CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-548

ADMINISTRATIVE DOCUMENTS

Patent Information

Pursuant to 21 C.F.R. § 314.53
for

TELZIR™ (fosamprenavir calcium) Tablets
NDA 21-548

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	TELZIR™
Active Ingredient:	fosamprenavir calcium
Strength(s):	700 mg fosamprenavir
Dosage Form:	Tablet; oral
NDA Number:	21-548

Applicable Patent Numbers and Expiration Dates:

Patent No.	6,436,989
Expires:	December 24, 2017
Owner:	Vertex Pharmaceuticals, Inc. Licensed to SmithKline Beecham Corp.
Type:	Drug Product Composition/Formulation Treatment of HIV infections

The undersigned declares that U.S. Patent No. 6,436,989, covers the composition, formulation, and/or methods of use of TELZIR™ (fosamprenavir calcium) Tablets. This U.S. patent should be included in Item 13 of NDA 21-548.

December 3 2002
Date

Karen L. Prus, Ph.D.
Registered Patent Attorney
Registration No. 39,337

Please address all communications to:

David J. Levy, Ph.D.
GlaxoSmithKline
Corporate Intellectual Property Department
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709
(919) 483-2723

NDA 21-548

Fosamprenavir Calcium Tablets

New Drug Application for Treatment of HIV Infection

DEBARMENT CERTIFICATION

GlaxoSmithKline 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.

Charles E. Mueller
Director, North America Clinical Compliance
Worldwide Regulatory Compliance

Date

EXCLUSIVITY SUMMARY for NDA # 21-548

Trade Name: LEXIVA™ Tablets Generic Name: fosamprenavir calcium
Applicant Name GlaxoSmithKline.
Approval Date October 20, 2003, HFD-530

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_✔_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_✔__/

   If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /_✔__/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity?

   YES /_✔__/ NO /___/

   If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

   Five

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__✔_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No – Please indicate as such).

YES /___/ NO /__✔_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_✔__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

Not applicable

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_✔__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Agenerase (amprenavir), NDAs 21-007, 21-039

2. Combination product.

   If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

   YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /_✔__/NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a

previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_✔__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_/ NO /__✔_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_✔_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # APV 30001:
Investigation #2, Study # APV 30002
Investigation #2, Study # APV 30003

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not re-demonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_✔__/
Investigation #2	YES /___/	NO /_✔_/
Investigation #3	YES /___/	NO /_✔_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_✔__/
Investigation #2	YES /___/	NO /_✔_/

Investigation #3 YES /___/ NO /_✔_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # APV 30001:
Investigation #2, Study # APV 30002
Investigation #2, Study # APV 30003

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND 58,627 YES /_✔_/ NO /___/ Explain:

Investigation #2

IND 58,627 YES /_✔_/ NO /___/ Explain:

Investigation #3

IND 58,627 YES /_✔_/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

!

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /__✔_/

If yes, explain: _____

Destry M. Sillivan
Signature of Preparer Date :October 15, 2003
Title: Regulatory Project Manager

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # :21-548 Supplement Type (e.g. SE5): Original NDA (pro-drug of amprenavir)

Stamp Date: December 20, 2003 Action Date: October 20, 2003

HFD-530 Trade and generic names/dosage form: LEXIVA™ (fosamprenavir calcium) Tablets.

Applicant: GlaxoSmithKline. Therapeutic Class: Anti-HIV

Indication(s) previously approved: (

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application: 1

Indication #1: This application provides for the use of LEXIVA™ (fosamprenavir calcium) 700 mg Tablets in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.

No: ✔ Please check all that apply: ✔ Partial Waiver ✔ Deferred Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver: N/A

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min 0 days	kg	mo.	yr.	Tanner Stage	
Max 4 weeds	kg	mo.	yr.	Tanner Stage	

Reason(s) for partial waiver:

- ✔ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ✔ Other: Product unlikely to be used in children less than four weeks of age.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min 4 weeks___kg_____ mo._____ yr.____ Tanner Stage_____
Max_ adolescence_kg_____ mo._____ yr.____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ✔ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (August 2006):

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____ kg____ mo._____ yr. 3 Tanner Stage_____
Max____ kg____ mo._____ yr. 16 Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Destry M. Sillivan
Regulatory Health Project Manager

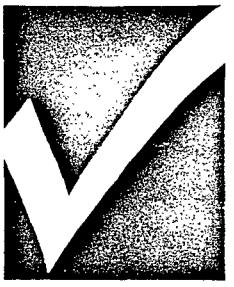
cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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

/s/

Destry Sillivan
10/27/03 12:20:51 PM



ROUTING SLIP FOR SIGN OFF AND CIRCULATION

Destry Sillivan, Project Management, HFD-530

TO:	Name:	Initials:	Date:
✓	Russ Fleischer	LSI	10/20/03
✓	George Lunn	LSI	10/20/03
✓	Steve Miller	LSI	10/20/03
✓	Lalji Mishra	LSI	10/20/03
✓	Jules O'Rear	LSI	10/20/03
✓	Hao Zhang	LSI	10/20/03
✓	James Farrelly	LSI	10/20/03
✓	Derek Zhang	LSI	10/20/03
✓	Kellie Reynolds	LSI	10/20/03
✓	Thomas Hammerstrom	LSI	10/20/03
✓	Guoxing Soon	LSI	10/20/03
✓	Thomas Hammerstrom	LSI	10/20/03
✓	Rosemary Johann-Liang	LSI	10/20/03
✓	Marsha Holloman	LSI	10/20/03
___	Jeff Murray	LSI	10/20/03
___	Debra Birnkrant	LSI	10/20/03
___	Destry Sillivan/DFS sign off	_____	_____

Comments:

Please initial and FORWARD. Or, return to PM.

IND/NDA: NDA 21-548

Document Type: NDA approval Package

CSO: Destry Sillivan _____ Date: **October 17, 2003**

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 21-548	Efficacy Supplement Type -	Supplement Number
Drug: LEXIVA™ (fosamprenavir calcium) Tablets	Applicant: GlaxoSmithKline.	
RPM: Destry M. Sillivan	HFD-530	Phone # (301) 827-2335
Application Type: (✓) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name): N/A	

❖ Application Classifications:	
• Review priority	(✓) Standard () Priority
• Chem class (NDAs only)	Type 2
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	October 20, 2003
❖ Special programs (indicate all that apply)	( ) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
User Fee Information	
• User Fee	(✓) Paid
• User Fee waiver	() Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception (The sponsor has paid a fee, but requested an exception due to Orphan Drug status. This request is pending.)	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (✓) No
• This application is on the AIP	( ) Yes (✓) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(✓) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(✓) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted N/A, since only applicable to 505(b)(2)	N/A
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified N/A

Exclusivity (approvals only)	
• Exclusivity summary	Yes
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_ (✓) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A
General Information	
❖ Actions	
• Proposed action	(✓) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(✓) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(✓) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(✓) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	✓
• Original applicant-proposed labeling	Not necessary
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews)	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	✓
• Reviews	See Chemistry Review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	✓
• Documentation of agreements relating to post-marketing commitments	✓
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	✓
❖ Minutes of Meetings	
• EOP2 meeting-	
• Pre-NDA meeting	
• Pre-Approval Safety Conference	
• Other (45 day filing meeting minutes, ect)	✓

Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (Division Director, Medical Team Leader)	✓
Clinical Information	
❖ Clinical reviews	✓
❖ Microbiology (efficacy) review	✓
❖ Safety Update review	N/A See Medical Officer's review
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	✓
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review	✓
❖ Biopharmaceutical review	✓
❖ Controlled Substance Staff review(s) and recommendation for scheduling	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
CMC review	✓
❖ Environmental Assessment	
• Categorical Exclusion	✓
• Review & FONSI	N/A
• Review & Environmental Impact Statement	See Chemistry Review
❖ Micro (validation of sterilization & product sterility) review	N/A
❖ Facilities inspection (provide EER report) See Chemistry Review	Date completed: (✓) Acceptable ( ) Withhold recommendation
❖ Methods validation PENDING	( ) Completed (✓) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review, including referenced IND reviews	✓
❖ Nonclinical inspection review summary	N/A
❖ Statistical review of carcinogenicity studies	N/A
❖ CAC/ECAC report	N/A

'03 DMS

User Fee Cover Sheet **CONFIDENTIAL**

December 12, 2002

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709-3398
Tel. 919 483 2100
www.gsk.com

Mellon Client Service Center Room 670
Food and Drug Administration
Food and Drug Administration 360909
500 Ross Street
Pittsburgh, PA 15262-0001

Re: NDA 21-548; TELZIR™ (fosamprenavir calcium) Tablets
User Fee: With Clinical Data; User Fee ID Number 4473

Please find enclosed GlaxoSmithKline check number [—] the amount of $533,400.00. This payment represents 100% of the application fee for the New Drug Application that is being filed with the Center for Drug Evaluation and Research, FDA.

Please find below requested information regarding this application:

Type of Application:	New Drug Application with Clinical Data	X
	New Drug Application without Clinical Data	
	Supplemental New Drug Application with Clinical Data	

Please contact me at (919) 483-6405 should you have any questions. Thank you.

Sincerely,

Anne N. Stokley, M.S.P.H.
Director
Antiviral/Antibacterial Regulatory Affairs

Attachment: GSK Check Number [ ]
Form FDA 3397

User Fee Cover Sheet CONFIDENTIAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

SmithKline Beecham Corporation d/b/a GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia PA 19101

2. TELEPHONE NUMBER *(Include Area Code)*

(919) 483-6405

3. PRODUCT NAME

TELZIR™ (fosamprenavir calcium) Tablets

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021548

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4473

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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ATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
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FORM FDA 3397 (4/01)

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 10-17-03

FROM: Debra Birnkrant, M.D.
Director, Division of Antiviral Drug Products, HFD-530

TO: Division File NDA 21-548

SUBJECT: Division Director's Memorandum for NDA 21-548 for Lexiva™(fosamprenavir calcium) Tablets for use in combination with other antiretroviral agents for the Treatment of HIV in Treatment-Naïve and Experienced Subjects

This memorandum is written in support of the approval of Lexiva™(fosamprenavir calcium) Tablets, for treatment of HIV-1 infection in adult treatment-naïve and experienced subjects. This regulatory action is based on the favorable risk/benefit profile of the drug as determined by a multidisciplinary review of the totality of the data contained in this NDA. This memorandum will focus on two phase 3 clinical trials in treatment-naïve subjects, 30001 and 30002, and a single trial in treatment-experienced subjects, 30003; an overall risk/benefit assessment will be described below.

BACKGROUND:

Agenerase®(amprenavir), a protease inhibitor, was approved for use in combination with other antiretroviral agents in 1999. The dosing of Agenerase® requires up to 16 pills per day and is quite difficult to take.
Lexiva™(fosamprenavir calcium) is the calcium salt of the phosphate ester of amprenavir and was developed as an improved formulation of amprenavir. Fosamprenavir is almost entirely converted to amprenavir(99%) and thus provides similar plasma exposure compared to amprenavir with a lower pill burden.

The NDA for Lexiva™ was submitted in December, 2002. It received a 10-month review and was not the subject of an advisory committee.

Treatment Results: Efficacy

NDA 21-548 contains three principal studies in adult naïve and experienced patient populations. Studies 30001 and 30002 examined the use of Lexiva™ in combination with abacavir and lamivudine in treatment naive subjects compared to a nelfinavir-containing regimen. Each study examined a different regimen of Lexiva™; study 30001 examined an unboosted dose of Lexiva™, 1400 mg as a twice daily regimen and study 30002 examined a boosted dose of Lexiva™ of 1400 mg with 200 mg of ritonavir as a once daily regimen. Both trials were designed as open-label, 48-week studies. The primary endpoint for both studies was the proportion of patients with HIV RNA < 400 copies /ml.

In trial 30001, patients appeared to be somewhat advanced for a naive patient population with a median CD_4 count of approximately 200 cells/mm^3 and 44% of the population also had viral loads greater than 100,000 at baseline. Participants in trial 30001 had a response rate of 64% compared to an underperforming nelfinavir arm that had a virological response rate of 49%(< 400 copies/ml). CD_4 cell count median change from baseline was approximately +200 cells per arm.

Study 30002 was also an open label study comparing Lexiva to nelfinavir in a somewhat advanced naive population with a median CD_4 count of 166 –177 cells/mm^3. This study had the same primary endpoint as study 30001. Results revealed a response rate of 69% in the fosamprenavir-containing arm compared to 68% in the nelfinavir-containing regimen for the endpoint of proportion < 400 copies/ml. The median change in CD_4 count in this trial was also about a +200 cell increase from baseline. Of interest, no amprenavir- associated resistance mutations were seen in study 30002 compared to 5/29 patients with virologic failure on the Lexiva™ arm in study 30001. A likely explanation is that coadministration of ritonavir with fosamprenavir increases plasma amprenavir exposures and maintains plasma concentrations of amprenavir above the amprenavir IC_{50} against HIV.

The third clinical trial in this NDA was conducted in treatment experienced subjects. Study 30003 enrolled PI-experienced adult patients experiencing virologic failure. Two Lexiva™-containing regimens were compared to a Kaletra-containing regimen in this study. The primary endpoint was different than the naive studies and examined the average change from baseline in plasma HIV RNA or AAUCMB at 48 weeks. The results of study 30003 failed to meet noninferiority parameters set forth in the trial for the primary endpoint. Upon examination of the secondary endpoints of proportion with HIV-1 RNA < 400 and < 50 HIV RNA copies/ml, boosted Lexiva™ at a dose of 700mg with ritonavir 100 mg twice daily had a similar point estimate as the control arm (58% vs 61% < 400 copies /ml and 46% vs. 50% < 50 copies/ml); the once daily boosted regimen of 1400 mg Lexiva™ with 200 mg of ritonavir was inferior to the twice daily boosted Lexiva™ regimen and the control arm. Although the point estimate for the secondary endpoints was numerically comparable between twice daily

Lexiva™ with ritonavir and Kaletra™, it cannot be concluded that Lexiva™ is equivalent to Kaletra™ based on this underpowered study. The conclusion that can be reached however is that boosted Lexiva™ in a twice daily regimen is an active regimen in this population. Per Dr. Hammerrstrom's analysis, Lexiva™ clearly has activity beyond that of a placebo based on a meta-analysis that supports the inference that boosted Lexiva™ as a twice daily regimen would have been statistically significantly superior to placebo with respect to viral load estimates at 48 weeks in this population. A larger clinical trial in this population that is powered for the primary endpoint of proportion undetectable would better characterize the performance of Lexiva™ compared to Kaletra™ when used in combination with other antiretroviral agents. Based on the results of 30003, a statement emphasizing that Lexiva™ is not equivalent to Kaletra™ in a PI-experienced population will be placed in the Indications and Usage section of the labeling as well as in the Description of Clinical Studies section.

Trial Results: Safety

The safety database contains data on more than 2000 HIV-infected subjects who received at least one dose of fosamprenavir. Specifically, the NDA contains data on 770 HIV-infected subjects who received Lexiva alone or in combination with ritonavir in studies 30001, 30002, and 30003.

Safety analysis revealed a similar adverse event profile similar to Agenerase®. The most common events we GI-related and included diarrhea, nausea, vomiting and abdominal pain. As seen with amprenavir, headache, fatigue, rash, paresthesias and depression were also seen in patients treated with Lexiva™. Laboratory abnormalities included those associated with the class of protease inhibitors. Patients who received Lexiva™ in combination with ritonavir experienced an increased incidence of diarrhea, vomiting, fat redistribution and laboratory abnormalities such as hyperglycemia and lipid abnormalities. Fosamprenavir contains a sulfonamide moiety and should be used with caution in patients with a known sulfonamide allergy. This wording appears prominently in labeling.

Hepatotoxicity was more commonly observed in subjects who were co-infected with hepatitis B or C. To address this safety issue, the following wording appears in product labeling:

Patients with underlying hepatitis B or C or marked elevations in transaminases at baseline may be at increased risk of developing transaminase elevations. Appropriate laboratory testing should be conducted prior to initiating therapy with Lexiva™ and patients should be monitored closely during treatment.

Resistance

Amprenavir resistance-associated mutations have been detected in patients receiving fosamprenavir. Five of 29 antiretroviral naïve subjects who experienced virologic failure had evidence of genotyoic resistance to amprenavir whereas no amprenavir-associated mutations were seen in naïve subjects receiving a boosted regimen of fosamprenavir. Regarding cross resistance with other PIs and virologic outcome at 48 weeks in study 30003, patients with baseline mutations D30N and N88D/S responded equally well with boosted Lexiva™ or Kaletra™. Subjects who received Lexiva™/ritonavir bid who had the I54V or I84V mutations responded less well than those randomized to receive Kaletra™. Of note, this analysis is informative, but incomplete because the number protease mutations and the activity of the NRTI backbone were not considered in this analysis.

Other Issues:

Regarding the manufacturing process for Lexiva™, please see reviews by Dr. Lunn, Dr. Zheng and Senior Clinical Reviewer, Russ Fleischer.

RISK/BENEFIT ASSESMENT:

To date, there are many treatment options for naïve patients with HIV, but treatment options are limited for patients with more advanced disease. Although, the ability to construct a potent antiviral regimen for naïve subjects is somewhat easier than for experienced subjects, adherence issues remain a major issue for all populations. Compared to complicated Agenerase® dosing regimens, use of Lexiva™ with or without ritonavir boosting will allow health care practioners to construct potent, yet simplified regimens with regard to pill burden.

Multiple regimens are being approved and require explanation. Dosing in treatment experienced patients is based on results of study 30003 and is twice daily Lexiva™ 700 mg with ritonavir 100 mg. Dosing in naïve patients is based on results from clinical studies 30001 and 30002 and from pharmacokinetic data to support the dose of Lexiva™ 700 mg with ritonavir 100 mg twice daily. Regarding the use of the Lexiva™ 1400 mg twice daily dosing regimen in naïve subjects, this was an active regimen in study 30001 based on DAVDP-sanctioned endpoints of viral load reduction and CD_4 cell increase. It also provides for use of a safe and effective treatment option for those patients who can not take ritonavir.

In sum, the data contained in this NDA demonstrate that Lexiva™ with or without ritonavir boosting provides statistically and clinically significant reductions in viral load and improvement in immunologic function as measured by increases in CD_4 counts. With regard to safety, the risk/benefit profile allows me to support approval of this marketing application.

Post-marketing commitments will be described in the approval letter.

TEAM LEADER'S MEMORANDUM

DATE:	October 17, 2003
TO:	Division File for NDA 21-548
FROM:	Rosemary Johann-Liang, M.D. Medical Team Leader. Division of Antiviral Drug Products HFD-530
DRUG and INDICATION:	Lexiva™ (fosamprenavir calcium) Tablets for the treatment of HIV-1 infection in combination with other antiretroviral agents

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This New Drug Application (NDA) for LEXIVA (fosamprenavir), a protease inhibitor (PI) that is a prodrug of amprenavir, is being recommended for regulatory approval. LEXIVA is a phosphate ester prodrug of Agenerase® (amprenavir) which is an already marketed HIV protease inhibitor. LEXIVA was developed and has been shown to be an improved formulation for delivery of amprenavir, reducing the pill burden from 8 pills twice a day to 2 pills once a day. I concur with the clinical review prepared by Russell Fleischer, PA-C, MPH. As stated in his review, the applicant (GlaxoSmithKline) has demonstrated that LEXIVA at the proposed doses for marketing is a safe and effective drug for the treatment of HIV-1 infection in adults when combined with other antiretrovirals.

Background

This NDA was submitted on December 19, 2002 and was granted a standard (10-month) review period. The application consisted of results of three principal trials (APV30001, APV30002, APV30003) as well as a large number of clinical pharmacology/pharmacokinetics/drug interaction studies. The applicant also included in the NDA brief reports from a number of ongoing clinical studies in which HIV-infected patients were receiving LEXIVA. Studies APC30001 and APV 30002 were in HIV treatment-naïve patients and in both studies a nucleoside analogue backbone of abacavir and lamivudine was used. LEXIVA was administered twice daily without boosting with ritonavir (APV 30001) and once daily with ritonavir boosting (APV 30002). The third study (APC30003) was in HIV treatment-experienced (PI failure) patients where LEXIVA was administered once or twice daily with ritonavir along with two nucleoside reverse transcriptase inhibitors (NRTIs). This memorandum will briefly describe the results from these trials and highlight several issues that were particular to this application via summary comments.

Mechanism of action

Fosamprenavir is rapidly converted to amprenavir by cellular or serum phosphatases in vivo. Amprenavir is an inhibitor of HIV-1 protease. Amprenavir binds to the active site of HIV-1 protease and thereby prevents the processing of viral Gag and Gag-Pol polyprotein precursors, resulting in the formation of immature non-infectious viral particles.

Efficacy Overview

Summary Table of Principal Clinical HIV-1 Studies

Protocol No. **Population** **Design** **Endpoint**	**Treatment Arms** **Dose/Frequency** **No. patients**	**Efficacy Results Virology**	**Efficacy Results Immunologic**	**Resistance Results on virologic failure (VF) patients (genotype)**
APV30001 Treatment naïve Multicenter, 2:1 randomized, open-label Primary Endpoint: Proportion of patients with HIV-1 RNA <400 c/mL at week 48	**Lexiva** 1400 mg +ABC 300 mg +3TC 150 mg All BID (n=166) VERSUS **NFV** 1250 mg +ABC 300 mg +3TC 150 mg All BID (n=83)	% with HIV-1 Viral Load < 400 c/mL (<50 c/mL) at wk 48: **Lexiva** Arm 64% (54%) VERSUS **NFV** Arm 49% (42%)	Mean change from baseline: CD4 cells/ mm^3 **Lexiva** Arm +139 cells/mm^3 VERSUS **NFV** Arm +136 cells/mm^3	Mutations *at baseline*: none Mutations *on therapy*: **Lexiva** Arm (n=29 VF) 5 pts with genotypic mutations associated with amprenavir: I54L/M, I54L+L33F, V32I+I47V, M46I+I47V **NFV** Arm (N=27 VF) 9 pts with genotypic mutations associated with NFV: D30N or N88D ± L90M
APV30002 Treatment naïve Multicenter, 1:1 randomized, open-label Primary Endpoint: Proportion of patients with HIV-1 RNA <400 c/mL at week 48	**Lexiva** 1400 mg **+ ritonavir** 200 mg (both QD) +ABC 300 mg BID +3TC 150 mg BID (n=322) VERSUS **NFV** 1250 mg +ABC 300 mg +3TC 150 mg All BID (n=327)	% with HIV-1 Viral Load < 400 c/mL (<50 c/mL) at wk 48: Lexiva Arm 69% (57%) VERSUS NFV Arm 68% (55%)	Mean change from baseline: CD4 cells/ mm^3 Lexiva Arm +137 cells/mm^3 NFV Arm +150 cells/mm^3	Mutations *at baseline*: none Mutations *on therapy*: Lexiva Arm (n=32 VF) none with amprenavir-resistance-associated mutations NFV Arm (N=54 VF) 28 pts with genotypic mutations associated with NFV: D30N
APV30003 PI failures Multicenter, 1:1:1 randomized, open-label Primary Endpoint: Average area under the curve minus baseline (AAUCMB) in plasma HIV-1 RNA at week 48	**(1) Lexiva** 1400 mg **+ ritonavir** 200 mg (both QD) +ABC 300 mg BID +3TC 150 mg BID (n=107) **(2) Lexiva** 700 mg **+ ritonavir** 100 mg (both BID) +ABC 300 mg BID +3TC 150 mg BID (n=105) **(3) LPV** 400 mg **+ritonavir** 100 mg (both BID) +ABC 300 mg BID +3TC 150 mg (n=103)	AAUCMB (log_{10}c/mL) (1) −1.38 (2) −1.39 (3) −1.66 both Lexiva arms inferior to Kaletra arm % with HIV-1 Viral Load < 400 c/mL (<50 c/mL) at wk 48: (1) 50% (37%) (2) 58% (46%) (3) 61% (50%) lower bound of 95% CI for (1) −25% (2) −16.6%	Mean change from baseline: CD4 cells/ mm^3 (1) Lexiva Arm +53 cells/mm^3 (2) Lexiva Arm +50 cells/mm^3 (3) LPV Arm +64 cells/mm^3	Mutations *at baseline* (Lexiva Arms): 8% of patients contained primary PI-resistance mutations consisting of D30N, M46I/L, I54V, V82A/F/TS, N88D. I84V, and L90M. In addition, V32I, G84V, I54L/M, N88S mutations were also present in some baseline HIV-1 isolates. Mutations *on therapy* (Lexiva arms): QDarm: 8/20 VF had one more mutations associated with amprenavir resistance: V31I, M46I/L, I47V, I50V, I54L/M, I84V BID arm: 15/29 isolates contained one or more amprenavir-resistance-associated mutations

ABC: abacavir, 3TC: lamivudine, NFV: nelfinavir, LPV: lopinavir

The demographic and patient distributions of the populations for both the study drug and the active control arms of each of the three trials were similar. There were no major discrepancies between discontinuation rates between the arms of the trials. For antiretroviral-naïve patients in studies APV30001 and APV30002, the efficacy data demonstrated that the antiretroviral drug regimen of LEXIVA (administered with and without ritonavir) plus abacavir and lamivudine was active and produced suppression of HIV-1 RNA below detectable levels that was sustained through 48 weeks. The proportions of patients with HIV-1 RNA suppression were comparable to the active control regimen that is generally used as a first-line PI regimen, nelfinavir plus abacavir and lamivudine. The results showed that the efficacy of LEXIVA was at least as good as nelfinavir. For PI-experienced patients in APV30003 study, LEXIVA/ritonavir (LEXIVA/r) administered once daily produced lower HIV-1 RNA reductions from baseline as well as lower proportions of patients with HIV-1 RNA suppression below detectable levels when compared to an established comparator agent, Kaletra® (lopinavir/ritonavir, LPV/r, Abbott Laboratories). LEXIVA/r administered twice daily also produced lower HIV-1 RNA reductions from baselines compared to LPV/r, but numerically similar proportions of patients with HIV-1 RNA suppression below detectable levels.

Specific Issues for Comment Regarding Study Populations and Efficacy Results

- **Race Demographics**: There were relatively high proportions of Hispanic and Black patients enrolled (Hispanic 45%; Black 32%; White 22%) in the APV30001 study, which may have been a function of the locations in which the study was conducted, i.e. Latin and South American and South Africa. However, the results of the study are important for the US since Blacks and Hispanics represent the fastest growing population of HIV infected persons. There were no statistically significant differences in the efficacy outcome by different ethnicities.

- **NFV Active Control:** The comparator arms for both APV30001 and APV 30002 studies were in fact the exact same regimen: nelfinavir 1250 mg + abacavir 300 mg + lamivudine 150 mg all as twice a day dosing. However, it is important to note that the efficacy results given as HIV-1 RNA suppression below detectable limits at 48 weeks were quite different in the two trials (49% in APV30001 versus 68% APV30002). Several study design factors may contribute to this differential result including patient numbers/randomization (2:1 randomization with n=249 total in APV30001 vs. 1:1 randomization with n=649 in APV30002) and initial sample size calculations (APV30001 based on AAUCMB vs. APV30002 based on HIV-1 RNA suppression <400 c/mL). Since the second study design (APV30002) is the more robust of the two studies, the results of this second study may hold more validity. This differential result between the control arms (same regimen) of the two trials are even more important to note because it tells us that we should not directly compare the results of the study drug arms from the two trials, a pertinent point discussed in the next bullet.

- **Ritonavir Boost:** LEXIVA is rapidly converted to amprenavir by cellular or serum phosphatases in vivo. Based on pharmacokinetic (PK) studies, coadministration of LEXIVA with ritonavir increases plasma amprenavir exposure (AUV and C_{min} increased by 50% and 4 to 6-fold on average, respectively) primarily through inhibition of amprenavir metabolism, thus maximizing and maintaining plasma amprenavir concentrations above the IC_{50} for HIV isolates from patients with various levels of HIV protease inhibitor experience, including PI-naïve and multiple-PI experienced patients. This favorable PK interaction allows for LEXIVA when boosted with ritonavir to be given once daily. This boosted regimen at once daily dosing was in fact studied in APV30002 and shown to be comparable to the NFV control arm and antiretroviral-naïve study population. However, clinical study APV30003

showed that in PI-experienced patients, LEXIVA/r should be dosed in a twice daily regimen. It is also important to point out that in the antiretroviral-naïve patients, efficacy response rates of LEXIVA given without the boost by ritonavir was comparable to the NFV control arm efficacy response rate (APV30001). And as discussed above, the efficacy response rate of LEXIVA alone cannot be compared directly to the results of the second study (APV30002) where a Lexiva boosted by ritonavir regimen was used. Hence, for the **therapy-naïve population,** it will be recommended in the label under DOSING and ADMINISTRATION that the following three regimens of Lexiva can be given as alternative choices depending on the clinical situation.

- LEXIVA 1,400 mg twice daily (without ritonavir)
- LEXIVA 1,400 mg once daily plus ritonavir 200 mg once daily
- LEXIVA 700 mg twice daily plus ritonavir 100 mg twice daily

This third alternative (the twice daily plus ritonavir dose) is supported by pharmacokinetic and safety data since no clinical study was performed to directly test this alternative dose in naïve patients. It should be noted that in this population, the use of ritonavir enhanced Lexiva (longer duration of exposure at higher levels of Lexiva) may translate into more durable antiviral responses and delayed emergence of resistance. This hypothesis is based on a finding that no amprenavir resistance-associated mutations emerged in patients who received Lexiva/r as compared to patients who received Lexiva without the ritonavir boost.

For the **PI-experienced patients,**

- LEXIVA 700 mg twice daily plus ritonavir 100 mg twice daily is being

recommended currently as the only option based upon results of the APV30003 study. Adjustment with ritonavir dose is also recommended based on PK studies when LEXIVA plus ritonavir are administered with efavirenz. An additional 100 mg/day (300 mg total)of ritonavir is recommended when efavirenz is administered with LEXIVA plus ritonavir once daily.

- **Efficacy Results of PI-experienced patients:** Elaboration regarding the efficacy results of the PI-experienced population study (APV30003) is warranted. The applicant used AAUCMB as the primary endpoint analysis. This analysis demonstrated that both LEXIVA/r regimens were inferior to LPV/r. Specifically, although the LEXIVA/r arms produced similar mean changes from baseline in HIV-1 RNA of -1.38 log10 c/mL for once daily and -1.39 log10 c/mL for twice daily, LPV/r produced a mean -1.66 log10 c/mL reduction of HIV-1 RNA from baseline. The lower bound of the 95% confidence intervals for the difference between LEXIVA/r once daily versus LPV/r was 0.01 (p=0.04), and for LEXIVA/r twice daily versus LPV/r it was 0 (p=0.05). Secondary efficacy endpoints included the comparisons of changes from baseline in CD4 cell counts, the proportions of patients with HIV-1 RNA <400 c/mL and 50 c/mL, and analysis of genotypic/phenotypic resistance. LPV/r and LEXIVA/r twice daily produced numerically similar proportions of patients with HIV-1 RNA <400 and <50 c/mL. LEXIVA/r (50% and 37%) once daily was, on all endpoints, inferior to both LEXIVA/r (58% and 46%) twice daily and LPV/r (61% and 50%). The lower bound of the 95% confidence limit for the proportion with HIV-1 RNA <400 c/mL between LEXIVA/r once daily and LPV/r was -25%, supporting the conclusion that LEXIVA/r once daily was significantly less efficacious than LPV/r. The 95% confidence intervals for the difference between LEXIVA/r twice daily and LPV/r was -16.6% and +10.1. Thus, in protease inhibitor-experienced patients, the study was not large enough to reach a definitive conclusion that LEXIVA/ritonavir and lopinavir/ritonavir are clinically equivalent. Clarifications about the efficacy results of this study as it relates to how the drug should be used in the PI-experienced patients will be made in the USAGE section of the label as follows.

The following points should be considered when initiating therapy with LEXIVA/ritonavir in protease inhibitor experienced patient (see Description of Clinical Studies)

- The protease inhibitor-experienced patient study was not large enough to reach a definitive conclusion that LEXIVA/ritonavir and lopinavir/ritonavir are clinically equivalent.
- Once daily administration of LEXIVA plus ritonavir is not recommended for protease inhibitor experienced patients

- **Cross-Resistance:** A cross-resistance Table is being placed under the Microbiology section of the label that shows that virologic response was impacted by the presence of certain protease mutations at baseline. Specifically, presence of I54V, I84V and V82/A/F/T/S were associated with a lower rate of response with LEXIVA/r compared to LPV/r. The Table is as follows.

Responders at study Week 48 by presence of baseline PI mutations, N(%)

PI-MUTATIONS*	GW908/RITONAVIR BID (n=88)	LPV/r BID (n=85)
D30N	21/22 (95%)	17/19 (89%)
N88D/S	20/22 (91%)	12/12 (100%)
L90M	16/31 (52%)	17/29 (59%)
M46I/L	11/22 (50%)	12/24 (50%)
V82A/F/T/S	2/9 (22%)	6/17 (35%)
I54V	2/11 (18%)	6/11 (55%)
I84V	1/6 (17%)	2/5 (40%)

Safety

The NDA contained safety data on over 2000 HIV-1 infected patients exposed to LEXIVA in short-term clinical pharmacology and long-term treatment studies. Data on 770 HIV-1 infected patients who received LEXIVA alone or in combination with ritonavir in the three pivotal clinical studies was submitted in the NDA. Median exposure to LEXIVA in these studies at the proposed marketing doses was a median of 350 days (range 1-560 days). Additional safety data was submitted from ongoing IND (n=754) and non-IND (n=270) studies.

The following is a brief statement of safety conclusions taken from the Clinical Review. Please see Russell Fleischer, PA-C, MPH's Clinical Review for details on the LEXIVA safety assessment.

Lexiva™ (GW908, fosamprenavir) is nearly 99% converted to an active compound, amprenavir, which is also the active component of Agnerase®. Amprenavir is a protease inhibitor with a well described and characterized adverse event profile when used with and without ritonavir as a component of multi-drug antiretroviral regimen. Pre-clinical animal studies demonstrated gastrointestinal toxicities (vomiting, soft and watery stools), increased cholesterol, decreased triglycerides, and increased serum AST and ALT. The most common clinical adverse events and laboratory abnormalities associated with amprenavir are diarrhea, nausea, vomiting, fatigue,

headache, rash, and peripheral/oral paresthesias. When co-administered with ritonavir, the frequency of diarrhea increases as does hypertriglyceridemia and hyperglycemia.

The most common events reported in patients treated with LEXIVA (with and without ritonavir) included diarrhea, nausea, vomiting, headache, fatigue, rash, pruritis, oral and peripheral paresthesia, and mood disorders/depression. Common laboratory abnormalities included hepatic transaminitis, increased cholesterol, triglycerides, and glucose levels. Most events were considered mild to moderate in severity. All of these events were predictable and expected based on preclinical data and data from clinical trials with amprenavir. Overall, addition of ritonavir led to an increase in the frequency and severity of diarrhea, vomiting, and triglyceride and cholesterol level increases. These events are comparable to the events reported among patients receiving Agenerase. No new types of adverse clinical or laboratory events were identified that could have been related to any remaining LEXIVA that is not converted to amprenavir.

Specific Issues for Comment Regarding Safety Results

- **Lipodystrophy:** Patients who receive long-term PI and NRTI-based therapies are at risk for changes in body habitus due to fat redistribution (facial, arm, leg, buttocks, and trunk wasting, abdominal girth, breast enlargement, fat lump on back of neck, and lipomatosis). In treatment naïve patients treated with LEXIVA, increased abdominal girth, buffalo hump, and breast enlargement were the most common fat redistribution symptoms reported. Overall <1% of patients who received LEXIVA reported "lipodystrophy" as an adverse event. However, there were more patients who received LEXIVA/r that experienced fat redistribution compared to those who received LEXIVA alone (5 vs. 2). In treatment experienced patients, new onset of fat redistribution occurred more often in patients treated with LEXIVA/r. In patients who did not have lipodystrophy at baseline, 10%, 15% and 7%, of patients in the LEXIVA/r once daily, LEXIVA/r twice daily, and LPV/r arms, respectively, reported lipodystrophy at week 48.

- **Triglyceride Levels:** Overall, the frequency of Grade 3-4 elevations of triglycerides (>1200 mg/dL) was higher among patients who received LEXIVA/r twice daily compared to LEXIVA alone or LEXIVA/r once daily, and higher than the frequency observed in LPV/r recipients. No adverse events directly related to high triglycerides were identified in the pivotal studies. Generally, this pattern was similar to that reported in clinical trials of patients treated with Agenerase®/ritonavir. Patients treated with LEXIVA with ritonavir are at higher risk for hypertriglyceridemia. All patients should undergo triglyceride monitoring during treatment and have elevated levels treated accordingly.

- **Sulfonamide allergy:** A total of 57/700 (8%) of LEXIVA recipients were known to have a preexisting sulfonamide allergy, 11 of whom (19%) reported rash. The median onset and duration were 11 and 13 days, respectively. One patient with a pre-existing sulfonamide allergy experienced Stevens-Johnson Syndrome. Across the comparator arms, 19/513 (9%) patients entered studies with a known sulfonamide allergy. Of these, 40% (19/47) reported rash. Overall, more patients without a history of sulfonamide allergy reported rash. Although the numbers of patients with sulfonamide allergy were small, the frequency and severity of rash in patients treated with LEXIVA was similar to that reported with Agenerase. Therefore, caution should be exercised when LEXIVA is to be administered to a patient with a known sulfonamide allergy.

- **Hepatotoxicity**: Most patients in the three pivotal studies had normal or mildly elevated baseline ALT and AST levels. The majority of shifts in these parameters were of one grade (e.g., Grade 1 to 2). A small proportion of patients experienced Grade 3 or 4 elevations, primarily among patients who entered the studies co-infected with hepatitis B or C. Overall, most patients had normalization of hepatic transaminase levels by the end of the studies. It did not appear that the addition of ritonavir significantly increased either the frequency or severity of ALT or AST increases. Total bilirubin elevations were reported rarely among patients treated with LEXIVA, 1% (2/166) of patients. There was a slight increase in bilirubin levels when LEXIVA was co-administered with ritonavir (13/534, 2%). The majority of bilirubin elevations were Grade 1 or 2 in severity. **Hepatotoxicity and Hepatitis Co-infected Patients:** Approximately 22% of patients who received LEXIVA had a baseline history of co-infection with chronic hepatitis B or C, or both. Overall, more patients with hepatitis co-infection developed Grade 3-4 ALT and AST elevations compared to non-co-infected patients. Almost twice as many patients with hepatitis C had a severe or Grade 3-4 adverse event (primarily elevated AST or ALT levels) compared to those without hepatitis C, 35% and 19%, respectively. A similar pattern was observed among patients co-infected with hepatitis B. Additional patients in IND and non-IND studies experienced significant hepatic transaminitis, all of whom were co-infected with a hepatitis virus. All patients who receive LEXIVA alone or with ritonavir should be monitored closely for hepatotoxicity during treatment. Patients co-infected with hepatitis B and/or C appear to be at a higher risk for drug induced hepatotoxicity. This precautionary information will be included in the labeling.

- **Abacavir Hypersensitivity (ABC HSR) Reaction:** The frequency and severity of ABC HSR was consistent with previously reported data. All the patients in studies APV30001 and APV30002 received ABC as a component of their background regimen. Hypersensitivity reaction (rash, fever, and constitutional symptoms) to ABC is a well-characterized toxicity reported to occur in between 3 and 9% of recipients. Abacavir hypersensitivity reaction was reported in a total of 9% of patients in the two studies, with 4% being of Grade 3 or 4 severity. The frequency and severity was generally comparable between treatment arms.

- **Pregnancy**: Pre-clinical data suggested that LEXIVA might have a negative impact on pregnancy. This concern did not appear to be borne out in the clinical database, but the number of pregnancies was very low (n=8 total). Because no adequate and well-controlled studies have been conducted, based on the pre-clinical data, LEXIVA will be classified as Pregnancy Category C.

A comment regarding LEXIVA Tablet Variants: The LEXIVA Phase 3 studies were initiated with Tablet Variant A. After initiating these studies, milling and scale up were introduced resulting in Tablet Variants B and C, respectively, which were then supplied to the Phase 3 study sites. Tablet Variant C was the proposed commercial formulation. A subsequent study demonstrated that Tablet Variant B was not bioequivalent to Variant A, and that Variant C was not bioequivalent to Variant B. Thus, Tablet Variant C was not bioequivalent to Tablet Variant A. Despite significant efforts, the applicant has not, to date, been able to explain these results. Thus, only Variant A is being approved in this application.

Recommendation

This New Drug Application (NDA) for LEXIVA (fosamprenavir), a protease inhibitor (PI) that is a prodrug of amprenavir, is being recommended for regulatory approval. LEXIVA is a phosphate ester prodrug of Agenerase® (amprenavir) which is an already marketed HIV protease inhibitor. LEXIVA was developed and has been shown to be an improved formulation for delivery of amprenavir, reducing the pill burden from 8 pills twice a day to 2 pills once a day. There does not appear to be new or increased safety concerns with this improved formulation. I concur with the clinical review prepared by Russell Fleischer, PA-C, MPH. As stated in his review, the applicant (GlaxoSmithKline) has demonstrated that LEXIVA at the proposed doses for marketing is a safe and effective drug for the treatment of HIV-1 infection in adults when combined with other antiretrovirals.

Phase IV commitments

Post-marketing commitments are being requested. The following is the list of phase IV commitments (agreed by the Applicant) that will be included in the approval letter.

1. Submit the results of *in vitro* testing for combination activity relationships with efavirenz and delavirdine, using conventional methodology.
   Study start – Ongoing.
   Final report submission – within 6 months of the date of this letter.

2. Provide data on the anti-HIV activity *in vitro* of amprenavir against multiple isolates from each of the HIV-1 clades and multiple isolates of HIV-2, using conventional methodology.
   Study start – Ongoing.
   Final report submission – within 6 months of the date of this letter.

3. Complete ongoing carcinogenicity studies in mice and rats and submit final reports.
   Protocol submissions – Completed.
   Study start – Ongoing.
   Final reports submission – within 33 months of the date of this letter.

4. Conduct 90-day rat toxicity studies on the [redacted] impurities associated with the manufacture of fosamprenavir calcium.
   Submission of study design for comment – within 2 months of the date of this letter.
   Study start – within 4 months after receiving feedback from DAVDP on the proposed study design.
   Final report submission – within 18 months after study initiation

5. Conduct human drug-drug interaction study of fosamprenavir calcium twice daily and nevirapine and fosamprenavir calcium/ritonavir twice daily and nevirapine.
   Protocol submission – Completed.
   Study start – Ongoing.
   Final report submission – within 14 months of the date of this letter.

6. Conduct a human drug-drug interaction study of fosamprenavir calcium twice daily and a proton pump inhibitor, and fosamprenavir calcium/ritonavir twice daily and a proton pump inhibitor.
   Submission of study design for comment – within 3 months of the date of this letter.
   Study start – within 4 months after receiving feedback from DAVDP on the proposed study design.
   Final report submission – within 14 months after study initiation.

7. Conduct a pharmacokinetic study with fosamprenavir calcium/ritonavir in patients with hepatic impairment to determine dosing.
   Submission of study design for comment – within 3 months of the date of this letter.
   Study start – within 4 months after receiving feedback from DAVDP on the proposed study design.
   Final report submission – within 18 months after study initiation.

8. Conduct a human drug-drug interaction study of fosamprenavir calcium/ritonavir twice daily with atazanavir.
   Submission of study design for comment – within 4 months of the date of this letter.
   Study start – within 6 months after receiving feedback from DAVDP on the proposed study design.
   Final report submission – within 18 months after study initiation.

9. Determine the combination activity relationships *in vitro* of amprenavir with atazanavir, lamivudine, stavudine, tenofovir, and T-20, using conventional methodology.
   Final report submission - within 12 months of the date of this letter.

10. Provide 96 week data on the genotypes and phenotypes of HIV-1 isolates from patients enrolled in studies APV 30003 and APV 30005.
    Final report submission - within 18 months of the date of this letter.

Concurrence
HFD-530/DivDirector/DBirnkrant

Cc: NDA 21-548
HFD-530/MO/Rfleischer
HFD-530/PM/DSillivan

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/s/

Rosemary Johann-Liang
10/20/03 05:36:23 PM
MEDICAL OFFICER

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CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-420)

DATE RECEIVED: September 25, 2003	**DESIRED COMPLETION DATE:** September 30, 2003 **PDUFA DATE:** October 20, 2003	**ODS CONSULT #:** 03-0261

TO: Debra Birnkrant, M.D.
Director, Division of Anti-Viral Drug Products
HFD-530

THROUGH: Destry Sillivan
Project Manager
HFD-530

PRODUCT NAME: — (primary name) **Lexiva** (alternate name) (Fosamprenavir Calcium Tablets) 700 mg **NDA #**: 21-548	**SPONSOR**: GlaxoSmithKline

FETY EVALUATOR: Alina R. Mahmud, R.Ph.

MMARY: In response to a consult from the Division of Anti-Viral Drug Products, the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary names —— and "Lexiva" to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name ——. However, DMETS has no objections to the use of the name "Lexiva". If the approval of the application is delayed beyond 90 days from the signature date of this review, the name, Lexiva, and its associated labels and labeling must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

2. DDMAC finds the name —— and "Lexiva" acceptable from a promotional perspective.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
›ne: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 25, 2003

NDA NUMBER: 21-548

NAME OF DRUG: ——— (primary name)
Lexiva (alternate name)
(Fosamprenavir Calcium Tablets)
700 mg

NDA SPONSOR: GlaxoSmithKline

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION

This consult was written in response to a request from the Division of Anti-Viral Drug Products (HFD-530) for an assessment of the proposed proprietary names, ——— and Lexiva. Labels and labeling were not provided for review.

This is the third and fourth proposed proprietary name for this NDA. The first two names, Telzir and ———, were found unacceptable by DMETS in previous reviews (ODS consult 02-0199 dated January 13, 2002 and ODS consult 03-121 dated June 27, 2003, respectively). The container label, draft package insert labeling and patient information leaflet were also reviewed in ODS consult 03-121.

PRODUCT INFORMATION

——— Lexiva contains the ingredient fosamprenavir calcium, a prodrug of amprenavir. Fosamprenavir calcium is an inhibitor of the human immunodeficiency virus (HIV) protease. ——— Lexiva is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. ——— Lexiva has been formulated as a 700 mg pink capsule shaped, biconvex tablet. The sponsor is seeking approval of ——— Lexiva to be administered alone or in combination with the medication ritonavir. The usual adult dose without ritonavir would be 1400 mg of fosamprenavir calcium twice a day. The usual adult dose in combination with ritonavir would be either 700 mg of fosamprenavir calcium twice a day plus 100 mg ritonavir twice a day, or 1400 mg of fosamprenavir calcium once a day plus 200 mg ritonavir once a day. ——— Lexiva may be taken with or without food.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[i,ii] as well as several FDA databases[iii] for existing drug names which sound-alike or look alike to ' ——— ' and "Lexiva" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[iv] and the data provided by Thomson & Thomson's SAEGIS™ Online Service[v] were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names, ——— and Lexiva. Potential concerns regarding drug marketing and promotion related to the proposed name was also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified three proprietary names, Protonix, Trizivir, and Retrovir, that have potential for confusion with ——— One proprietary name, Lessina, was identified to have the potential for confusion with Lexiva. After an independent review, three additional names were found to have a look-alike and/or sound-alike potential with Lexiva. These products are listed in Table 1 and 2 (see page 4 and 5) respectively, along with the dosage forms available and usual FDA-approved dosage.

2. DDMAC did not have any concerns with ——— or Lexiva in regard to promotional claims.

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[i] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[ii] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[iii] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

[iv] WWW location http://www.uspto.gov.

[v] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

Product Name	Dosage form(s), Established name	Usual adult dose*	Other
Lexiva	Fosamprenavir Calcium Tablets Tablets, 700 mg	Treatment of HIV: (3 regimens) Take two tablets twice a day; Take one tablet twice a day (along with ritonavir 100 mg twice a day); or Take two tablets once a day (along with ritonavir 200 mg once a day).	
Lessina	Ethinyl Estradiol and Levonorgestrel Tablets 20mcg/0.1 mg	One tablet once daily.	Look-alike, Sound-alike
Levora	Ethinyl Estradiol and Levonorgestrel Tablets 30 mcg/0.15 mg	One tablet once daily.	Look-alike
Levitra	Vardenafil Hydrochloride Tablets 2.5 mg, 5 mg, 10 mg, and 20 mg	10 mg taken 60 minutes prior to sexual activity.	Look-alike

*Frequently used, not all-inclusive.
Note: This review contains proprietary and confidential information and should not be released to the public.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for each proposed proprietary name to determine the degree of confusion of [redacted] and Lexiva with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 127 health care professionals (pharmacists, physicians, and nurses) for each name. This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for [redacted] and Lexiva (see page 6). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
—	Fosamprenavir Calcium Tablets Tablets, 700 mg	Treatment of HIV: (3 regimens) Take two tablets twice a day; Take one tablet twice a day (along with ritonavir 100 mg twice a day); or Take two tablets once a day (along with ritonavir 200 mg once a day).	
Protonix (Rx)	Pantoprazole Sodium Delayed-Release Tablets 20 mg and 40 mg	*Erosive esophagitis associated with GERD:* 40 mg once daily for up to 8 weeks. *Maintenance:* 40 mg daily. *Pathological hypersecretory conditions including Zollinger-Ellison syndrome:* The recommended adult starting dose is 40 mg twice daily. Doses up to 240 mg/day have been administered.	Look-alike
Trizivir (Rx)	Abacavir Sulfate, Lamivudine, Zidovudine Tablets 300 mg/150 mg/300 mg	1 tablet twice daily.	Look-alike, sound-alike
Retrovir (Rx)	Zidovudine Tablets: 300 mg Capsules: 100 mg Syrup: 50 mg/5 mL Injection: 10 mg/mL	HIV infection: *Adults (oral):* Recommended dose is 600 mg/day in divided doses in combination with other antiretroviral agents. *Adults (IV):* Recommended IV dose is 1 mg/kg infused over 1 hour. Administer this dose 5 to 6 times daily (5 to 6 mg/kg/day). *Children (oral):* Recommended dose in children 6 weeks to 12 years of age is 160 mg/m^2 every 8 hours in combination with other antiretroviral agents. Maternal-Fetal HIV transmission: *Maternal dosing (oral):* 100 mg orally 5 times per day until the start of labor. *Maternal dosing (IV):* During labor and delivery, administer IV zidovudine at 2 mg/kg over 1 hour followed by a continuous IV infusion of 1 mg/kg/h until clamping of the umbilical cord. *Neonatal dosing(oral):* 2 mg/kg orally every 6hours starting within 12hours after birth and continuing through 6 weeks of age. *Neonatal dosing (IV):* Neonates unable to receive oral dosing may be given zidovudine IV at 1.5 mg/kg, infused over 30 minutes, every 6hours.	Look-alike, sound-alike
*Frequently used, not all-inclusive.			

Table 2: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: — 2 tabs po bid #120	—, 2 tabs by mouth twice a day, disp. #120
Inpatient RX: — 2po BID #60	

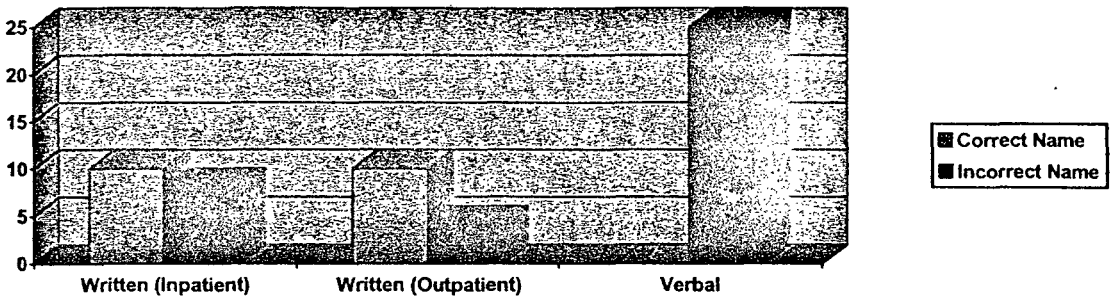
LEXIVA

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Lexiva 2 tabs po bid #60	Lexiva, 2 tabs by mouth twice a day, disp. #120
Inpatient RX: Lexiva 2 tabs po BID #60	

2. Results for —

The results are summarized below.

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	43	18 (42%)	10 (56%)	8 (44%)
Written Outpatient	43	14 (33%)	10 (71%)	4 (29%)
Verbal	41	25 (61%)	0 (0%)	25 (100%)
Total	127	57 (45%)	20 (35%)	37 (65%)



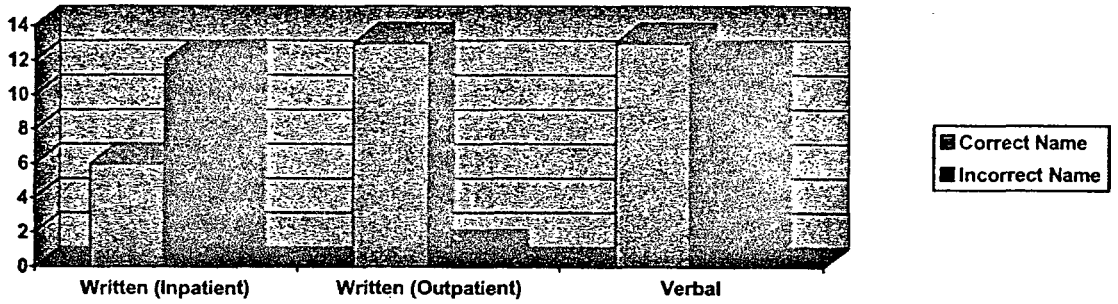
Among the verbal prescription study participants for [redacted] 100% of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of [redacted]. The incorrect responses were [redacted]. None of the interpretations are similar to a currently marketed drug product.

Among the written prescription study participants for [redacted] 12 of 32 (38%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of [redacted]. The incorrect responses were [redacted]. None of the interpretations are similar to a currently marketed drug product.

3. Results for **Lexiva**:

The results are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	43	18 (42%)	6 (33%)	12 (67%)
Written Outpatient	43	14 (33%)	13 (93%)	1 (7%)
Verbal	41	25 (61%)	13 (52%)	12 (48%)
Total	127	57 (45%)	32 (56%)	25 (44%)



Among the verbal prescription study participants for Lexiva, 12 of 25 (48%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of "Lexiva". The incorrect responses were *Nexiva, Lexivar, Lexeva (7), Lexevia (2),* and *Lexceva.* One respondent commented that the proposed name looks too similar to Levitra, a currently marketed drug product.

Among the written prescription study participants for [redacted] 13 of 32 (41%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of "Lexiva". The incorrect responses were *Levixa, Lexira (6), Lexera (3), Lexora, Lexura,* and *Lexeva.* None of the interpretations are similar to a currently marketed drug product.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name " [redacted] , the primary concerns raised were related to three look-alike and/or sound-alike names that are currently available in the U.S. marketplace: Protonix, Trizivir, and Retrovir. The names thought to have potential for confusion with Lexiva include Lessina, Levora, Levitra, and [redacted]

1. [redacted]

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between [redacted] and the prescription drug products Protonix, Trizivir, or Retrovir. However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size. In the verbal prescription study, the first four letters of the proposed name was consistently misinterpreted as [redacted] . The majority of interpretations provided in the written prescription studies were misspelled/phonetic variations of the proposed name [redacted]

a. Protonix was identified to have look-alike potential with the proposed proprietary name [redacted] Protonix contains pantoprazole sodium and is indicated for short-term treatment and symptomatic relief of erosive esophogitis. The names Protonix and [redacted] share a similarly scripted beginning (Prot- vs [redacted], respectively) yet the endings (-onix vs. [redacted] respectively) are distinguishable when scripted (see writing sample below). Although, the names overlap in dosage form and dosing regimen, the drug products differ in product strength and prescribed dosage strength. Additionally, the products will not be stored next to each other on pharmacy shelves. Given these differences along with a lack of convincing look-alike potential, the risk of inadvertent dispensing is minimal.

[redacted] Protonix

b. Trizivir was indicated as having look-alike and sound-alike potential with [redacted] Trizivir is a combination drug product containing 300 mg of abacavir, 150 mg of lamivudine, and 300 mg of zidovudine. Trizivir is indicated for the treatment of HIV infection. Trizivir and [redacted] contain three syllables each and share the letters [redacted] . Although both names [redacted] and share a rhyming quality, the names are distinguishable in sound due to differences in the second syllable (-ziv- vs. [redacted] respectively). When scripted, the names look similar if the letter "z" in Trizivir is written in script (not cursive) which can resemble the letter [redacted] in [redacted] (see writing sample on page 9). Similarly, if the letter [redacted] is scripted as shown below, it looks similar to the letter "v" in Trizivir. A prescription for either Trizivir or [redacted] does not need to indicate a strength as both products will be available in one strength. The drug products also share a twice a day dosing regimen, dosage form, patient and prescriber populations. Given the look-alike similarity between Trizivir and [redacted] , in addition to the similarities in product characteristics, DMETS believes that the potential for confusion is likely.

[redacted] Trizivir

c. Retrovir has the potential to look and sound similar to [redacted]. [redacted] Retrovir is the proprietary name for zidovudine and is indicated for use in combination with other antiretrovirals for the treatment of HIV infection. Retrovir and [redacted], when pronounced, possess a rhyming quality which contributes to its sound-alike characteristics. However, the second and third syllables distinguish one name from the other (tro- vs. [redacted] and -veer vs [redacted]). The names begin with the similarly scripted letter [redacted] vs. "R". The remainder of the name is somewhat similar, except for the letter "v" in Retrovir versus the letter [redacted] in [redacted] However, if the [redacted] is not written in cursive, the names look similar (see below). The products share an overlapping dosage form, route of administration, dosing regimen (twice daily), and patient and prescriber population. Although [redacted] and Retrovir do not share an overlapping strength, the strengths may look similar when scripted (700 mg vs. 100 mg). Additionally, a prescription written to "D/C [redacted] may be misinterpreted as "D/C Retrovir" or vice versa if a patient is prescribed these medications concomitantly. Post-marketing experience has shown medication errors resulting from the above-mentioned scenario. DMETS believes that the potential for medication errors between Retrovir and [redacted] is likely given the look-alike similarity as well as the product characteristics.

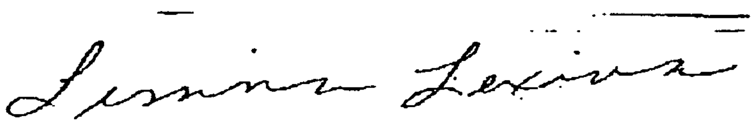
Retrovir 100 mg [redacted] 700 mg

2. Lexiva

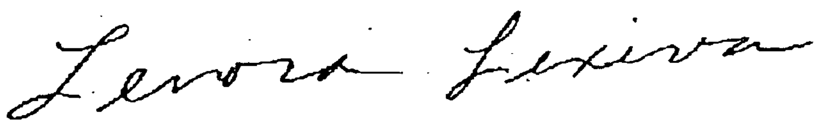
We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Lexiva and the prescription drug products Lessina, Levora, Levitra, or [redacted]. However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size. One study participant commented that Lexiva is too similar to Levitra. A second and third participant in the written prescription study provided the interpretation Lexora which is similar to the currently marketed drug product Levora. The majority of interpretations provided in the written prescription studies were misspelled/phonetic variations of the proposed name, Lexiva.

a. Lessina was thought to have look-alike and sound-alike potential to Lexiva. Lessina is an oral contraceptive containing ethinyl estradiol and levonorgestrel. Lessina sounds similar to Lexiva due to the "Le" beginning and "a" ending. Additionally, the names share an "s" and long "e" sound in the middle. However, the ending "seena" in Lessina differs from the ending "eeva" in Lexiva. The names are similar in script since the beginning (Le) is identical and they share the similarly scripted letters "ina" in Lessina versus "iva" in Lexiva. The middle of the names "x" versus "ss" is somewhat distinguishable (see writing sample on page 10). The drug products overlap in dosage form and route of administration. Although the products are available in different strengths, a prescription can be written for either one in which the strength is omitted. The products also differ in dosing regimen, packaging, dosing strength, and indication. Most likely these drug products will not be stored near one another on pharmacy shelves. Given the differences and a lack of convincing look-alike and sound alike potential, the likelihood for confusion is minimal.

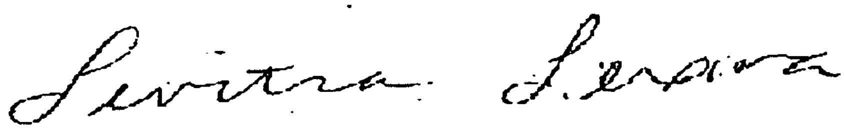
* This review contains proprietary and confidential information that should not be release to the public.



b. Levora was thought to have look-alike potential to Lexiva. Levora is an oral contraceptive containing ethinyl estradiol and levonorgestrel. The names look similar in script since the beginning (Le) is identical and the remaining letters are similarly scripted (see writing sample below). The drug products overlap in dosage form and route of administration. Although the products are available in different strengths, a prescription can be written for either one in which the strength is omitted. The products differ in packaging, dosing strength, and indication of use. Even though Lexiva can be given as a once daily dosing regimen, the dosing instructions would vary from Levora since the number of tablets is increased to two whereas Levora is given as one tablet once daily. Given these differences, the likelihood for confusion is minimal even though the names share a slight look-alike potential.



c. Levitra and Lexiva have the potential to look similar. Levitra contains vardenafil and is indicated for erectile dysfunction. Levitra and Lexiva begin with the letters "Le" and end with the similarly scripted letters "ra" vs. "va". In addition, each name contains the letter "i" in the middle of the name. However, the upstroke of the letter "t" in Levitra helps to distinguish it from Lexiva (see below). The products share an identical dosage form, route of administration, and possibly patient and prescriber population. The products differ with respect to other characteristics such as strength and dosing regimen. Levitra is prescribed on an as needed basis whereas Lexiva is prescribed on a daily basis. A prescription for Levitra must be written with a strength since it is available in multiple strengths whereas Lexiva will be available as one non-overlapping strength. Although there is a slight look-alike potential between Lexiva and Levitra, the likelihood for confusion is minimal due to the differences in product characteristics.



** This name is proprietary and confidential and should not be released to the public.

[redacted] Lexiva

IV. COMMENTS TO THE SPONSOR

DMETS does not recommend the use of the proprietary name [redacted]. However, DMETS has no objections to the use of the name "Lexiva". The products considered having the potential for confusion with [redacted] include Retrovir and Trizivir.

Retrovir has the potential to look and sound similar to [redacted] Retrovir is the proprietary name for zidovudine and is indicated for use in combination with other antiretrovirals for the treatment of HIV infection. Retrovir and [redacted], when pronounced, possess a rhyming quality which contributes to its sound-alike characteristics. However, the second and third syllables distinguish one name from the other (tro- vs [redacted] and -veer vs. [redacted]. The names begin with the similarly scripted letter [redacted] vs. "R". The remainder of the name is somewhat similar, except for the letter "v" in Retrovir versus the letter [redacted] in [redacted] However, if the [redacted] is not written in cursive, the names look similar (see below). The products share an overlapping dosage form, route of administration, dosing regimen (twice daily), and patient and prescriber population. Although [redacted] and Retrovir do not share an overlapping strength, the strengths may look similar when scripted (700 mg vs. 100 mg). Additionally, a prescription written to "D/C [redacted]" may be misinterpreted as "D/C Retrovir" or vice versa. Post-marketing experience has shown medication errors resulting from the above-mentioned scenario. DMETS believes that the potential for medication errors between Retrovir and [redacted] likely given the look-alike similarity as well as the product characteristics.

Retrovir 100 mg [redacted] 700 mg

Trizivir was indicated as having look-alike and sound-alike potential with [redacted] Trizivir is a combination drug product containing 300 mg of abacavir, 150 mg of lamivudine, and 300 mg of zidovudine. Trizivir is indicated for the treatment of HIV infection. Trizivir and [redacted] contain three syllables each and share the letters [redacted] Although both names [redacted] and share a rhyming quality, the names are distinguishable in sound due to differences in the second syllable (-ziv- vs. [redacted], respectively). When scripted, the names look similar if the letter "z" in Trizivir is written in script (not cursive) which can resemble the letter [redacted] in [redacted] (see writing sample on page 12). Similarly, if the letter [redacted] in [redacted] is scripted as shown below, it looks similar to the letter "v" in Trizivir. A prescription for either Trizivir or [redacted] does not need to indicate a strength as both products will be available in one strength. The drug products also share a twice a day dosing regimen, dosage form, patient and prescriber populations. Given the look-alike similarity between Trizivir and [redacted], in addition to the similarities in product characteristics, DMETS believes that the potential for confusion is likely.

[redacted] Trizivir

RECOMMENDATIONS

A. DMETS does not recommend the use of the proprietary name ' [redacted] . However, DMETS has no objections to the use of the name "Lexiva".

B. DDMAC finds the name [redacted] and Lexiva acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

/S/

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Alina Mahmud
10/6/03 02:47:47 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/6/03 03:58:28 PM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
10/6/03 04:52:16 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

RECORD OF INDUSTRY MEETING

Date of Meeting: **September 22, 1999**

IND: **58,627**

Drug: **GW433908**

Indication: **Treatment of HIV-1 Infection**

Sponsor: **Glaxo Wellcome**

Type of Meeting: **Drug Development Meeting**

FDA Attendees:
Heidi Jolson, M.D., M.P.H., Director, Division of Antiviral Drug Products
Debra Birnkrant, M.D., Deputy Director, Division of Antiviral Drug Products
Walla Dempsey, Ph.D., Assoc. Director, Division of Antiviral Drug Products
Therese Cvetkovich, M.D., Medical Team Leader
John Martin, M.D., Medical Officer
Ekopimo Ibia, M.D., Medical Officer
Vanitha Sekar, Ph.D., Pharmacokinetics Reviewer
Kellie Reynolds, Ph.D., Pharmacokinetics Team Leader
Lalji Mishra, Ph.D., Microbiology Reviewer
Lauren Iacono-Connors, Ph.D., Microbiology Team Leader
Hao Zhang, M.D., Pharmacology Reviewer
Jim Farrelly, Ph.D., Pharmacology Team Leader
George Lunn, Ph.D., Chemistry Reviewer
John Lazor, Ph.D., Division Director, Division of Pharmaceutical Evaluation III
Sandra Suarez, Ph.D., Pharmacokinetics Reviewer, Division of Pharmaceutical Evaluation III
Kathleen Uhl, M.D., Pharmacokinetics Reviewer
Jen DiGiancinto, Pharm.D., Clinical Pharmacology Fellow, U.I.C. College of Medicine
Melissa Truffa, R.Ph., Regulatory Project Manager
Leslie Stephens, R.N., M.S.N., Regulatory Project Manager

External Constituents:
Robert Watson, Director, Regulatory Affairs
Mike Rogers, Ph.D.
David Cocchetto, Ph.D.
Daniel Stein, M.D.
Louise Peneault, M.D.

Lynn Smiley, M.D.
Joseph Woolley, Ph.D.
Steve Kutz, Ph.D.
Eric Furfine, Ph.D.
MaryBeth Wire, Pharm.D.
Grace Pagano, M.S.
Judith Millard, Ph.D.

Background:

The sponsor requested a meeting to discuss the clinical development of GW433908, the amprenavir prodrug for the treatment of HIV-1 infection.

Questions:

1. Is APV20001 acceptable as the pivotal study to support the approval of GW433908 tablets based on the rationale of equivalent exposure as provided in the IND?

Based on information reviewed to date, FDA reviewers consider it unlikely that Study 20001 will show comparable pharmacokinetic profiles for the amprenavir prodrug and amprenavir. If the appropriate pharmacokinetic parameters are not comparable, a clinical study will be needed to establish safety and efficacy of the APV prodrug. If comparable pharmacokinetics between the two drugs is demonstrated, further discussion with the Division regarding the requirement for the clinical data will be needed.

Given that pharmacokinetic studies are unlikely to provide a basis for approval of the APV prodrug, inclusion of 24-week clinical safety and efficacy data, such as a comparison of APV to the APV prodrug, is the minimum acceptable basis for accelerated approval in an NDA submission for the amprenavir prodrug. A Phase IV commitment for submission of 48-week data from that study would be anticipated.

Considering the Sponsor's [redacted], the utility of additional long-term studies of APV is limited. A possible alternate approach to a 48-week comparison of the APV prodrug to APV was discussed. If, in a study of APV vs. APV prodrug, the sponsor seeks to demonstrate that efficacy at 24 weeks is independent of Cmax, and that equivalence of other parameters can be established, the most convincing argument would provide PK and virology data in the same study and the same patients; in a large study, a sub-set of patients could be used for PK and virology determinations. Post-approval, 48-week durability could be shown in a separate study(e.g., APV prodrug vs. NFV) as a Phase IV commitment.

Both of these strategies for APV prodrug approval depend on obtaining traditional approval for APV. The Sponsor was informed that in the absence of traditional approval for APV, two 48-week safety and efficacy studies will be needed to support approval of the APV prodrug.

2. Are the human safety data from phase 1 and 2 studies and APV30001 (3 months at time of NDA submission) sufficient for the NDA?

(See response to Question 1).

3. Are the proposed timelines for submission of nonclinical and clinical data acceptable for an NDA for accelerated approval of GW433908?

(See response to Question 1).

4. Does DAVDP agree that the 48-week results of PROAB3001 and PROAB3006 (plus reports of results from other clinical studies on APV provide a sufficient characterization of the durability of Agenerase to comprise a Supplemental NDA for traditional approval?

Based on the summary information on studies 3001 and 3006 that we have been provided, we have determined that the traditional approval package proposed by the sponsor would be fileable. Full reports of smaller, uncontrolled Phase II studies are not required, as results of these studies are unlikely to materially alter the conclusions of the review. To avoid delay in submission of the NDA, executive summaries of Phase II studies are acceptable.

Action Items:

1. The Division agreed to provide the sponsor with written comments on the submitted protocols.

Minutes preparer: [signature] **Date:** 11/12/99

Conference Chairperson: [signature] **Date:** 12 Nov 99

Concurrence:
HFD-530/Dir/Jolson
HFD-530/MTL/Cvetkovich
HFD-530/MO/Martin
HFD-530/MO/Ibia
HFD-530/Biopharm/Sekar
HFD-530/BiopharmTL/Reynolds
HFD-530/RPM/Stephens

Distribution:
Original IND 58,627
Division file
HFD-530/MO/Martin
HFD-530/MO/Ibia
HFD-530/PT/Zhang
HFD-530/Micro/Mishra
HFD-530/Chem/Lunn
HFD-530/BPH/Sekar
HFD-530/RPM/Stephens

IND 58,627/September 22, 1999

Meeting Minutes

Div. File 530

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

RECORD OF INDUSTRY MEETING

Date of Meeting: **August 3, 2000**

IND: **58,627**

Drug: **GW433908**

Indication: **Treatment of HIV-1 Infection**

Sponsor: **Glaxo Wellcome**

Type of Meeting: **Drug Development Meeting**

FDA Attendees:
Heidi Jolson, M.D., M.P.H. Director, Division of Antiviral Drug Products
Therese Cvetkovich, M.D., Medical Team Leader
Russell Fleischer, PA-C, M.P.H., Clinical Reviewer
Kellie Reynolds, Ph.D., Pharmacokinetics Team Leader
Hao Zhang, M.D., Pharmacology Reviewer
Jim Farrelly, Ph.D., Pharmacology Team Leader
Jooran Kim, Pharm.D., Biopharmaceutics Reviewer
Jen DiGiancinto, Pharm.D., Biopharmaceutics Reviewer
Kellie Reynolds, Pharm.D., Biopharmaceutics Team Leader
Girish Aras, Ph.D., Statistics Team Leader
Tony DeCicco, R.Ph., Chief, Project Manager
Melissa Truffa, R.Ph., Regulatory Project Manager
Leslie Stephens, R.N., M.S.N., Regulatory Project Manager

External Constituents:
Robert Watson, Director, Regulatory Affairs
Mike Rogers, Ph.D., Clinical Research
David Cocchetto, Ph.D., Regulatory Affairs
Louise Pedneault, M.D., Clinical Research
Lynn Smiley, M.D., Clinical Research
Joseph Woolley, Ph.D., Biometabolism
MaryBeth Wire, Pharm.D., Clinical Pharmacology
Judith Millard, Ph.D., Clinical Research
Michelle Berrey, M.D., Clinical Research
Lynn Dix, Ph.D., Biostatistics
Josie Wolfram, M.S., Biostatistics
Paul Struve, Preclinical Toxicology

Background:
The sponsor requested a meeting to discuss the clinical development plan (serial number 021, dated June 7, 2000) of GW433908, the amprenavir prodrug for the treatment of HIV-1 infection. The discussion centered on the three proposed phase 3 trials of GW433908 as outlined below:

30001
Because the sponsor has now proposed a richer development program for GW433908, we indicated that a head-to-head comparison to amprenavir as discussed during the previous drug development meeting may not be necessary. However, the sponsor provided their rationale for needing a link to the amprenavir database. That is, they believe that dosing recommendations for GW433908 alone should be included the label for GW433908, for those patients who cannot tolerate ritonavir.

In further planning for this study, the sponsor should consider the following points:

- Durable clinical data (24 week with 48 week to follow) will be required to answer the question about differences in the pharmacokinetic profiles of amprenavir and GW433908, particularly Cmax.
- It is unlikely that a comparison that includes amprenavir will be an attractive option to treatment-naïve patients, and we would recommend that consideration be given to other more attractive options, such as nelfinavir or efavirenz.
- It is likely that while the study should provide durable efficacy and safety data, the size of the study would not necessarily need to be fully powered to demonstrate non-inferiority.

The sponsor agreed to submit a draft protocol that incorporates the elements under discussion.

30002
- We requested that the sponsor provide the results of study APV20001 prior to initiation of 30002. In addition, because there are no data available on the proposed dose of GW433908 in combination with ritonavir, pharmacokinetic sampling should be included in an early phase of the study and the results provided for review before the study becomes more fully enrolled.
- The study should be blinded if possible. If not, sensitivity analyses will need to be performed. We can provide our recommendations for these analyses.
- The use of a 10-12% difference is recommended for calculation of sample size; the sponsor should recognize that because many other factors are utilized to determine the success of a treatment arm, the actual percentage used to define non-inferiority will likely be a review issue.

30003
- A non-inferiority comparison to "standard of care " in a treatment-failure population could be very problematic, particularly in patients who have failed multiple protease inhibitors. The sponsor may wish consider a comparison to ABT 378.

- Amprenavir's resistance profile may be useful in guiding the design of this study.
- The sponsor should clearly define the population to be studied (i.e., first-failure, multiple-class failure, etc.) as this will have a significant impact on the choice of endpoint.
- The various options available as endpoints should be carefully considered, as well as their impact on the size of the study.

Other issues:

[redacted]

Ritonavir
We recommend that the sponsor initiate discussions with Abbott about use of ritonavir as a pharmacokinetic enhancer.

Drug-drug interactions
The sponsor believes that interactions with GW433908 will be the same as previous interactions with amprenavir. Thus, they do not plan to conduct additional drug-drug interaction studies.

We will need to evaluate amprenavir-ritonavir and GW433908-ritonavir interaction results before determining whether amprenavir results can be extrapolated to GW433908.

Concurrence:
HFD-530/DivDir/Jolson
HFD-530/MTL/Cvetkovich
HFD-530/BiopharmTL/Reynolds
HFD-530/RPM/Stephens

Distribution:
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HFD-530/PT/Zhang
HFD-530/Micro/Mishra
HFD-530/Chem/Lunn
HFD-530/BPH/DiGiancinto
HFD-530/RPM/Stephens

IND 58,627/sn021/August 3, 2000

Location: V:\DAVDP\CSO\Stephens\IND\58,627\Minutes\000803mm.doc

Meeting Minutes

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

RECORD OF DAVDP/INDUSTRY TELECON

Date of Teleconference: August 5, 2003

NDA: 21-548

Drug: GW433908

Sponsor: GlaxoSmithKline (GSK)

DAVDP Participants:

Debra Birnkrant, M.D., Division Director, DAVDP
Jeffrey Murray, M.D., Deputy Director, DAVDP
Russell Fleischer, PA-C, M.P.H., Senior Clinical Analyst and Acting Medical Team Leader, DAVDP
James Farrelly, Ph.D., Pharmacology/Toxicology Team Leader, DAVDP
Hao Zhang, M.D., Pharmacology/Toxicology Reviewer, DAVDP
Kellie Reynolds, PharmD. Clinical Pharmacology Team Leader, DAVDP
Derek Zhang, Ph.D., Clinical Pharmacology Reviewer, DAVDP
Jules O'Rear, Ph.D., Microbiology Team Leader, DAVDP
Lalji Mishra, Ph.D, Microbiology Reviewer, DAVDP
Guoxing Soon, Ph.D., Biometrics Team Leader, DAVDP
Thomas Hammerstrom, Ph.D., Biometrics Reviewer, DAVDP
Stephen Miller, Ph.D., Chemistry Team Leader, DAVDP
George Lunn, Ph.D., Chemistry Reviewer, DAVDP
Destry Sillivan, Regulatory Project Manager, DAVDP

External Participants, GlaxoSmithKline:

David Cocchetto, PhD, Vice-President, Regulatory Affairs
Robert Watson, Group Director, Regulatory Affairs
Anne Stokley, Director, Regulatory Affairs
Melody Courtney, Associate Director, CMC Regulatory Affairs
Doug Manion, MD, Vice-President, Clinical Development and Medical Affairs
Judith Millard, PhD, Director, Medical Affairs
Mary Beth Wire, PharmD, Clinical Pharmacokineticist
Mark Shelton, Pharm D, Clinical Pharmacokineticist

Subject:

GSK requested a teleconference with the Division of Antiviral Drug Product's (DAVDP) review team in order to assure mutual understanding of the current status of the review, and also to discuss the course of the final three months of the review cycle.

Discussion:

(GSK's questions and discussion are represented in normal font, and FDA's questions and discussion are represented in **bold** font.)

To clarify, GSK's purpose in requesting this teleconference is twofold:

1. To discuss the current status of the review as we approach the end of the review cycle.

2. As GSK moves towards conducting production campaigns, we would like to obtain CMC feedback regarding the production of additional batches of tablets which would allow us to market the product soon after approval.

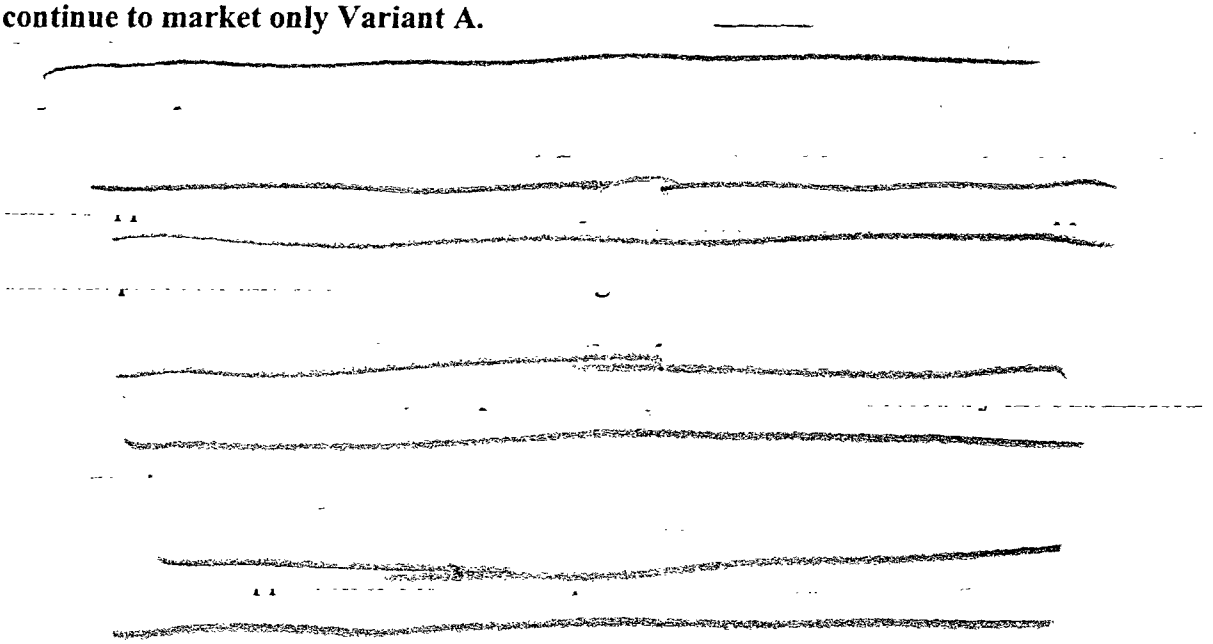
Nonclinical Pharmacology & Toxicology:

1. This section appears to be complete. Does the review team have any requests or feedback for GSK's team?

   This section is complete, and DAVDP is pleased that the [redacted] impurities associated with the manufacture of fosamprenavir calcium issue will be addressed via a phase IV commitment

2. CMC: We believe that GSK and DAVDP are close to an agreement on an acceptable CMC section of this NDA. We welcome the review team's further feedback.

   DAVDP stated that going forward with Variant A will be acceptable, as long as you continue to market only Variant A.



This issue will be discussed internally, and DAVDP will respond. GSK's position with respect to this matter is not satisfactory, and would not be solved by

3. Clinical: 48 week results of study APV30003: (1) One option is for GSK and DAVDP to agree to submission of an Amendment to this NDA as soon as possible in order to provide a final report for study APV30003. We welcome the Division's guidance on circumstances under which such an Amendment would not incur an extension to the review clock. (2) The second option is for GSK and DAVDP to agree to submission of the final report as a future Supplemental NDA in order to avoid the addition of new information to the application at this time. We welcome DAVDP's feedback on these two options.

   GSK would like to avoid having any new submission to the NDA considered a major amendment to the NDA, and therefore triggering an extension of the PDUFA clock. Could we submit the final study report for APV 30003 to the IND?

   DAVDP noted that the final study report for APV 30003 must be submitted to the NDA. We wish to include the data from this study in the label for this application. DAVDP will try to review this data during the existing time frame. Some of this could be couched as a safety issue, and AE's and emergence of resistance need to be weighed against the efficacy data. We do not believe it is appropriate to delay inclusion of the final APV 30003 data in the label. When do you intend to formally submit the final APV 30003 data?

   GSK stated that the datasets for the clinical portions will not be submitted before August 18, 2003.

4. Clinical Pharmacology: With the Amendments, we believe that this section now provides the required evidence of human bioequivalence for the proposed commercial tablet, as well as studies to enable appropriate labeling for drug-drug interactions in support of the proposed regimens of fosamprenavir as a sole protease inhibitor and fosamprenavir plus low-dose ritonavir. We welcome DAVDP's feedback.

   DAVDP concurs with GSK's conclusions.

5. Virology: Submission of 48-week virology data for APV30003 will be in agreement with plans for the clinical data (see Clinical question above).

   DAVDP has just received the APV30003 virology data and has not yet had a chance to view it.

6. Proprietary Name: We welcome DAVDP's feedback on GSK's perspective that this step is a substantial step to address DMETS' concern and makes an acceptable proprietary name for fosamprenavir calcium.

DAVDP stated that it cannot at this time confirm that the tradename [redacted] will be acceptable, even [redacted] DAVDP will make every effort to address confirming a tradename for this product as soon as possible.

7. Draft Labeling: We welcome the Division's feedback on whether to submit revised draft labeling in order to incorporate information on 48-week results from study APV30003. Alternatively, the Division may prefer to provide the review team's comments on draft labeling to GSK as the next step.

   DAVDP agrees that revised labeling should be submitted along with the 48-week results from study APV30003.