

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-652

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY for NDA #: 21-652 SUPPL #:

Trade Name: Epzicom™

Generic Name: abacavir sulfate/lamivudine fixed dose combination

Applicant Name: GlaxoSmithKline

Approval Date:

HFD-530: Division of Antiviral Drug Products

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/ X / NO / ___ /

b) Is it an effectiveness supplement? YES / ___ / NO / X /

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 / X / 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 / X / NO / ___ /

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

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

YES / X / 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)

1. Single active ingredient product. N/A

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).

NDA #:

NDA #:

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 / X / NO / ___ /

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

NDA # ZIAGEN (tablets) 20-977
NDA # ZIAGEN (oral solution) 20-978
NDA # EPIVIR (tablets) 20-564
NDA # EPIVIR (oral solution) 20-596
NDA # TRIZIVIR (tablets) 21-205
NDA # COMBIVIR (tablet) 20-857

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 / X / 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 / /

- **The clinical trials used to support this approval were first used to approve NDAs 20-977 (S-012) and 20-978 (S-014)**

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:

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 redemonstrate 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 / ___ /

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 / ___ /

If you have answered "yes" for one or more investigations, identify the NDA in which

a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

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"):

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 #

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: _____

Additional comment:

- **The clinical trials used to support this approval were first used to approve NDAs 20-977 (S-012) and 20-978 (S-014)**

Signature of Preparer Date
Title:

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

This
Original

Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

Appears This Way
On Original

Appears This Way
On Original

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # : 21-652 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: October 8, 2004

Action Date: August 2, 2004

HFD- 530_

Trade and generic names/dosage form: EPZICOM (abacavir sulfate and lamivudine) Tablets

Applicant: GlaxoSmithKline___ Therapeutic Class: Antiretroviral/nucleoside analog. (7030241)

Indication(s) previously approved: Treatment of HIV-1 infection

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

Number of indications for this application(s):1

Indication #1: 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:

- 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 _____ kg _____ mo. 0 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. < 3 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

NDA 20-977
NDA 20-978
Page 2

Other: _____

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 _____ kg _____ mo. 3 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 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 (mm/dd/yy): _____

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. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ 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}

Tanima Sinha, M.S., Regulatory Project Manager

cc: NDA 21-652
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Virginia Behr
8/12/04 12:02:18 PM

NDA 21-652
Abacavir Sulfate and Lamivudine Tablets

New Drug Application for the
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

Sinha, Tanima

From: CDERDocAdmin
nt: Monday, August 02, 2004 11:38 AM
o: SINHAT@cder.fda.gov; SOONG@cder.fda.gov; SMITHF@cder.fda.gov;
HUQUE@cder.fda.gov; JAMESA@cder.fda.gov; BIRNKRANT@cder.fda.gov
Subject: DFS Email - N 021652 N 000 07-Oct-2003 - Review (noted no comments - NAI)

Document room close out the following assignments:

	Personnel Code	Sup-Concur	St
N 021652 N 000 07-Oct-2003	95W	02-Aug-2004	NR

Document Type: Review (noted no comments - NAI)

Submission Description: Abacavir / Lamivudine Combination Tablet for Antiretroviral Therapy Naive HIV-1 Subjects

Author(s)/Discipline(s)

1. Fraser Smith, BIOMETRICS

Signer(s)

1. Fraser Smith

The statistical review for the Abacavir Once-A-Day submission (sNDA 20-977 / SE2-012 and sNDA 20-978 / SE2-014) also applies to this NDA. This NDA has the same pivotal phase III study (CNA30021) and the same PK study as the ABC OAD submission.
02-Aug-2004

MEMORANDUM

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

DATE: July 23, 2004

FROM: Martin K. Yau, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. _____
Associate Director – Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 21-652,
Abacavir sulfate/lamivudine Tablets (Epivir/Ziagen®), Sponsored
by Glaxo SmithKline

TO: Debra B. Birnkrant, M.D.
Director
Division of Antiviral Drug Products (HFD-530)

At the request of HFD-530, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following bioequivalence study:

Protocol CAL10001: An Evaluation of the Bioequivalence of a Combined Formulated Tablet (600mg/300mg abacavir/lamivudine) Compared to ZIAGEN (abacavir) 2 x 300mg Tablets and EPIVIR (lamivudine) 2 x 150 mg Tablets Administered Concurrently and the Effect of Food on Absorption of the Combined Formulation in Healthy Adult Subjects.

The clinical portion of the above study was conducted at [_____]
The analytical portion of the study was conducted at [_____]

Following the inspection at the clinical site (6/15-16/04), no objectionable practice was noted and no Form FDA 483 was issued. Following the inspection at the analytical site (6/22-25/04), Form FDA 483 (Attachment 1) was issued. The objectionable item at the analytical site and our evaluation are provided below:

Analytical Site for Protocol CAL10001: _____

1. **Reassays of study samples due to low internal standard (IS) response were not conducted in a consistent manner. Different minimum IS response criteria were used in different analytical runs. For example, in _____ samples with IS response outside _____ were identified for reassay. In _____ samples with IS response _____ the average IS response were reassayed. In _____ samples that failed to meet an analyst defined minimum IS response criteria were reassayed.**

In their July 13, 2004 written response to the 483 item (see Attachment 2), _____ stated that they had exercised the discretion allowed by their SOP by using the different options available within the regression analysis software (i.e., _____ of average IS response, analyst defined criteria) to identify samples for reassay. Their choice was based on knowledge of the assay _____

_____ also stated that their SOP was subsequently improved in _____ to state that the minimum IS threshold would be based on a percentage \ _____ of the mean IS area.

To avoid bias, samples identified for reassay should be based on objective rather than subjective (e.g., analyst defined) reassay criteria. This principle was related to _____ by the FDA investigators during the inspection. However, as the number of samples reassayed due to low internal standard response were small _____, the above 483 observation is not likely to have a significant impact on the study outcomes.

Conclusion:

DSI recommends that data from Protocol CAL10001 can be accepted for review. After you have reviewed this transmittal memo, please append it to the original NDA submissions.

Martin K. Yau, Ph.D.

Final Classifications:

cc:

HFA-224

HFD-45/RF

HFD-48/Yau(2)/Himaya/CF

HFD-530/Sinha/NDA 21-652

HFD-880/Reynolds/Zheng

HFR-CE3560/Sands

HFR-SW1540/Martinez

Drafted: MKY/7/23/04

FACTS: 531525

DSI O:\BE\eircover\21652gsk-epivir&ziagen.doc

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

/s/

Michael Skelly
7/26/04 04:53:19 PM
PHARMACOLOGIST

Dr. Yau signed the original paper copy 7/23/04; Dr.
Viswanathan signed the original paper copy 7/26/04; photocopies
follow.



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

DATE: July 22, 2004

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

FROM: Mark Avigan, MD, CM, Director
Division of Drug Risk Evaluation, HFD-430

Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

Gerald DalPan, MD, MHS, Director
Division of Surveillance, Research, and Communication Support, HFD- 410

DRUG: Ezicom™ Tablets (abacavir sulfate and lamivudine); NDA 21-652
Related Products: Ziagen® (abacavir sulfate) Tablets and Oral Solution;
NDA 20-977 and NDA 20-978 and Trizivir® (abacavir,
lamivudine and zidovudine) Tablets; NDA 21-205

APPLICANT: GlaxoSmithKline (GSK), North Carolina

SUBJECT: Risk Management Options submitted October 8, 2003

PID: D040397

1 EXECUTIVE SUMMARY

This consult is in response to a June 23, 2004 request from the Division of Antiviral Drug Products (DAVDP) to comment on risk management options for the fixed-dose combination product Ezicom™ (abacavir and lamivudine) as treatment for HIV-1 infection, submitted on October 8, 2003. If approved, Ezicom™ will be the 3rd abacavir-containing product available in the U.S.

The primary toxicity of abacavir is a serious and sometimes fatal hypersensitivity reaction (HSR). HSRs occur in about 8% of patients initiating abacavir. Failure to stop abacavir or reintroduction of abacavir in patients with a prior HSR has resulted in more severe and fatal multi-organ hypersensitivity reactions. Postmarketing adverse event and epidemiologic data have

failed to indicate a clear signal of an increased risk of serious or fatal HSRs with the introduction of the second abacavir-containing product, Trizivir® into the market. However, there is a concern that a relatively long period of time has passed (6 and 4 years, respectively) since the introduction of Ziagen® and Trizivir® into the market and that prescribers and patients may not be as informed about the potentially serious consequences of inadvertently reintroducing abacavir in patients with a previous hypersensitivity reaction. With the potential introduction into the market of a 3rd abacavir-containing product DAVDP is concerned about serious hypersensitivity reactions with inadvertent reintroduction of abacavir in a different product with a different tradename.

GlaxoSmithKline (GSK) is proposing professional labeling (including a Box Warning), a Medication Guide, and a Warning Card for Ezicom™, tools currently used to address the safety concern with the two currently available abacavir-containing products, Ziagen® and Trizivir®. Additionally, GSK has proposed postmarketing commitments for Ezicom™ mainly directed at education and promotion that are outlined in June 30, 2004 submission entitled Phase IV commitments.

Comments are provided on the risk minimization tools and Phase IV Commitments currently proposed by GSK. Further comments are provided on additional options that may be considered if HFD-530 feels that the GSK-proposed education plans would be inadequate to manage the risk of HSR with abacavir-containing products.

2 BACKGROUND

2.1 Product Information

Ezicom™ is a fixed-dose combination tablet that contains abacavir sulfate and lamivudine. There are currently two abacavir-containing products available in the U.S. Information regarding all three abacavir-containing products is provided below.

Product	Ingredients	Abacavir Dose	NDA	FDA Approval
Ziagen® Tablets and Solution	Abacavir 300mg	300mg twice daily	20-977 20-978	December 17, 1998
Trizivir® Tablets	Abacavir, 300mg Lamivudine 150mg Zidovudine 300mg	300mg twice daily	21-205	November 14, 2000
Ezicom™ Tablets	Abacavir, 600mg Lamivudine 300mg	600mg once daily	21-652	pending

2.2 Regulatory history

Abacavir sulfate is a nucleoside analog approved December 1998 for the treatment of HIV-1 infection in combination with other antiretroviral agents. The primary toxicity of abacavir is a

serious and sometimes fatal hypersensitivity reaction (HSR). HSRs occur in about 8% of patients initiating abacavir. Failure to stop abacavir or reintroduction of abacavir in a patient with a previous HSR to abacavir has resulted in serious and fatal multi-organ hypersensitivity reactions.

Several risk management initiatives have been utilized to address the HSR risk with abacavir. A Medication Guide and Warning Card were included in the initial product labeling to address this safety issue. The Abacavir Hypersensitivity Reaction Registry was established to collect information from physicians on patients that have experienced a hypersensitivity reaction. In January and July of 2000, respectively two Dear Healthcare Provider letters were issued with regard to new safety issues with abacavir. These letters cautioned that fatal abacavir hypersensitivity reactions had occurred in patients presenting with respiratory symptoms and there were recent reports of severe or fatal hypersensitivity reactions that can occur within hours after Ziagen® reintroduction in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy. The abacavir label was revised to reflect these new safety concerns.

In November 2000, Trizivir®, a triple nucleoside combination (ABC/ZDV/3TC) for the treatment of HIV infection, was approved with the same labeling requirement as Ziagen®, a Medication Guide and Warning Card. While GSK considered this simplified combination product as a huge benefit to patients, DAVDP had concerns about safety. They were concerned that prescribers would inadvertently give this product to patients with a documented abacavir HSR resulting in an increased occurrence of serious adverse events and fatalities because they were unaware the new product contained abacavir. Of particular interest were incarcerated patients, patients with English as a second language, and socially and economically depressed patients. DAVDP included Phase IV commitments in the approval letter to address this safety concern. The applicant was also asked to conduct a postmarketing epidemiological program to compare rates of HSR, HSR-associated rechallenge, HSR-associated hospitalization, and HSR-associated death in patients receiving Trizivir® Tablets compared to Ziagen® products.

2.3 Proposed Labeling

GSK has proposed the standard abacavir labeling for Ezicom™ that is currently approved for Ziagen® and Trizivir®. This includes a Box Warning, a Medication Guide, and a Warning Card. DAVDP has requested that GSK revise and strengthen the current Warnings, Contraindications, Medication Guide, and warning card; and add a safety statement to the *Indication and Usage* section of all the abacavir-containing products. The draft Medication Guide has been reviewed separately by DSRCS¹.

2.4 Proposed Proprietary Name

The proposed proprietary names were reviewed under DMETS consults 03-0244, 04-0121, and 04-0121-1. The reviews were completed on January, 9, 2004, May 14, 2004 and May 28, 2004 respectively.

¹ Best, Jeanine. DSRCS Review of Medication Guide and Warning Card for Ezicom®, dated July 14, 2004.

2.5 Proposed Packaging/Formulation

The sponsor has proposed modifications to the labels of Ezicom™, Ziagen®, and Trizivir® to alert practitioners that abacavir is contained in all three products. DMETS has completed a separate review of the labels and labeling for Ezicom™. We refer you to consult 04-0121-3 for comments on this proposal.²

3 RISK ASSESSMENT

3.1 Synopsis of division's safety concerns or safety summary

The DAVDP has expressed two concerns regarding the safety of Ezicom™:

- Clinical trial data with the once daily administration of abacavir 600mg indicates an increased incidence of Grade 3/Grade 4 hypersensitivity reactions (i.e. hypotension) in comparison to the rates observed in clinical trials with the twice daily administration of abacavir 300mg. The review division plans to address this risk with revised professional and patient labeling.
- With the potential introduction into the market of 3rd abacavir-containing product, DAVDP is concerned that serious and potentially fatal hypersensitivity reactions will occur at an unacceptable rate because of the inadvertent reintroduction of abacavir in a different product with a different tradename. While there are risk management tools in place for the currently approved abacavir products, there is a feeling that sufficient time has passed (6 and 4 years, respectively) since the introduction of Ziagen® and Trizivir® into the market and that prescribers and patients may not be as informed about the potentially serious consequences of inadvertently reintroducing abacavir in patients with a previous hypersensitivity reaction.

3.2 Summary of risk assessment of safety data conducted by ODS staff

Postmarketing adverse event and epidemiologic data have failed to indicate a clear signal of an increased risk of serious or fatal HSRs with the introduction of Trizivir® into the market.

3.2.1 Adverse Event Reporting System

The Adverse Event Reporting System (AERS) reporting rates of abacavir HSRs from 1999 to 2004 are consistent, and there has not been an increase in the reporting of serious HSRs or deaths associated with a hypersensitivity reaction after the approval of Trizivir®. There has also not been a signal in AERS of inadvertent rechallenge of abacavir (Trizivir®) in patients who previously experienced a HSR with Ziagen® or vice versa. However, these are labeled events, which could affect reporting behavior.

² Denise Toyer. Consult 04-0121-1:DMETS Review of Labels and Labeling for Ezicom®, dated July 7, 2004 (DFS date July 13, 2004)

There have been rare reports of medication error cases involving patients that did not discontinue their therapy despite recommendation from their physician. Also, remaining pills in their possession were inadvertently administered following discontinuation of the abacavir-containing product. Patient education needs to better stress these messages.

3.2.2 Epidemiologic Study

The Epidemiologic Study developed for Trizivir® as a Phase IV commitment was designed to monitor hypersensitivity reactions among users and to identify the risk of inadvertent rechallenge by health care providers. This study was not able to identify a statistically significant risk of inadvertent rechallenge. The study, as designed, had the ability to detect *only* catastrophic differences in HSR and rechallenge risks and the data, as presented, suggested no catastrophic differences in risks. The Division of Drug Risk Evaluation (DDRE) epidemiologic review identified the following study design issues and inconsistencies that affected the results of the study.

- a) An apparent change in protocol that excluded patients from the analytical cohort because exposure occurred prior to consent;
- b) Missing records;
- c) Ambiguous and ill-defined denominator for calculating rechallenge rates;
- d) Overwhelming preponderance of data points for Ziagen® compared to Trizivir®;
- e) HSR frequencies lower (3.6% for Ziagen® and 3.1% for Trizivir®) than the 5% expected;
- f) Rechallenge events and hospitalizations rates lower than expected for both exposure groups;
- g) No deaths were observed although, based on the number of individuals in the cohorts, none would be expected.

The data consistently demonstrated no statistically significant differences between Ziagen® and Trizivir® in the frequency of observed HSR and rechallenge events for this population. DDRE, however, disagreed with the sponsor who stated that the study showed no difference between Ziagen® and Trizivir® rechallenge rates. Although not statistically significant, the rechallenge rates for definite/probable/possible rechallenge cases suggested a possible difference between Ziagen® and Trizivir®. The difference could be confirmed or refuted with additional cases, but unfortunately the numbers were too small in this study to make a determination either way. Because case accession was lower than expected and the benefit of extending the study would not yield meaningful data, the study was terminated.

Although the study was not able to identify a statistically significant risk of inadvertent rechallenge, the concern remains particularly with the introduction of a third abacavir-containing product with yet another tradename. DDRE presented the findings of the sponsor's Epidemiologic Study to the DAVDP on March 15, 2004 (please refer to appendix 1 and 2). The review with final comments was forwarded to DAVDP on March 15, 2004.

10 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Ezicom RMP Review Team

Jeanine Best, MSN, RN, PNP, Patient Product Information Specialist, DSRCS /s/7-20-04

Mary Dempsey, Project Management Officer, ODS /s/7-22-04

Claudia Karwoski, PharmD, Scientific Coordinator of RMP (Detail), ODS IO /s/7-22-04

Rita Ouellet-Hellstrom, Ph.D, Epidemiologist, DDRE /s/7-20-04

Toni Piazza-Hepp, Pharm.D., Deputy Director, DSRCS /s/7-21-04

Denise Toyer, Pharm.D., Team Leader, DMETS /s/7-20-04

Melissa M. Truffa, R.Ph., Safety Evaluator, Team Leader, DDRE /s/7-20-04

Leslie Wheelock, M.S., R.N., Associate Director, DSRCS /s/7-22-04

Mary Willy, Ph.D., Epidemiology Team Leader, DDRE /s/7-20-04

Mark Avigan, MD, CM, Director

Division of Drug Risk Evaluation, HFD-430

Carol Holquist, RPh, Director

Division of Medication Errors and Technical Support, HFD-420

Gerald DalPan, MD, MHS, Director

Division of Surveillance, Research, and Communication Support, HFD- 410

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

/s/

Mary Dempsey
7/22/04 02:28:25 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
7/22/04 02:40:49 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/22/04 03:54:13 PM
DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
7/22/04 04:39:20 PM
MEDICAL OFFICER

MEMORANDUM

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

DATE: July 14, 2004

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

VIA: Tanima Sinha, Regulatory Health Project Manager
Division of Antiviral Drug Products
HFD-530

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
(DSRCS), HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication
Support (DSRCS), HFD-410

SUBJECT: DSRCS Review of Medication Guide and Warning Card for
Ezicom (abacavir sulfate and lamivudine) Tablets, NDA 21-652

Background and Summary

The attached Medication Guide and Warning Card represents the revised patient risk communication materials for Ezicom (abacavir sulfate and lamivudine) Tablets, NDA 21-652. The Medication Guide has been reviewed by DSRCS and by DDMAC. We have simplified the wording, made it consistent with the prescribing information, removed promotional and other unnecessary information and put it in the format that is specified under 21 CFR § 208.20, *Content and format of a Medication Guide*.

These revisions are based on draft labeling (prescribing information or PI) submitted in an e-mail by the sponsor July 13, 2004. The Medication Guide should always be consistent with the PI. All future changes to the PI should also be reflected in the Medication Guide.

We also have the following comment:

Comments to the review division in the Medication Guide are **bolded**, underlined and *italicized*. We can provide revised documents (Medication Guide and Warning Card) in Word if requested by the review division. Please call us if you have any questions.

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

/s/

Jeanine Best
7/14/04 05:39:40 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
7/14/04 06:08:12 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: July 23, 2004

DESIRED COMPLETION DATE:
August 3, 2004

ODS CONSULT #: 04-0197

PDUFA DATE: August 8, 2004

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

THROUGH: Tanima Sinha
Project Manager
HFD-530

PRODUCT NAME:

Epzicom
(Abacavir Sulfate and Lamivudine Tablets)
600 mg/300 mg

SPONSOR:

GlaxoSmithKline

NDA #: 21-652

SAFETY EVALUATOR: Linda Y. Kim-Jung, Pharm.D.

RECOMMENDATIONS:

1. Limited data was available to complete a comprehensive analysis of the proprietary name, Epzicom. DMETS is concerned about potential confusion between Epzicom and Eпивir based on post-marketing experience between products that contain an overlapping ingredient and strength from the same manufacturer. We recognize that the Division and sponsor will approve the product with the name, Epzicom per Dr. Birnkrant's email to DMETS on August 2, 2004. The sponsor should initiate an education campaign at launch and ensure the trade dress is dissimilar to Eпивir in order to minimize confusion between Eпивir and Epzicom.
2. DDMAC finds the name Epzicom acceptable from a promotional perspective.

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

**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: July 29, 2004

NDA NUMBER: 21-652

NAME OF DRUG: **Epzicom**
(Abacavir Sulfate and Lamivudine Tablets)
600 mg/300 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 an expedited request from the Division of Anti-Viral Drug Products for an assessment of the proprietary name "Epzicom" regarding potential name confusion with other proprietary and/or established drug names. Container labels and carton labeling were provided for review and comment.

This is the fifth proprietary name review for this application. The names "Epivir/Ziagen" and "Kivexa" were initially reviewed and found unacceptable by DMETS on November 9, 2003 (see ODS consult 03-0244). Subsequently, the proprietary names, Ezicom and Zanvirez were found acceptable by DMETS on May 6, 2004 (see ODS consult 04-0121). However, DDMAC objected to the use of the proprietary name "Ezicom" from a promotional perspective. DDMAC found the name Ezicom "overly fanciful or Ezi or EZ may be pronounced as "easy."

PRODUCT INFORMATION

Epzicom is the proposed proprietary name for a combination tablet containing abacavir 600 mg and lamivudine 300 mg. It is recommended for the treatment of HIV infection in combination with other antiretroviral drugs. The recommended dose is one tablet once daily. Epzicom will be supplied in 30 count bottles.

II. RISK ASSESSMENT

Since this was a priority review, the routine analysis was not performed. The DMETS' safety evaluator was only able to conduct a search of several standard published drug product reference texts^{i,ii} as well as several FDA databasesⁱⁱⁱ for existing drug names which sound-alike or look-alike to Epzicom 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 SAEGISTM Online Service^v were also conducted.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion is usually held by DMETS to gather professional opinions on the safety of the proposed proprietary name. Potential concerns regarding drug marketing and promotion related to the proposed name are 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. However, no Expert Panel was held for the proprietary name, Epzicom, due to time constraints and priority of the review. DDMAC (Tom Abrams) provided their opinion via voicemail on July 29, 2004 and finds the name Epzicom acceptable from a promotional perspective.

B. DATABASE SEARCH

Through independent analysis, DMETS identified four proprietary names as having the potential for confusion with Epzicom. See Table 1 (see page 4) for dosage forms available and usual dosage.

ⁱ MICROMEDEX Integrated Index, 2004, 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 98-04, 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.

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

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Epzicom (Rx)	Abacavir Sulfate and Lamivudine 600 mg/300 mg Tablets	Take one tablet daily.	
Epifoam (Rx)	1 % Hydrocortisone Acetate and 1% Pramoxine Hydrochloride Aerosol, Metered	Apply sparingly to affected areas 2 to 4 times daily.	Look-alike
Epipen	Epinephrine 1:1000 (1 mg/mL) in 0.3 mL single-dose auto-injectors Injection	Inject the delivered dose of the EpiPen auto-injector (0.3 mL epinephrine injection, USP, 1:1000) intramuscularly into the anterolateral aspect of the thigh, through clothing if necessary.	Look-alike
Epivir	Lamivudine (3TC) 150 mg and 300 mg Tablets	Adults: 300 mg/day, administered as either 150 mg twice daily or 300 mg once daily, in combination with other antiretroviral agents. Children (3 months up to 16 years of age): 4 mg/kg twice daily (up to a maximum of 150 mg twice a day) administered with other antiretroviral agents.	Look-alike
*Frequently used, not all-inclusive. ***NOTE: This information is confidential and is not FOIable.			

C. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

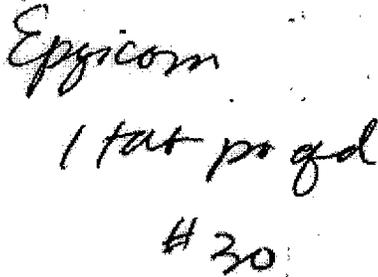
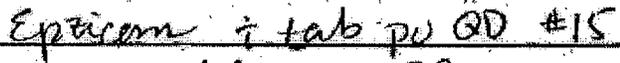
As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The POCA did not identify any additional names that were thought to have significant phonetic or orthographic similarities to Epzicom.

D. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary names to determine the degree of confusion of Epzicom 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 122 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 Epzicom (see

below). 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 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.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p> <p style="text-align: center;">  </p>	<p>Epzicom #30</p> <p>One daily.</p>
<p><u>Inpatient RX:</u></p> <p style="text-align: center;">  </p>	

2. Results

DMETS generally allows ten days to receive responses back from the prescription study participants. However, due to the expeditious nature of this name review, the results were obtained approximately four days post initiation of the study and few responses were recorded. See appendix A for a complete listing of interpretations from the verbal and written studies.

E. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Epzicom", the products considered to have potential for name confusion with Epzicom include Epifoam, _____, EpiPen, and Epivir.

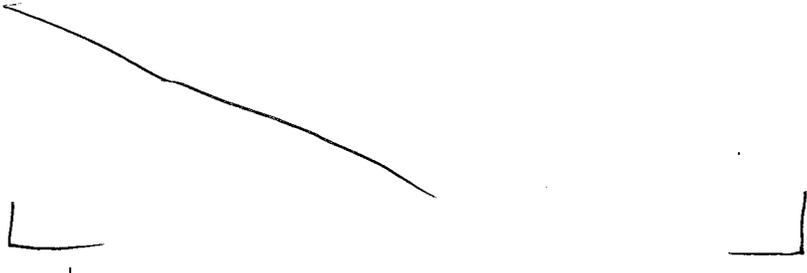
We conducted prescription studies to simulate the prescription ordering process. There was no confirmation that Epzicom could be confused with any of the aforementioned drug products. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. One participant from the voice prescription studies responded with the interpretation of "Asacol" which sounds similar to the currently marketed drug product Asacol. Asacol is indicated for treatment of chronic inflammatory bowel disease. Asacol is available as 400 mg tablets and the usual dosage is two tablets 3 to 4 times daily for a total dose of 2.4 grams/day for 6 weeks. Asacol and Epzicom share the same dosage form and route of administration. However, the products differ in strength, dosing frequency and prescriber population. Given the product differences in addition to lack of convincing sound-alike potential, the likelihood for confusion is minimal. Thus, Asacol will not be discussed further in this review. The remaining interpretations from the verbal and written prescription studies were phonetic misinterpretations or spelling variations of the drug name, Epzicom.

- a. Epifoam and Epzicom were identified as having look-alike potential when scripted. Epifoam is a metered aerosol foam used to help relieve redness, swelling, itching, and discomfort of many skin problems. The usual dose is to apply to affected areas 2 to 4 times daily. Epifoam and Epzicom begin with the letters "Ep" and share the similarly scripted endings "oam" vs. "com". Additionally the names share a down stroke letter ("f" vs. "z") in the middle of the name. Moreover, both are combination products and available in only one strength, thus a prescription for either drug product may omit the strength because a strength would not be necessary to dispense a product. However, there are no additional overlapping product characteristics between Epifoam and Epzicom. The products do not share a similar dosing interval (apply 2-4 times daily vs. one tablet once daily), dosage form (aerosol vs. tablet), route of administration (topical vs. oral), and indication for use. The differences in product characteristics, and different directions of use would help to differentiate the two product names.

Epifoam
Epzicom

b.

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

- 
- c. EpiPen and Epzicom may look-alike when scripted. EpiPen is indicated for the emergency treatment of allergic reactions (anaphylaxis) to insect stings, or bites, foods, drugs and other allergens as well as idiopathic or exercise induced anaphylaxis. Both EpiPen and Epzicom share the same first two letters, “E and P”, and the down stroke of the second “P” in EpiPen and the down stroke of the letter “Z” in Epzicom may contribute to the look-alike similarities between the two drug product names. Additionally, the difference in the directions of use will help to differentiate between the two names. For example, a prescription for EpiPen may have general directions of “use as directed”, whereas a prescription for Epzicom is most likely to have a direction of “take one tablet once daily.” Moreover, different product characteristics such as the dosage form (injection vs. tablets), route of administration (subcutaneous vs. oral) may help to differentiate between the two products. Despite some orthographic similarities between the two names, the differences in the product characteristics will help to minimize potential confusion between EpiPen and Epzicom.

EpiPen
Epzicom

- d. Epivir and Epzicom may look-alike when scripted. Epivir is indicated for the treatment of HIV infection in combination with other antiretroviral agents. Additionally, both are manufactured by GlaxoSmithKline. Both product names begin with the letters, “Ep” which contributes to the look-alike similarities between the names. However, when scripted, the down stroke of the letter “z” in Epzicom may help to differentiate the two names. Epivir is available in two different strengths (150 mg and 300 mg). A prescription for Epivir would include a single strength, whereas since Epzicom is only available in one combination, and thus the strength may be omitted. Epivir and Epzicom overlap in one ingredient (lamivudine) which also overlaps in strength (300 mg). In addition, the two products will likely be stored in close proximity to one another and have the same prescriber and patient population. Post-marketing experience has shown that products having an overlapping ingredient in addition to strength increases the potential for confusion. Thus, it is important to educate healthcare practitioners to the introduction of this new combination product as well as differentiating the container labels.

epivir
epzicom

III. RECOMMENDATIONS

- A. Limited data was available to complete a comprehensive analysis of the proprietary name, Epzicom. DMETS is concerned about potential confusion between Epzicom and Epivir based on post marketing experience between products that contain an overlapping ingredient and strength from the same manufacturer. We recognize the Division and sponsor will approve the product with the name, Epzicom per Dr. Birnkrant's email to DMETS on August 2, 2004. The sponsor should initiate an education campaign at launch and ensure the trade dress is dissimilar to Epivir in order to minimize confusion between Epivir and Epzicom.
- B. DDMAC finds the name Epzicom acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. 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 301-827-2102.

Linda Y. Kim-Jung, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Denise P. Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A. DMETS prescription study results for Epzicom

Inpatient	Outpatient	Voice
Epzicerm		
Epticom	Epgicom	Asacon
Epzicem	Epgicom	Axicom
Epzicem	Epyicom	Episicon
Epzicem	Epyricom	Epsicom
Epzicem	Epyscom	Epsicom
Epzicern	Epyscom	Epsicom
Epzicern	Epzicom	Epsicom
Epzicom	Epzicom	Epsicom
Epzicom	Epzicom	Epsicon
Epzicom	Epzicom	Etsicom
Epzicom	Epzicom	Exacom
Epzicom	Epzicom	Execom
Epzicom		Exicom
Epzicom		
Epzicom		
Epzicom		

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

/s/

Linda Kim-Jung
8/2/04 06:06:47 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/2/04 06:10:51 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

DATE: June 11, 2004

TO: HFD-530 Division File

FROM: Tanima Sinha, Regulatory Project Manager, HFD-530

SUBJECT: **Trade name discussion with GlaxoSmithKline**
NDA 21-652, Ezicom [abacavir sulfate (ABC) and lamivudine
(3TC) fixed dose combination] tablets

Per an internal discussion within the Division and a few members of the review team, it was decided that both Ezicom and Zanvirez were acceptable. This was communicated to the sponsor (GlaxoSmithKline) verbally on June 10, 2004. It was also communicated that if the sponsor were to choose Ezicom for their trade name for the ABC/3TC FDC, that the 'Zi' should be a different color. The sponsor should also consider this for their other products that contain abacavir sulfate, Ziagen® and Trizivir®. This can bring attention to the fact that all of these products contain abacavir sulfate.

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

/s/

Tanima Sinha
7/6/04 10:54:27 AM
CSO
ABC-3TC FDC tradename discussion memo (NDA 21652)
Please sign off asap. Thanks.

Rosemary Johann-Liang
7/6/04 11:44:26 AM
MEDICAL OFFICER

**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

NDAs: 20-977 (S-012), 20-978 (S-014) and 21-652

Drug: Abacavir sulfate (OAD) and Abacavir sulfate/lamivudine combination tablets

Date: June 7, 2004

To: Ms. Martha Anne A. Moore

Sponsor: GlaxoSmithKline

From: Tanima Sinha, M.S. Regulatory Project Manager

Through: Jenny H. Zheng, Ph.D. Clinical Pharmacology Reviewer

Concur: Rosemary Johann-Liang, M.D. Medical Team Leader
Andrea James, M.D. Medical Reviewer
Kellie Reynolds, Pharm.D. Clinical Pharmacology Team Leader

Subject: Clinical Pharmacology comments for NDAs 20-977 (S-012), 20-978 (S-014) and 21-652.

Please reference your NDAs 20-977 (S-012), 20-978 (S-014) and 21-652. The following comment is from Dr. Zheng, the Clinical Pharmacology reviewer for these submissions. Dr. Zheng would like to have the response within 48 hours after you receive these comments.

1. Please submit all raw data from study CNAA2001, CNAB2002, CNAB3001, CNAB3003 that were used for population PK analysis. The data should be submitted as SAS transport files.
2. Please submit data files used for base model and final model.
3. Please submit output files ("txt" file with file extension of ".txt") from base model and final model.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-827-2335 if you have any questions regarding the contents of this transmission.

Tanima Sinha
Regulatory Project Manager
FDA/CDER/DAVDP

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

/s/

Tanima Sinha
6/7/04 10:11:33 AM
CSO
PK request for ABC and ABC/3TC combo. 6-7-04.

Rosemary Johann-Liang
6/8/04 11:46:03 AM
MEDICAL OFFICER



MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-652

Drug: Abacavir sulfate/lamivudine combination tablets

Date: June 4, 2004

To: Ms. Martha Anne A. Moore

Sponsor: GlaxoSmithKline

From: Tanima Sinha, M.S. Regulatory Project Manager

Through: Rao Kambhampati, Ph.D. Chemistry Reviewer

Concur: Rosemary Johann-Liang, M.D. Medical Team Leader
Andrea James, M.D. Medical Reviewer
Stephen Miller, Ph.D. Chemistry Team Leader
Kellie Reynolds, Pharm.D. Clinical Pharmacology Team Leader
Jenny H. Zheng, Ph.D. Clinical Pharmacology Reviewer

Subject: CMC comments for NDA 21-652 for ABC/3TC combination tablet

Please reference your submission for abacavir sulfate/lamivudine combination tablets, NDA 21-652. The following comment is from Dr. Kambhampati, the Chemistry reviewer for your combination drug abacavir sulfate/lamivudine tablet.

CMC COMMENT TO THE APPLICANT

During the development of the analytical method for the *Determination of Abacavir and Lamivudine Release by Dissolution of Abacavir-Lamivudine Tablets by _____ Analysis* (3.2.P.5.3, pages 1-8), Batch# 18129-001-12 was used for conducting the dissolution studies at paddle speeds of _____ 75, _____ RPM. Please provide the significant CMC differences between this batch and the batches that were used in the bioequivalence and clinical studies.

NDA 21-652
June 4, 2004

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-827-2335 if you have any questions regarding the contents of this transmission.

Tanima Sinha
Regulatory Project Manager
FDA/CDER
Division of Antiviral Drug Products

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

/s/

Tanima Sinha
6/4/04 11:02:36 AM
CSO
CMC fax to sponsor for abc/3tc combo tablet. 6-4-4

Rosemary Johann-Liang
6/8/04 11:43:52 AM
MEDICAL OFFICER



MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-652

Drug: Abacavir sulfate/lamivudine combination tablets

Date: June 4, 2004

To: Ms. Martha Anne A. Moore

Sponsor: GlaxoSmithKline

From: Tanima Sinha, M.S. Regulatory Project Manager

Through: Dr. Lisa Naeger Microbiology Reviewer

Concur: Dr. Julian O'Rear Microbiology Team Leader
Dr. Andrea James Medical Reviewer
Dr. Rosemary Johann-Liang Medical Team Leader

Subject: Microbiology comments regarding NDA 21-652.

Please reference your submission NDA 21-652. Dr. Lisa Naeger, the microbiology reviewer has the following comments/requests for you:

Please provide genotypic and phenotypic resistance data on the post-BL samples from 6 additional patients from study 30021. The patient numbers are 51124, 51550, 51676, 51818, 52643 and 52761.

Also, we immediately need the *in vitro* combination relationship analyses and the resistance datasets for the ABC trials discussed in the previous teleconference.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-827-2335 if you have any questions regarding the contents of this transmission.

Tanima Sinha
Regulatory Project Manager
FDA/CDER
Division of Antiviral Drug Products

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

/s/

Tanima Sinha
6/4/04 12:12:11 PM
CSO
Genotypic and Phenotypic Resistance info. request on patients for
NDA 21-652

Rosemary Johann-Liang
6/8/04 11:44:57 AM
MEDICAL OFFICER

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: March 18, 2004

TO: Sinha Tanima, Regulatory Project Manager
Andrea James, Medical Officer
Division of Antiviral Drug Products, HFD-530

THROUGH: Khin Maung U, M.D., Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D
Good clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-652

APPLICANT: GlaxoSmithKline

DRUG: Ziagen (abacavir sulfate) Tablets

CHEMICAL CLASSIFICATION: 6

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Antiretroviral Therapy Naïve HIV Infected Subjects.

CONSULTATION REQUEST DATE: September 30, 2003

ACTION GOAL DATE: August 3, 2004

I. BACKGROUND:

Ziagen is currently recommended for administration at a dose of 300mg twice daily in adolescents and adults, in combination with other antiretroviral agents. The sponsor is seeking approval for abacavir sulfate 300mg tablets and oral solution for dosing at 600mg once daily in adolescents and adults, based primarily upon 48-week results from CNA30021, an adequate and well-controlled clinical trial.

The primary study objective of CNA30021 was to compare the antiretroviral efficacy of ABC once a day (OAD) based therapy to ABC twice a day (BID) based antiretroviral therapy (ART) as measured by the

proportion of subjects with plasma HIV-1 RNA <50 copies/mL at 48 weeks as defined by the time to loss of virologic response (TLOVR algorithm) and to test the non-inferiority of ABC QD versus ABC BID. Secondary objectives presented here include comparisons of safety by recorded clinical adverse events and clinical laboratory abnormalities, proportion of patients with plasma HIV-1 RNA <50 copies/mL and <400 copies/mL at Week 48, time to loss of virologic response (TLOVR), and immunologic effects by absolute changes in CD4+ lymphocyte cell count.

II. RESULTS

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Bellos	Dallas	TX	Sep-30-03	Dec-8-03	NAI/AEH
Lang	Charlotte	NC	Sep-30-03	Nov-18-03	VAI/AEH
Sands	Jacksonville	FL	Sep-30-03	Dec-23-03	VAI/AEH
Weinberg	Atlanta	GA	Sep-30-03	Dec.16-03	VAI/AEH

A. Protocol #CNA30021

1. Bellos Site

This site consented 22 subjects for the study; 19 subjects were randomized; three (3) subjects were discontinued and reason(s) were documents (insufficient viral load, adverse events, and lost to follow-up). Discontinued subjects were accurately documented. The records for 19 subjects were reviewed during the inspection and compared source data to their respective case report forms (CRFs). The review included IRB correspondence, consent forms, site monitoring log, adverse events, screen failures, drug accountability records, inclusion/exclusion criteria, and primary and secondary efficacy end points including laboratory results. No deviations from federal regulations or study protocol were noted. Data generated from this site appears to be acceptable in support of the pending NDA.

2. Lang Site

This site screened 26 subjects for this study; 5 subjects were screen failures; 21 subjects were randomized; 5 subjects were discontinued prior to study completion and 16 subjects completed the study. Dropouts were accurately reported to both the sponsor and IRB. The records for 21 subjects were reviewed during this inspection and compared to their respective case report forms (CRFs). The review included consent forms, adverse events, drug accountability and efficacy end points including laboratory results. The source documents disclosed that all subjects met inclusion criteria, received the study drug and adhered to the protocol. The investigator's source documents were well organized, complete and legible. The investigator documented subjects condition prior to and during the study. Although concomitant therapy and intercurrent illness were noted in the case report forms, two subjects received concurrent medications not listed in the case report forms. The investigator acknowledged the inspectional observations and promised to be more careful in the future.

3. Sands Site

This site screened 23 subjects; 6 subjects were screen failures and seventeen subjects were enrolled; two (2) subjects were discontinued due to missing visits and non-compliance; four (4) subjects were reported as lost to follow-up and eleven (11) subjects completed the study.

The records and shadow charts/source documents for all subjects were verified and the files for five subjects were reviewed in depth. The medical records disclosed that all subjects (except subject 51390 and 53268) met inclusion criteria, received the study drug and adhered to the protocol. The investigator documented subjects condition prior to and during the study. Drug accountability records were not complete. The investigator acknowledged the inspectional observations and promised to exercise more care in the future and with ongoing studies.

4. Weinberg Site

The source records for all subjects were reviewed during the inspection and were compared to the data listing provided by the sponsor/case report forms. This site enrolled 22 subjects for this study and three (3) subjects were discontinued prior to completion. The reason(s) were accurately reported. The review of all 22 records included consent forms, adverse events, drug accountability records, and the laboratory results for primary and secondary efficacy end points. The source documents disclosed that all subjects met inclusion criteria except (51184/Hepatitis C) and certain subjects missed their schedule visits. The investigator's source documents were well organized, complete and legible. The investigator and his staff acknowledge the inspectional findings and promised to exercise more care in the future.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

There were no limitations to the four sites inspected. Data generated from these sites appear to be acceptable in support of the two pending NDAs. No follow is necessary at this time. No major deficiencies were noted in the selected sites that could compromise the reliability and integrity of the data generated. Thus, the data reviewed is acceptable.

Key to Classification:

NAI = No deviation from regulations. Data acceptable

VAI = Minor deviation(s) from regulations. Data acceptable

Antoine El-Hage, Ph.D
Regulatory Pharmacologist
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

Page 4 – Clinical Inspection Summary – NDA 21-652

DISTRIBUTION:

NDA 21651

HFD-45/Division File / Reading File)

HFD-46/AEH

O:\AEH\Clinical Inspection Summary\21-652.inspectsumm.doc

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

/s/

Sherry George
3/18/04 11:22:23 AM
TECHNICAL
Signed by Drs. El-Hage and U on 3/18/04



MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-652

Drug: Abacavir sulfate/lamivudine combination tablets

Date: February 23, 2004

To: Ms. Martha Anne A. Moore

Sponsor: GlaxoSmithKline

From: Tanima Sinha, M.S. Regulatory Project Manager

Through: Dr. Lisa Naeger Microbiology Reviewer

Concur: Dr. Julian O'Rear Microbiology Team Leader
Dr. Andrea James Medical Reviewer
Dr. Rosemary Johann-Liang Medical Team Leader

Subject: Microbiology comments regarding NDA 21-652.

Please reference your submission NDA 21-652. Dr. Lisa Naeger, the microbiology reviewer has the following comments/requests for you:

From clinical study CNA30021, please provide the data on the non-clade B isolates in the random sample (n = 13) and the virologic failures (n = 5) in the template format. Please indicate the clade of the isolates and if they responded to therapy. Please provide a timeframe for the submission of this requested data.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-827-2335 if you have any questions regarding the contents of this transmission.

Tanima Sinha
Regulatory Project Manager
FDA/CDER
Division of Antiviral Drug Products

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

/s/

Tanima Sinha

2/23/04 11:28:33 AM

CSO

Micro fax regarding ABC/3TC combo tablet.

Micro fax regarding ABC/3TC combo tablet.

Rosemary Johann-Liang

2/23/04 12:00:13 PM

MEDICAL OFFICER



MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-652

Drug: Abacavir sulfate/lamivudine combination tablets

Date: February 13, 2004

To: Ms. Martha Anne A. Moore

Sponsor: GlaxoSmithKline

From: Tanima Sinha, M.S. Regulatory Project Manager

Through: Dr. Andrea James Medical Reviewer

Concur: Dr. Rosemary Johann-Liang Medical Team Leader

Subject: Comments regarding proposed name

Please reference your submission for abacavir sulfate/lamivudine combination tablets, NDA 21-652. The following comments are from DMETS regarding the proposed name for your combination drug abacavir sulfate/lamivudine tablet.

COMMENTS TO THE SPONSOR

- A. DMETS does not recommend the use of the proposed proprietary name, Epivir/Ziagen due to its potential to sound and look like either Epivir or Ziagen, alone.

The sponsor is proposing to use the existing proprietary names Epivir and Ziagen (separated by a slash) for the combination product of the same active ingredients that are currently marketed separately. DMETS believes that the use of both names as the proprietary name for the proposed product may cause confusion and ultimately result in errors. The currently marketed products Epivir and Ziagen contain either 150 mg or 300 mg of lamivudine and 600 mg of abacavir, respectively whereas the proposed product "Epivir/Ziagen" contains a combination of 300 mg of lamivudine and 600 mg of abacavir in one tablet. DMETS has concerns that a prescription written as "Epivir/Ziagen 1 po QD" may be misinterpreted as "Epivir 1 po QD" and "Ziagen 1 po QD". In this scenario, the patient may receive the individually marketed products as opposed to the combination product. Although clarification will be sought for the strength of Epivir (since it is individually available in two different strengths), the Ziagen component may be dispensed as

the 300 mg strength since it is individually available in only one strength. The proposed combination product contains 600 mg of Ziagen; therefore the patient may be under-dosed.

Additionally, it is likely that a prescription written for Epivir/Ziagen may be misinterpreted as Epivir HBV depending on the scripted clarity of "/Ziagen" in Epivir/Ziagen (see writing sample below). In this case Epivir HBV, which is indicated for chronic hepatitis B, may be dispensed. Consequently the patient expecting the Epivir/Ziagen product, who receives Epivir HBV, will be severely under-dosed since Epivir HBV only contains 100 mg of lamivudine. As per the package insert for Epivir, if Epivir-HBV is prescribed for a chronic hepatitis B patient with unrecognized or untreated HIV infection, it is likely that HIV resistance will result due to a subtherapeutic dose and inappropriate monotherapy. Furthermore, Epivir/Ziagen will be stored near Epivir on pharmacy shelves, thus increasing the risk of errors related to product selection. For example, if a prescription was correctly filled for "Epivir 150 mg twice daily, dispense #30", and a product selection error occurred resulting in a patient receiving Epivir/Ziagen instead of Epivir, this would result in the patient receiving twice the dose of Epivir as intended. DMETS' concerns are further heightened because four respondents in the written prescription studies and one respondent in the verbal studies identified the proposed drug name as Epivir. Additionally, two respondents identified the proposed name as Epivir with a numerical modifier following the name (Epivir 12 and Epivir 27), which could potentially be interpreted as number of tablets, and could result in a patient receiving an incorrect dose of the medication.

DMETS discourages the use of the proposed name Epivir/Ziagen for the combination drug product of lamivudine and abacavir. The use of these names for a combination drug product increases the risk of confusion and errors relating to product selection, product strength, as well as incorrect dose.

Writing Sample

Epivir HBV vs. Epivir/Ziagen

The image shows two handwritten samples of medication names. The first sample is 'Epivir HBV' and the second sample is 'Epivir/Ziagen'. The handwriting is somewhat cursive and the two samples are placed side-by-side to illustrate how they might be confused.

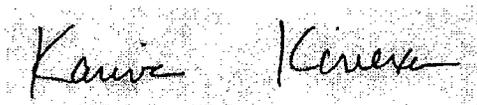
B. DMETS does not recommend the use of the proprietary name, Kivexa, due to its potential to look similar to the currently marketed drug product, Kariva.

Kariva has look-alike similarities to the proposed name, Kivexa (see below). Kariva contains desogestrel and ethinyl estradiol, and is indicated for the prevention of pregnancy. Both names consist of six letters, and have the same letter at the beginning of each name ("K"). The second and third letters ("ar" vs. "iv") in addition to the ending of the names ("iva" vs. "exa") can look similar when scripted. Kariva and Kivexa share an overlapping dosage form (tablet), route of administration (oral), and dosing regimen (once daily). Although Kariva has special packaging, both medications are packaged with a one month supply. Also, Kariva and Kivexa both are available in only one strength. Therefore, it is possible for a prescription to be written for either Kariva or Kivexa without a strength being indicated. For example, a prescription written for "Kivexa, one po daily, dispense a one month supply" may be misinterpreted as "Kariva, one po daily, dispense a one month supply", and vice versa. If Kivexa were misinterpreted as Kariva, and dispensed to a patient, this may result in an immuno-compromised patient not receiving potentially life saving medication. Should Kivexa be misinterpreted as Kariva, and dispensed to a patient, this may result in an unintentional pregnancy and alternations in hormones.

Additionally, the patient would be at risk for experiencing side effects associated with Kivexa such as headache, malaise, gastrointestinal upset, neuropathy, dizziness, and sleep disorders. DMETS believes that the look-alike similarities in the names, in addition to the similarities in dosage form, route of administration, and dosing regimen, increases the risk of confusion and error between Kariva and Kivexa .

Kariva

Kivexa

Handwritten signatures of the words "Kariva" and "Kivexa" in cursive script, positioned below their respective underlined printed versions.

Additionally, DMETS reviewed the package insert labeling from a safety perspective. There are no comments at this time.

RECOMMENDATIONS

- A. DMETS does not recommend the use of the proposed names, "Epivir/Ziagen" or "Kivexa".
- B. DMETS recommends that container labels and carton labeling be submitted for review and comment upon receipt.
- C. DDMAC finds proprietary the names "Epivir/Ziagen" and "Kivexa" acceptable from a promotional perspective.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-827-2335 if you have any questions regarding the contents of this transmission.

Tanima Sinha
Regulatory Project Manager
FDA/CDER
Division of Antiviral Drug Products

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

/s/

Tanima Sinha

2/13/04 03:09:51 PM

CSO

Abacavir sulfate/lamivudine name consult fax to sponsor.

Abacavir sulfate/lamivudine name consult fax to sponsor.

Rosemary Johann-Liang

2/13/04 03:12:33 PM

MEDICAL OFFICER



FILING REVIEW LETTER

NDA 21-652

GlaxoSmithKline
Attention: Martha Anne A. Moore, R.Ph.
Antiviral/Antibacterial US Regulatory Affairs
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Moore:

Please refer to your October 7, 2003 new drug application NDA 21-652 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for abacavir sulfate/lamivudine (ABC/3TC) combination tablet.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on December 7, 2003 in accordance with 21 CFR 314.101(a).

In our filing review, we have not identified any review issues; however, we request that the following information be provided to the Division.

MICROBIOLOGY:

- Please determine antiviral activity *in vitro* of abacavir and lamivudine for multiple isolates from each of the different clades of HIV-1 and for HIV-2.
- You agreed to examine *in vitro* drug combination activity analyses for drug interactions of ABC/3TC with all approved anti-HIV agents and submit results in early-mid 2004.
 - Please provide a statement on the *in vitro* combination activity relationship of abacavir and lamivudine to tenofovir (TNV) and emtricitabine (FTC), and ribavirin (for HCV coinfecting patients).
- You agreed to examine the cross-resistance profile of ABC/3TC against primary resistant isolates for each approved NRTI and NNRTI drug and a selected panel of PI resistant isolates. In addition, you will examine the antiviral activity of all approved NRTIs and NNRTIs against isolates containing major mutations observed in clinical trials of ABC/3TC, specifically M184V ± K65R, Y115F, and/or L74V. These results should be submitted in early-mid 2004.

CLINICAL PHARMACOLOGY:

- Please provide the completed analytical reports, including blood sample stability information, for Studies CNA10905 and CAL10001.

CLINICAL:

- For study CAL 10001 (Bioequivalence Study), there is only one study subject listed for concurrent medication section of the datasets. Please clarify if this is accurate.

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have any questions, please contact Tanima Sinha, M.S., Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

Debra Birnkrant
12/16/03 12:57:20 PM
NDA 21-652



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

45-DAY FILING MEETING MINUTES

NDAs: 21-652

DATE: November 19, 2003

DRUG: abacavir sulfate/lamivudine combination tablets

APPLICANT: GlaxoSmithKline (GSK)

PARTICIPANTS:	Debra Birnkrant, M.D.	Division Director
	Rosemary Johann-Liang, M.D.	Medical Team Leader
	Andrea James, M.D.	Medical Reviewer
	Ozlem Belen, M.D.	Medical Reviewer
	Kuei-Meng Wu, Ph.D.	Pharmacology/Toxicology Reviewer
	Zi Qiang Gu, Ph.D.	Chemistry Reviewer
	Jules O'Rear, Ph.D.	Microbiology Team Leader
	Lisa Naeger, Ph.D.	Microbiology Reviewer
	Greg Soon, Ph.D.	Statistics Team Leader
	Fraser Smith, Ph.D.	Statistics Reviewer
	Kellie Reynolds, Pharm.D.	Biopharmaceutics Team Leader
	Jenny H. Zheng, Ph.D.	Biopharmaceutics Reviewer
	Antoine El Hage, Ph.D.	Pharmacologist
	Tanima Sinha, M.S.	Regulatory Project Manager
	Virginia Yoerg	Regulatory Project Manager

BACKGROUND:

This new drug application has been submitted in support of GlaxoSmithKline's (GSK) drug abacavir sulfate/lamivudine combination tablet for use in the treatment of HIV-1 infected patients.

This NDA was submitted on October 7, 2003, and was received on October 8, 2003. GSK has submitted this NDA entirely in the common technical document (CTD) format.

CHEMISTRY (CMC):

This submission is fileable from the CMC perspective. There are no comments to convey at this time.

PHARMACOLOGY/TOXICOLOGY:

This submission is fileable from the Pharm/Tox perspective. There are no comments to convey at this time.

MICROBIOLOGY:

This submission is fileable from the Microbiology perspective. However, the following comments will be conveyed to the sponsor in the 74-day letter.

- Please determine antiviral activity *in vitro* of abacavir and lamivudine for the multiple isolates from each of the different clades of HIV-1 and for HIV-2.
- The sponsor has agreed to examine *in vitro* drug combination activity analyses for drug interactions of ABC/3TC with all approved anti-HIV agents and submit results in early-mid 2004.
 - Please provide a statement on the *in vitro* combination activity relationship of abacavir and lamivudine to TNV and FTC, and ribavirin (for HCV coinfecting patients).
- The sponsor has agreed to examine the cross-resistance profile of ABC/3TC against primary resistant isolates for each approved NRTI and NNRTI drug and a selected panel of PI resistant isolates. In addition, they will examine the antiviral activity of all approved NRTIs and NNRTIs against isolates containing major mutations observed in clinical trials of ABC/3TC, specifically M184V ± K65R, Y115F, and/or L74V. These results should be submitted in early-mid 2004.

CLINICAL PHARMACOLOGY:

This submission is fileable from the Biopharmaceutics perspective. However, the following comment will be conveyed to the sponsor in the 74-day letter.

- Please provide the completed analytical reports including blood sample stability information for Study CNA10905 and CAL10001.

CLINICAL:

This submission is fileable from the Clinical perspective. However, the following comment will be conveyed to the sponsor in the 74-day letter.

- For study CAL 10001 (Bioequivalence Study), there is only one study subject listed for concurrent medication section of the datasets. Please clarify if this is accurate.

DIVISION OF SCIENTIFIC INVESTIGATIONS:

This submission is fileable from the division of scientific investigations perspective. Please note that inspections for CNA30021 in support of this application will not be ordered because the same

pivotal study was used in support of sNDAs 20-977 (s-012) and 20-978 (s-014) and inspections have been requested through those sNDAs.

STATISTICS:

This submission is fileable from the statistical perspective. There are no comments to convey at this time.

CONCLUSION/ACTION ITEMS:

- This application is fileable and will be granted a standard review.
- The microbiology, clinical pharmacology and clinical comments will be sent to the sponsor in the 74-day letter.
- The PDUFA date is August 8, 2004.

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

/s/

Rosemary Johann-Liang
12/11/03 04:40:53 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-652

GlaxoSmithKline
Attention: Martha Anne A. Moore, R.Ph.
Antiviral/Antibacterial US Regulatory Affairs
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Moore:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Abacavir sulfate/Lamivudine Combination Tablet
Review Priority Classification:	Standard (S)
Date of Application:	October 7, 2003
Date of Receipt:	October 8, 2003
Our Reference Number:	NDA 21-652

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 8, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 8, 2004.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a

determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Division Document Room, N115
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Division Document Room, N115
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 21-652

Page 3

If you have any questions, please call Tanima Sinha, M.S., Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Anthony W. DeCicco, R.Ph.
Chief, Project Management Staff
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

Tony DeCicco
10/24/03 04:15:59 PM



IND 63,468

GlaxoSmithKline
Attention: Martha Anne A. Moore, R.Ph.
Antiviral Group, Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Moore:

Please refer to the meeting between representatives of your firm, GlaxoSmithKline (GSK) and the Food and Drug Administration/Division of Antiviral Drug Products (FDA/DAVDP) on July 30, 2003. The purpose of the pre-NDA meeting was to discuss clinical/statistical issues regarding your upcoming submission scheduled for the fall of 2003.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Tanima Sinha, M.S., Regulatory Project Manager, at 301-827-2335.

Sincerely yours,

{See appended electronic signature page}

Anthony W. DeCicco, R.Ph.
Chief, Project Management Staff
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure



Record of Industry Meeting

Date/Time: July 30, 2003, 1:30 PM EDT

Application: IND 63,468

Drug: Abacavir sulfate/Lamivudine combination tablets

Sponsor: GlaxoSmithKline (GSK)

Type of Meeting: Type B pre-NDA meeting to discuss clinical/statistics concerns.

Participants: **Attendees from DAVDP/DSPIDP:**

Jeffrey Murray, M.D.	Deputy Division Director
Russ Fleischer, PA-C, M.P.H.	Acting Team Leader-Medical Reviewer
Andrea James, M.D.	Medical Reviewer
Rosemary Johann-Liang, M.D.	Medical Reviewer (DSPIDP)
Kim Struble, Pharm.D.	Clinical Reviewer
Jules O'Rear, Ph.D.	Microbiology Team Leader
Lalji Mishra, Ph.D.	Microbiology Reviewer
Lisa Naeger, Ph.D.	Microbiology Reviewer
Ingrid Markovic, Ph.D.	Microbiology Reviewer
James Farrelly, Ph.D.	Pharmacology/Toxicology Team Leader
Kellie Reynolds, Pharm.D.	Clinical Pharmacology Team Leader
Jenny H. Zheng, Ph.D.	Pharmacology Reviewer
Anita Patel, Pharm.D.	Pharmacology Fellow
Greg Soon, Ph.D.	Statistics Team Leader
Fraser Smith, Ph.D.	Statistics Reviewer
Tanima Sinha, M.S.	Regulatory Project Manager

Attendees from GlaxoSmithKline:

Trevor Scott	Clinical Development
Jamie Hernandez	Medical Safety Monitor
Douglas Manion	Global TA Leader, HIV, R&D
Randall Lanier	Clinical Virology
Steve Weller	Clinical Pharmacologist
Amy Cutrell	Clinical Statistician
Henry Zhao	Clinical Statistician
David Gibbons	Epidemiologist
Alice White	Epidemiologist
David Cocchetto	Regulatory Affairs
Martha Anne Moore	Regulatory Affairs

Background

A request was made by GlaxoSmithKline (GSK) for a pre-NDA meeting with FDA/DAVDP to discuss the clinical/statistics issues for their upcoming NDA submission.

In the background package submitted on June 11, 2003, GSK posed questions regarding clinical/statistical concerns.

Slides were presented by GSK outlining regulatory history/milestones and a brief clinical summary for their abacavir sulfate/lamivudine combination tablet. Below are the questions that were discussed during the July 30, 2003 meeting.

For each discussion point, GSK's question/position is shown in bold font, followed by FDA/DAVDP's response in *italicized font*.

- 1. In view of the prospective discussions and understandings between GSK and DAVDP of the study design, patient selection criteria, endpoints and sample size in protocol CNA30021, does the Division agree that the results from study CNA30021 merit submission, acceptance for filing, and review of the New Drug Application (NDA) 21-652?**

DAVDP agreed that the results from study CNA30021 merit submission, however, determination whether the application is fileable is made at the 45-day filing meeting after the NDA is submitted to the Agency.

- 2. Do you agree that an NDA containing 48-week data from CNA30021, bioequivalence results from CAL10001 and plasma abacavir and intracellular carbovir triphosphate data from CNA10905 (as well as previously submitted studies on Ziagen and Epivir products providing evidence of durable antiviral effect) is a reasonable basis for requesting traditional approval for the new ABC/3TC tablet?**

DAVDP agreed that an NDA containing 48-week data from CNA30021, bioequivalence results from CAL10001 and plasma abacavir and intracellular carbovir triphosphate data from CNA10905 (as well as previously submitted studies on Ziagen and Epivir products providing evidence of durable antiviral effect) is a reasonable basis for requesting traditional approval for the new ABC/3TC tablet.

- 3. Does the review team agree with our proposal to examine the Trizivir Epidemiology program in support of the NDA for ABC/3TC tablet, as well as our proposal to expand the program to include the new ABC/3TC fixed-dose tablet?**

The DAVDP review team agreed with GSK's proposal to examine the Trizivir Epidemiology program in support of the NDA for ABC/3TC tablet, as well as your proposal to expand the program to include the new ABC/3TC fixed-dose tablet.

- 4. Given that the results of CNA30021, CAL10001 and CNA10905 (along with existing data on Ziagen and Epivir products that provide strong confirmatory evidence of the durability of effect of abacavir and lamivudine) and in view of the well-characterized nature of the HSR syndrome, we believe that a review of the data included in this NDA by the Antiviral Drugs Advisory Committee is not warranted. Do you agree?**

DAVDP agreed that a review of the data included in this NDA by the Antiviral Drugs Advisory Committee is not warranted given that the results of CNA30021, CAL10001 and CNA10905 (along with existing data on Ziagen and Epivir products that provide strong confirmatory evidence of the durability of effect of abacavir and lamivudine) and in view of the well-characterized nature of the HSR syndrome.

- 5. We are aware that NDAs receive a review classification after the Division receives the application and performs an initial review. We have provided our rationale for a Priority Review status determination for this new combination tablet product in Attachment 5 (Briefing Document), Appendix 8. We would benefit from your preliminary view of whether this NDA will receive a Standard or Priority review classification.**

DAVDP cannot make the final determination whether this NDA will receive a standard or priority review classification, however, it will most likely receive a standard review classification. The final decision is made at the 45-day filing meeting after the NDA is submitted to the Agency.

Following the discussion of the questions in GSK's background package, there was a brief discussion of GSK's protocol ESS30009. A protocol amendment was submitted by GSK to the Agency on July 29, 2003 terminating the tenofovir (TDF) + abacavir and lamivudine (ABC/3TC) fixed dose combination tablet arm. GSK stated they will analyze the data obtained from this arm and submit their findings.

DAVDP recommended that GSK address the high discontinuation rate (30%) in their submission, including whether this rate was abnormally high compared to other abacavir studies and what the reasons were for discontinuation.

There was a brief mention of a name for the abacavir sulfate/lamivudine combination tablet, with Epivir®/Ziagen® Tablet as GSK's first choice and Kivexa™ Tablets as a second choice. A formal submission will be sent shortly.

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

/s/

Jeffrey Murray
8/26/03 09:45:36 AM



IND 63,468

GlaxoSmithKline
Attention: Martha Anne A. Moore, R.Ph.
Antiviral Group, Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Moore:

Please refer to the teleconference between representatives of your firm, GlaxoSmithKline (GSK) and the Food and Drug Administration/Division of Antiviral Drug Products (FDA/DAVDP) on July 21, 2003. The purpose of the pre-NDA teleconference was to discuss chemistry, manufacturing and controls (CMC) and common technical document (CTD) format for the upcoming submission scheduled for the fall of 2003.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the teleconference outcomes.

If you have any questions, please call Tanima Sinha, M.S., Regulatory Project Manager, at 301-827-2335.

Sincerely yours,

{See appended electronic signature page}

Anthony W. DeCicco, R.Ph.
Chief, Project Management Staff
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure



Record of Industry Meeting

Date/Time: July 21, 2003, 2:00 PM EDT

Application: IND 63,468

Drug: Abacavir sulfate/Lamivudine combination tablets

Sponsor: GlaxoSmithKline (GSK)

Type of Meeting: Type B pre-NDA teleconference to discuss chemistry, manufacturing and controls (CMC) data and common technical document (CTD) format.

Participants: Attendees from FDA/DAVDP:

Debbie Birnkrant, M.D.	Division Director
Russ Fleischer, PA-C, M.P.H.	Acting Medical Team Leader
Andrea James, M.D.	Medical Reviewer
Kellie Reynolds, Pharm.D.	Pharmacokinetics Team Leader
Fraser Smith, Ph.D.	Statistics Reviewer
Steve Miller, Ph.D.	Chemistry Team Leader
Zi-Qiang Gu, Ph.D.	Chemistry Reviewer
Jules O'Rear, Ph.D.	Microbiology Team Leader
Lisa Naeger, Ph.D.	Microbiology Reviewer
Gary Gensinger	IT Specialist
Virginia Yoerg	Regulatory Health Project Manager
Tanima Sinha, M.S.	Regulatory Project Manager

Attendees from GlaxoSmithKline:

Trevor Scott, Ph.D.	Clinical
Amy Cutrell, M.S.	Statistics
Henry Zhao, Ph.D.	Statistics
Barbara Devens	Global Safety
Grace Pagano, M.S.	Regulatory
Martha Anne Moore, R.Ph.	Regulatory
Gary Goodson	Product Development
Sue Long, Ph.D.	Analytical chemist, product development
Jim Zisek, B.S.	CMC regulatory

Background

A request was made by GlaxoSmithKline (GSK) for a pre-NDA meeting with FDA/DAVDP to discuss chemistry, manufacturing and controls (CMC) data, as well as the general content and format of their upcoming NDA submission.

In the background packages submitted on June 11, 2003 and June 19, 2003, GSK posed questions regarding clinical, labeling, content, format and administration issues as well as chemistry, manufacturing and controls (CMC) data. Below are the questions that were discussed during the July 21, 2003 teleconference. The numbering below follows the order posed by GSK in their communications.

For each discussion point, GSK's question/position is shown in bold font, followed by FDA/DAVDP's response in *italicized font*.

Clinical

- 6. As results from only one pivotal clinical trial (CNA30021) are being submitted, do you agree that a separate Integrated Summary of Efficacy (ISE) and Safety (ISS) will not be required? The safety and efficacy information historically summarized in the ISS and ISE documents will be summarized in the Clinical Summaries of Efficacy and Safety as described in the CTD guidance (Module 2, Sections 2.7.3 and 2.7.4, respectively).**

DAVDP agrees that a separate Integrated Summary of Efficacy (ISE) and Safety (ISS) will not be required. DAVDP also agreed with the safety and efficacy information being summarized in the Clinical Summaries of Efficacy and Safety as described in the CTD guidance Module 2, Sections 2.7.3 and 2.7.4, respectively.

Labeling

- 1. Do you agree that the proposed approach to labeling issues is reasonable (i.e., Microbiology, Indications and Usage; Description of Clinical Studies and Adverse Reactions), as outlined in this document, including using VIREAD as the most recent example of the Division's thoughts on HIV labeling (Microbiology Section)?**

The following three pre-NDA microbiology comments were faxed to GSK on July 18, 2003.

Pre-NDA Microbiology Comments for GSK:

- Please provide in vitro drug combination activity analyses for drug interactions of ABC/3TC with all approved anti-HIV agents.*
- The cross-resistance profile of ABC/3TC should be provided showing the antiviral activity of ABC/3TC against resistant isolates for each approved anti-HIV drug.*
- In addition, information should be provided showing the antiviral activity of all approved NRTIs and NNRTIs against isolates resistant to ABC/3TC. Please describe the clinical resistance data that you plan to submit for ABC/3TC tablets. The DAVDP has a format and template for submitting HIV resistance data that can be sent to you.*

Microbiology data for ABC and ABC/3TC NDAs should be placed in Module 5 in the CTD under 5.3.5.4 "Other studies" using the heading in the link below. There should be a summary of the microbiology in module 2.

<http://www.fda.gov/cder/regulatory/ersr/5640comprhtocv3b.pdf>

Content, Format, and Administration

1. We will be submitting this NDA in the Common Technical Document (CTD) format.

- **Do you agree with our proposal to submit this application electronically? GSK intends to submit the entire archival copy of the NDA for ABC/3TC tablet in electronic format (with the exception of documents requiring an original signature), per the draft August 1, 2000 "Guidance for Industry – Submitting Marketing Applications According to the ICH-CTD Format – General Considerations."**

DAVDP agrees with GSK's proposal for this NDA to be submitted electronically, per the draft August 1, 2000 "Guidance for Industry – Submitting Marketing Applications According to the ICH-CTD format – General Considerations."

- **Do you anticipate the need for any paper review copies of components of this NDA? From GSK's perspective, as the company's and Division's familiarity and experience with e-submissions increases, our hope is that the need for paper review copies will diminish over time.**

As with the Ziagen Traditional approval submission, DAVDP anticipates the need for paper review copies.

2. GSK intends to submit the NDA for the ABC/3TC tablet in electronic format, per the January 1999 "Guidance for Industry – Providing Regulatory Submissions in the Electronic Format – NDAs." Do you agree?

DAVDP agrees with GSK's intention to submit the NDA for ABC/3TC tablet in electronic format, per the January 1999 "Guidance for Industry – Providing Regulatory Submission in the Electronic Format – NDAs."

3. As described in Attachment 5, Section 5 (Briefing Document – Summary of Proposals for NDA), do you agree with the following:

- **Safety data from ongoing clinical trials (GSK-sponsored and GSK-supported other trials) will be included in this submission from January 1, 2003 through May 31, 2003. Please note that via cross-reference, we will be incorporating safety data for Ziagen (most notably the sNDA for Traditional Approval) and Epivir to NDAs 20-977 and 20-564, respectively.**

DAVDP asked which trials GSK was referencing.

GSK stated that they were referring to the ones listed in the briefing document: GSK-sponsored and GSK-supported trials, ABC and 3TC together or alone, once daily. GSK will send a list of the studies in question. See Addendum.

- **We believe that the nonclinical databases previously submitted for both ABC and 3TC fully support this application for once daily dosing of ABC and 3TC. We propose no additional nonclinical data be submitted in support of this formulation and dosing regimen. Nonclinical data from Ziagen NDA 20-977 and Epivir NDA 20-564 will be included via cross-reference.**

DAVDP agrees with GSK's proposal that no additional nonclinical data be submitted in support of this formulation and dosing regimen.

- **We propose that the 120-Day Safety Update for this NDA submission be made four months (January 2004) after submission of the NDA (September 2003). The timeframe for inclusion of clinical trial data in this submission will be June 1, 2003 through October 31, 2003.**

DAVDP agrees with GSK's proposal that the 120-Day Safety Update for this NDA submission be made four months after submission of the NDA.

- **Use of the ABC/3TC tablets will not be recommended in adolescent and adult patients who weigh less than 40 kilograms. The fixed dose combination tablet cannot be dose reduced according to patient weight. Both Ziagen and Epivir are available as solutions for oral administration. We propose to provide no Pediatric Use data for this submission.**

DAVDP agrees with GSK's proposal to provide no Pediatric Use data for this submission.

4. **Do you agree with the overall content and format of the proposed NDA as summarized in Attachment 5, Section 6 (Briefing Document – CTD/Module Specific Proposals for the NDA for Traditional Approval)?**

DAVDP agrees with the overall content and format of the proposed NDA as summarized in Attachment 5, Section 6 (Briefing Document – CTD/Module Specific Proposals for the NDA Traditional Approval).

- **Does the review team agree with our proposal to describe hypersensitivity reaction as outline in Attachment 5 (Briefing Document), Section 6, Module/Section 1.8 (Risk Management) and Module/Section 2.7.4.2.1.5 (analysis of Adverse Events by Organ System or Syndrome)?**

The DAVDP review team agrees with GSK's proposal to describe hypersensitivity reaction as outlined in Attachment 5 (Briefing Document), Section 6, Module/Section 1.8 (Risk Management) and Module/Section 2.7.4.2.1.5 (analysis of Adverse Events by Organ or Syndrome).

5. **Do you agree that submission of case report forms from only pivotal clinical trial CNA30021 (deaths, discontinuations due to adverse events and suspected hypersensitivity reactions) is acceptable?**

DAVDP agrees with the submission of case report forms from only pivotal clinical trial CNA3002; however, DAVDP requested case reports from all discontinuations no matter the reason. If other case reports are needed for any reason, DAVDP will request them at that time.

6. **We propose to provide financial disclosure information from pivotal clinical trial CNA30021 and pivotal bioequivalence study CAL10001; financial disclosure data will not be provided from supportive pharmacokinetic study CNA10905 because it does not meet the definition of a "covered study." Do you agree?**

DAVDP agrees that financial disclosure data from the supportive pharmacokinetic study CNA10905 was not necessary because it does not meet the definition of a "covered study."

7. Does the Division believe it is of value to have a small team of GSK staff available to meet with the reviewers [approximately 30 days after submission] to facilitate their use of the electronic submission and discuss the CTD format?

FDA found the demonstration on navigation and use for the Ziagen Traditional approval very useful and would appreciate the same demonstration for this CTD submission.

Chemistry, Manufacturing and Controls (CMC)

Dr. Miller announced that Dr. Zi-Qiang Gu will be the review chemist for NDA 21-652.

1. Please indicate if the proposed _____ shelf-life for ABC/3TC Tablets is generally acceptable to the Agency, although it is of course contingent on satisfactory Agency review of the stability data aforementioned. Please also indicate if the timing of submission of the _____ update is acceptable to the Agency and will not trigger a review period extension.

2. In order to reduce the number of batch records provided in the NDA, our intention is to submit the executed batch record for Batch B060661. This batch serves as both a biobatch and a primary stability batch and the batch record is representative of the commercial process. It is our understanding that the Field Office is supportive of the approach of providing one representative batch record in cases such as this. Please indicate whether this proposal is acceptable to the Agency.

Regarding the proposal to include a single executed batch record for the drug product manufacturing process, it is acceptable to DAVDP to include only the record for batch B060661, which is both the biobatch and one of the primary stability batches.

DAVDP additional comments on manufacturing facilities:

1. *DAVDP recommends that the facilities involved in commercial manufacture, packaging and testing of the drug product be included in section P.3.1 (Manufacturers). Facilities that were employed during the IND and NDA phases, but which are not intended to be used post-approval may be listed in other relevant sections of the application if appropriate (e.g.,*

_____ > Alternately, if GSK wants to include these facilities in section P.3.1, please clearly indicate in that section what their responsibilities are and whether they will be used after approval.

2. Please list the site where abacavir sulfate was manufactured for the batches that were used to produce the primary tablet stability batches. On page 3 of the June 19, 2003 briefing package, the abacavir sulfate source for the third full-scale batch of tablets (which will have 3-months of stability data) was listed as _____ and it was unclear if that was different from the other stability batches.

GSK clarified during the teleconference that the abacavir drug substance used to manufacture the three primary stability lots of abacavir sulfate/lamivudine tablets were synthesized at the _____ facility.

DAVDP agrees that this is an appropriate plan (low potential that site of abacavir manufacture would affect stability of abacavir sulfate/lamivudine tablets; _____ was approved for abacavir sulfate synthesis in April 2003).

Addendum

A list of the ongoing GSK-sponsored and GSK-supported studies for the abacavir sulfate/lamivudine tablet NDA was provided by GSK via email communication after the conference call.

Studies that include either ABC QD, 3TC QD or ABC QD + 3TC QD:

GSK sponsored:

1. CAL30001
2. ESS30008
3. ESS30009

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

/s/

Debra Birnkrant
8/5/03 10:20:04 AM



IND 63,468

GlaxoSmithKline
Attention: Martha Anne A. Moore, R.Ph.
Antiviral Group, Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Moore:

We received your May 9, 2003 correspondence on May 12, 2003 requesting a meeting to discuss and agree on the format and content of your NDA submission as well as to discuss chemistry, manufacturing, and controls (CMC) data. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

- Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.
- Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].
- Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at <http://www.fda.gov/cder/guidance/2125fnl.htm>.

You requested a Type B meeting. The teleconference is scheduled for:

Date: 21 July 2003
Time: 2:00 – 3:30 p.m.

Division of Antiviral Drug Products participants:

Debra Birnkrant, MD	Division Director
Jeffrey Murray, MD	Deputy Division Director
Anthony DeCicco, RPh	Chief, Regulatory Project Manager
Andrea James, MD	Medical Reviewer
Russell Fleischer, PA-C, MPH	Acting Medical Team Leader
Rao Kambhampati, PhD	Chemistry Reviewer
Steve Miller, PhD	Chemistry Team Leader

Lalji Mishra, PhD	Microbiology Reviewer
Julian O'Rear, PhD	Microbiology Team Leader
Derek Yuanchao Zhang, PhD	Pharmacokinetics Reviewer
Kellie Reynolds, Pharm D	Pharmacokinetics Team Leader
Fraser Smith, PhD	Statistics Reviewer
Guoxing Soon, PhD	Statistics Team Leader
Kuie-Meng Wu, PhD	PharmTox Reviewer
James Farrelly, PhD	PharmTox Team Leader
Tanima Sinha, MS	Regulatory Project Manager
Virginia Yoerg	Regulatory Health Project Manager

Please provide the background information for this meeting at least one month prior to the meeting. If we do not receive it by June 21, 2003, we may need to reschedule the teleconference. The agenda for the meeting is as follows:

2:00 – 2:30 common technical document (CTD) format
2:30 – 3:30 chemistry, manufacturing and controls (CMC) data.

If you have any questions, please call me at 301-827-2335.

Sincerely,

{See appended electronic signature page}

Tanima Sinha, MS
Regulatory Project Manager
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

Tony DeCicco
6/10/03 11:53:29 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-652	Efficacy Supplement Type	Supplement Number
Drug: EPZICOM (Abacavir sulphate and lamivudine) Tablets		Applicant: GlaxoSmithKline
RPM: Tanima Sinha, M.S.		HFD-530 Phone # (301) 827-2335
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		SE2
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> 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.		
		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		N/A
N/A, since only applicable to 505(b)(2)		
• 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).		<input type="checkbox"/> 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)	✓
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)	✓
• 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	N/A
• 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 meetings	✓
• Pre-Approval Safety Conference	N/A
• Other (45 day filing meeting minutes, etc.)	✓

❖ 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 (<i>NME approvals only</i>)	N/A
❖ Statistical review	✓
❖ Biopharmaceutical review	✓
❖ Controlled Substance Staff review(s) and recommendation for scheduling	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	✓
• Bioequivalence studies	✓
CMC Information	
❖ CMC review	✓
❖ Environmental Assessment	
• Categorical Exclusion	N/A
• 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	() Completed () Requested () Not yet requested N/A (SE7)
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

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

/s/

Virginia Behr
8/12/04 11:58:47 AM