for similar products. At the request of FDA the phrase "[redacted] was added to the container label. Drug substance Variant A, as used in this product, may be used with or without ritonavir. [redacted]

ritonavir. In the original draft of the container label it was felt that the added phrase was lost in the other verbiage on the label and at the request of the FDA the phrase was printed in larger type, bolded, and separated from the rest of the wording.

Satisfactory stability data for batches manufactured from variant A drug substance and stored at 30°C/60% RH for and 40°C/75% RH for are supplied. Additionally satisfactory stability data for batch manufactured from variant B drug substance and stored at 30°C/60% RH for and 40°C/75% RH for are supplied. There are no out of specification results and no obvious trends.

The tablets stored in closed containers does not change significantly. However, it is noticeable that tablets stored in open bottles at 30°C/60% RH and 40°C/75% RH . Since dissolution data are not available for these open-container studies, it is not possible to know if this affected the dissolution. At the request of FDA the sponsor agreed to add the phrase "keep container tightly closed" to the labeling.

A statistical analysis was performed on the stability data. Although the slopes were common the data were not poolable because the intercepts were different. Based on the assay and total impurities values an expiration dating period of months was predicted. An expiration dating period of 30 months has been assigned.

Data are supplied to show that this product qualifies for a categorical exclusion from the requirement to file an Environmental Assessment.

A complete Methods Validation package is supplied. Validation is not expected prior to the approval of this NDA (see Regional Information, Section R3).

An Establishment Evaluation Request was submitted. The and Glaxo, Ware, UK facilities were inspected and found to be acceptable. The other facilities were found to be acceptable based on profile. An overall recommendation of Acceptable was provided on October 15, 2003.

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

Lexiva (fosamprenavir calcium) is indicated in combination with other antiretroviral agents for the treatment of HIV infection. The recommended dose is 1 or 2 tablets twice daily, with or without ritonavir boosting, respectively. Fosamprenavir calcium is supplied as a package of 60 tablets in an HDPE bottle.

An expiration dating period of 30 months is approved, based on months of long-term stability data for lots. These data also support the storage statement, "Store at 25 °C (77

°F); excursions permitted to 15 °C to 30 °C (59 °F to 86 °F) (see USP Controlled Room Temperature). Keep container tightly closed"

C. Basis for Approvability or Not-Approval Recommendation

The drug substance manufacturing process is well controlled and described in detail. The specifications are appropriate and justified and the retest date is supported by appropriate data. The composition, manufacturing process, and specifications for the tablets are appropriate and the expiration dating period is supported by adequate data. The container-closure system and labeling are appropriate. After evaluation all manufacturing sites were 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} Date of draft review 10/8/03

B. Endorsement Block

Stephen P. Miller, Ph.D.

C. CC Block

Chi-wan Chen, Ph.D.
Destry Sillivan, M.S.

45 Page(s) Withheld

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
10/24/03 11:53:41 AM
CHEMIST

Fosamprenavir NDA in pdf format

Stephen Paul Miller
10/24/03 12:18:32 PM
CHEMIST
Entry into DFS delayed by server issues on 10/20
and rendering problems identified subsequently.

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21548/000
Org Code : 530
Priority :

Sponsor: GLAXOSMITHKLINE
1 FRANKLIN PLAZA
PHILADELPHIA, PA 191017929

Stamp Date : 20-DEC-2002
PDUFA Date : 20-OCT-2003
Action Goal :
District Goal: 21-AUG-2003

Brand Name : TELZIR (FOSAMPRENAVIR CALCIUM)700MG TABS
Estab. Name:
Generic Name: FOSAMPRENAVIR CALCIUM
Dosage Form: (TABLET)
Strength : 700 MG

FDA Contacts:			
D. SILLIVAN	Project Manager	(HFD-530)	301-827-2335
G. LUNN	Review Chemist	(HFD-530)	301-827-2393
S. MILLER	Team Leader	(HFD-530)	301-827-2392

Overall Recommendation: ACCEPTABLE on 15-OCT-2003by S. ADAMS (HFD-322) 301-827-9051

Establishment : CFN : [redacted] FEI : [redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-OCT-03
Decision : ACCEPTABLE
Reason : DUPLICATE MILESTONE FROM FACTS

Establishment : CFN : [redacted] FEI : [redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 29-JAN-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9610411 FEI : 1000291018

GLAXO OPERATIONS UK LTD

PRIORITY STREET

WARE, HERTFORDSHIRE, UK

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

Profile : TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 29-SEP-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9610421 FEI : 3002807078

GLAXO WELLCOME LTD

DL128DT

BARNARD CASTLE, , UK

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 13-JAN-03

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : 9610414 FEI :

GLAXO WELLCOME OPERATIONS UK

DA1 5AH

DARTFORD, KENT, UK

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STABILITY TESTER

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-APR-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [redacted] FEI : [redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-OCT-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Establishment : CFN : [redacted] FEI : [redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-JAN-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [redacted] FEI : [redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CSN OAI Status: NONE

Last Milestone: INSPECTION PERFORMED

Milestone Date: 08-OCT-03

:

:
