CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-205

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-205

Glaxo Wellcome Inc.
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 your new drug application, NDA 21-205 dated December 16, 1999, received December 17, 1999, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Trizivir™ (abacavir sulfate, lamivudine, and zidovudine) Tablets.

Your submission dated September 13, 2000, received September 14, 2000 constitutes a complete response to our June 9, 2000 action letter. The user fee goal date is November 14, 2000.

Further, we acknowledge receipt of your submissions dated: August 3, 2000, August 22, 2000, October 27, 2000, November 8, 2000 (2), and November 10, 2000.

This new drug application provides for the use of Trizivir either alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection.

We have completed the review of this application, as amended, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to demonstrate that TRIZIVIR is safe and effective for use as recommended in the agreed upon draft labeling text dated November 14, 2000. Accordingly, this application is approved under 21 CFR 314 Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the submitted labeling (text for the package insert dated November 14, 2000, text for the Medication Guide and Warning Card dated November 14, 2000 and immediate containers and carton labels dated September 13, 2000). Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten copies on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format-NDAs* (January 1999). For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 21-205. Approval of this submission by FDA is not required before the labeling is used.

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ON ORIGINAL

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your responsibility to conduct post-marketing studies under Subpart H for NDA 20-977 and NDA 20-978 for ZIAGEN (abacavir sulfate) as specified in the December 17, 1998 approval letter for these NDAs.

In addition, we reference the outstanding Phase 4 commitments for ZIAGEN (abacavir sulfate) as specified in the December 17, 1998 approval letter. Further, we note the following Phase 4 commitments for TRIZIVIR, specified in your submission dated November 14, 2000. These commitments include:

1. The applicant will conduct a postmarketing epidemiological program that will compare rates of hypersensitivity (HSR), HSR-associated rechallenge, HSR-associated hospitalization, and HSR-associated death in patients receiving Trizivir Tablets compared to Ziagen products. This program will be conducted in accordance with the protocols, data analysis plan, and plan for periodic updates as submitted to us by Glaxo Wellcome on November 8, 2000.

   Anticipated timeframe for completion: It is anticipated that the epidemiologic program for Trizivir will be ongoing for a minimum of 3 years based upon the expected numbers of patients being enrolled. Summaries of accumulated data will be submitted following the biannual review, with the first review planned for six months after the date of this letter.

2. The applicant acknowledges the need to incorporate a fifth database in their epidemiologic program as discussed during the October 25, 2000 telephone conference. The applicant will contact appropriate investigators for databases capturing health care data on prescriber and patient populations of special interest (i.e., non-HIV specialists and marginalized patients), working to identify the research questions that can be answered from each database, and identifying any limitations of each database.

   Anticipated timeframe for completion: The applicant will submit the results of this effort, along with their recommendation on how to proceed, no later than February 15, 2001.

In addition, the applicant has agreed to submit any labeling supplements that revise safety information contained in the abacavir, COMBIVIR, lamivudine, or zidovudine labeling to the Trizivir NDA 21-205, so that the changes to these labels may be considered for inclusion in the Trizivir labeling.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

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We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of dissemination of the labeling or initial publication of the advertisement.

Validation of the regulatory methods has not been completed. At present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

Please submit one market package of Trizivir tablets when it is available.

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). We note that at this time you have fulfilled the requirements of 21 CFR 314.55 for adolescents. We are waiving the requirement for studies in pediatric patients from birth to 12 years of age because TRIZIVIR is a fixed-dose combination tablet that is inappropriate for use in this pediatric age group.

We remind you that you must comply with the requirement for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Ms. Melissa M. Truffa, R.Ph., Regulatory Project Manager, at (301) 827-2335.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

/s/

Deborah Birnkrant
11/14/00 03:05:22 PM

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APPROVABLE LETTER

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Rockville MD 20857

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

JUN 9 2000

Dear Ms. Moore:

Please refer to your new drug application, NDA 21-205 dated December 16, 1999, received December 17, 1999, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Trizivir™ (abacavir sulfate, lamivudine, and zidovudine) Tablets.

Your User Fee Date is June 17, 2000.

We acknowledge receipt of your submissions dated:

November 3, 1999	March 17, 2000	May 1, 2000
March 6, 2000	March 27, 2000	May 11, 2000
March 8, 2000	April 17, 2000	May 23, 2000
March 16, 2000	April 28, 2000	June 2, 2000

We have completed the review of this application, as amended, and have concluded that Trizivir™ (abacavir sulfate/lamivudine/zidovudine) for the treatment of HIV-1 infection either alone or in combination with other antiretroviral agents is approvable under 21 CFR 314 Subpart H. Before this application may be approved, it will be necessary for you to adequately address the following deficiencies:

1. You will be required to conduct a prospective postmarketing epidemiological study that will compare rates of hypersensitivity, rechallenge, and death occurring in ZIAGEN and TRIZIVIR recipients. This study is being required to address our concern that TRIZIVIR may be used by health care providers and patients who are less familiar with the adverse event profile of abacavir and that such use may increase the incidence of fatalities due to hypersensitivity reactions. Prior to an approval action on NDA 21-205, you are required to:

   a. Submit and obtain agreement on the study protocol.

   b. Provide evidence that study centers and investigators have been engaged to conduct the study, and that the study will be initiated at the time of product launch.

   c. Provide a plan to submit interim reports of information collected during the course of this study.

   d. Submit a timeframe for providing the final study report.

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As discussed during the June 6, 2000 teleconference, the Division of Antiviral Drug Products (DAVDP) is available to provide guidance on the specific design elements of the study.

Additionally, in this teleconference, you indicated interest in the development of educational aids, such as video presentations, to provide prescribers with information regarding the safe use of TRIZIVIR. We encourage development of educational aids or other risk management approaches, and we are interested in reviewing your proposals.

2. In addition, you are required to submit revised draft/final printed labeling that will satisfactorily address all outstanding labeling issues. Our current comments regarding the TRIZIVIR package insert and Medication Guide are enclosed. Specifically:

   a. The TRIZIVIR package insert should reflect all important information from the relevant approved product labels and should exclude any wording that is not contained in the currently approved labeling for these products, except as supported by NDA 21-205 and agreed upon by DAVDP, or as specifically requested by the DAVDP.

   b. To facilitate review of the TRIZIVIR label, you should provide the labels for each of the approved products upon which the TRIZIVIR label is based. These labels should indicate the wording from each label included in the TRIZIVIR label.

   c. New safety information, currently under review for the ZIAGEN package insert, should be included in the TRIZIVIR label.

If additional information relating to the safety or effectiveness of TRIZIVIR becomes available, revisions of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Ms. Melissa M. Truffa, R.Ph., Regulatory Project Manager, at (301) 827-2335.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

/S/

Heidi M. Jolson, M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

Concurrence:
HFD-530/DepDir/Birnkrant 6/9/00
HFD-530/TLMO/Cvetkovich 6/7/00
HFD-530/MO/Martin 8 JUN 00
HFD-530/MicroTL/Connors 9 Jun 00
HFD-530/Micro/Mishra 6/7/00
HFD-530/PharmTL/Farrell 6/8/00
HFD-590/Pharm/Verma 6/9/2000
HFD-530/ChemTL/Miller 6/8/00
HFD-530/Chem/Kambhampati 6/9/2000
HFD-530/Stat/Hammerstrom 6/9/2000
HFD-530/StatTL/Aras 6/7/00
HFD-530/BiopharmTL/Reynolds for 6/9/00 KSR 6/9/00
HFD-530/Biopharm/Rajagopalan 6/9/00
HFD-530/SCSO/DeCicco 6.8.00
HFD-530/CSO/Truffa 6/8/00

cc:
Original NDA 21-205
Division File
HFD-002/ORM
HFD-104/Office File
HFD-094/DDMS
District Office
HFD-530/Cvetkovich
HFD-530/Martin
HFD-530/Jolson
HFD-530/Rajagopalan
HFD-530/Reynolds
HFD-530/Mishra
HFD-530/Truffa
HFD-40/DDMAC/Redman

Drafted by: Truffa/June 6, 2000
Initialed by:
Final:
Filename: V:DAVDP/CSO/Truffa/NDA/NDA21205/Letters/Aeltr

APPROVABLE (AE)

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ON ORIGINAL

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FINAL PRINTED LABELING