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:

Please refer to your new drug application (NDA) dated October 7, 2003, received October 8, 2003 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EPZICOM™ [abacavir sulfate (equivalent to 600 mg abacavir) and lamivudine (300 mg)] fixed dose combination Tablets.

We acknowledge receipt of your submissions dated:

October 7, 2003	April 30, 2004	June 30, 2004 (5)
October 30, 2003	May 02, 2004	July 02, 2004
November 14, 2003	May 07, 2004	July 06, 2004
November 21, 2003 (2)	June 08, 2004	July 08, 2004
November 24, 2003	June 14, 2004 (2)	July 09, 2004
January 19, 2004	June 16, 2004 (2)	July 14, 2004
February 25, 2004	June 17, 2004	July 22, 2004
March 02, 2004	June 18, 2004 (2)	July 29, 2004
March 11, 2004	June 24, 2004	July 30, 2004 (3)
April 19, 2004	June 25, 2004 (2)	August 2, 2004 (4).

This new drug application provides for the use of EPZICOM™ Tablets, dosed once daily in combination with other antiretroviral agents for the treatment of HIV-1 infection.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, Medication Guide, and Warning Card). Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this

submission "**FPL for approved NDA 21-652**." Approval of this submission by FDA is not required before the labeling is used.

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. We are waiving the pediatric study requirement for ages less than three months and deferring pediatric studies for ages 3 months to 17 years for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients ages three months to 17 years.

   Final Report Submission: December 31, 2007.

   Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated "**Required Pediatric Study Commitments**".

In addition we remind you of your postmarketing study commitments in your submission dated July 30, 2004, which are listed below.

2. Assess baseline and failure RT resistance mutations and failure phenotypes of HIV-1 isolates from patients who experience virologic failure in clinical study CAL30001, a study comparing 600mg once daily abacavir vs. 300mg twice daily abacavir (in combination with other drugs). Submit an analysis of genotypic and phenotypic results of study CAL30001 and submit these data in Division of Antiviral Drug Products (DAVDP's) HIV Resistance Template Format.

   Timeline: Submit results of these assessments within 12 months of the date of this letter.

3. Assess phenotypes for baseline HIV-1 isolates from all patients in clinical study CAL30001, a study comparing 600mg once daily abacavir vs. 300mg twice daily abacavir (in combination with other drugs). Submit phenotypic data in DAVDP's HIV Resistance Template Format.

   Timeline: Submit results within 18 months of the date of this letter.

4. Draft a "Dear Healthcare Provider" letter for submission to DAVDP for review and comment, followed by distribution of this letter soon after approval of this product. As in previous letters to healthcare providers, the draft letter should encourage providers to report hypersensitivity reactions and provide telephone numbers and other contact information for reporting reactions to GlaxoSmithKline and MedWatch.

   Timeline: Submit a draft letter to DAVDP for review and comment within 15 days of the date of this letter.

5. Evaluate practical aspects of use of the Medication Guide and Warning Card in order to obtain information on the utility of these sources of information for patients. Specific questions to be addressed in a study are (a) Do patients receive the Medication Guide and Warning Card? (b) Do patients read the Medication Guide and Warning Card? (c) Do patients understand why they receive a Medication Guide and Warning Card? (d) Do patients take action (e.g., ask their doctor or pharmacist follow-up questions) based on the Medication Guide and Warning Card?
   a. Submit a proposal for this evaluation to DAVDP within 6 months of the date of this letter
   b. Submit a final report within 30 months of the date of this letter.

6. Conduct a multifaceted educational program to communicate the important risk information about potential hypersensitivity reactions to abacavir. Specific activities within this multifaceted educational program are listed below.
   a. Introduce EPZICOM™ (abacavir/lamivudine) Tablet with the following activities directed to clinical investigators in future GSK-sponsored clinical studies on the abacavir/lamivudine tablet:
      i. Protocols will include language describing the diagnosis and management of abacavir-related hypersensitivity reactions, consistent with information in FDA-approved labeling.
      ii. Studies will continue to use a standard Case Report Form Module to facilitate collection of standardized information on cases of HSR.
      iii. All pre-study meetings with clinical investigators will include a discussion on reporting of adverse events, including attention to timely detection and reporting of hypersensitivity reactions.

   b. Introduce EPZICOM™ Tablet into US distribution channels with the following items intended for use by health care professionals with patients:
      i. FDA-approved Medication Guide
      ii. FDA-approved Warning Card
      iii. A Patient Brochure providing general information on HIV infection and product-specific information on the abacavir/lamivudine tablet.
      iv. Pads of tear-off sheets showing the full text of the Warning Card plus statements to highlight the names of three different products (ZIAGEN®, TRIZIVIR® and EPZICOM™) containing abacavir.

   c. Prepare and make available a slide kit, entitled "What You Need to Know About ZIAGEN®, TRIZIVIR®, EPZICOM™ and the Abacavir in Them". The audience for this slide kit is patients and the slide kit will be offered to community organizations and health care providers for use with patients. The proposed slide kit will be submitted to DDMAC for review and comment after the final labeling is approved by DAVDP.

   d. Organize and host a teleconference intended to provide information to patient community organizations for people living with HIV infection: This teleconference will occur after approval and prior to commercial availability of the product. The purpose of the teleconference is to summarize key information about this new product, including its abacavir content and contraindication for use in any patient with a history of hypersensitivity to abacavir.

   Timeline: Submit an annual summary of the above educational programs concurrent with the deadline for the NDA Annual Report on the first and second anniversaries of the date of this letter.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these post marketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Antiviral Drug Products and two copies of both the promotional materials and the package insert, Medication Guide and Warning Card directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please note that the stability data presented in the application for this approval support the use of EPZICOM™ in the ICH Climatic Zones I and II.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Sincerely yours,

{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

Enclosure: Approved Draft Labeling (Package Insert, Medication Guide and Warning Card)

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
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