CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-003 / 21-004

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 21-003

Food and Drug Administration
Rockville MD 20857

DEC 8 1998

Glaxo Wellcome
Attention: David M. Cocchetto, Ph.D.
Group Director, Regulatory Affairs
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709

Dear Dr. Cocchetto:

Please refer to your new drug application (NDA) dated June 24, 1998, received June 25, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Epivir®-HBV™ (lamivudine) Tablets.

We acknowledge receipt of your submissions dated

June 29, 1998	July 6, 1998	July 29, 1998
July 30, 1998	August 28, 1998	September 8, 1998
October 23, 1998	November 13, 1998	November 17, 1998
November 23, 1998	November 25, 1998	December 3, 1998

This new drug application provides for the use of Epivir-HBV (lamivudine) Tablets for the treatment of chronic hepatitis B associated with evidence of hepatitis B viral replication and active liver inflammation.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted December 3, 1998 with the deletion of proposed virologic references numbered 1 and 2, as agreed during teleconference on December 8, 1998; immediate container and carton labels submitted November 17, 1998). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-003." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submission dated December 3, 1998 and as discussed during telephone conversations on December 7, 1998 and December 8, 1998. These commitments, along with any completion dates agreed upon, are listed below.

1. Continue to conduct studies of lamivudine involving various subpopulations of patients with chronic hepatitis B, including patients who are candidates for liver transplant, patients with decompensated liver disease, HIV/HBV co-infected patients, and at-risk ethnic groups (especially, Asians and African-Americans).

2. Continue to study the safety and efficacy of lamivudine in pediatric patients with chronic hepatitis B.

3. Establish a pregnancy registry to collect information on maternal-fetal outcomes of pregnant women exposed to lamivudine. The existence of this pregnancy registry and the telephone contact number for practitioners will be included in the package insert.

4. Conduct further evaluations of virologic breakthrough during treatment with lamivudine and genotypic mutations associated with reduced susceptibility of HBV to lamivudine.

5. Conduct further analysis on data from ongoing clinical studies of the patterns of changes in hepatic function tests around the time of HBeAg seroconversion. In addition, Glaxo Wellcome will continue to assess posttreatment changes in liver function test.

6. Conduct studies to assess long-term outcomes (i.e., clinically decompensated cirrhosis, hepatocellular carcinoma, and death) of patients treated with lamivudine.

7. Complete additional studies to further evaluate the optimal duration of treatment with lamivudine in patients with chronic hepatitis B.

8. Collaborate with others to study potential combination therapies for patients with chronic hepatitis B.

9. Explore the feasibility of assessing the effects of lamivudine on maternal-fetal transmission of HBV.

10. Draft a Patient-Oriented Brief Summary for Epivir-HBV products for submission to the reviewing Division by the end of March, 1999.

11. Submit labeling supplements for Epivir products covered under NDAs 20-564 and 20-596 to provide consistency of information in the package inserts for different products containing lamivudine and to ensure appropriate differentiation between Epivir and Epivir-HBV.

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 314.82(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."

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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

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

If you have any questions, contact Anthony M. Zeccola, Regulatory Management Officer, at (301) 827-2335.

Sincerely,

/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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 21-004

Food and Drug Administration
Rockville MD 20857

DEC 8 1998

GlaxoWellcome
Attention: David M. Cocchetto, Ph.D.
Group Director, Regulatory Affairs
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709

Dear Dr. Cocchetto:

Please refer to your new drug application (NDA) dated June 29, 1998, received June 30, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Epivir®-HBV™ (lamivudine) Oral Solution.

We acknowledge receipt of your submissions dated

July 6, 1998	July 29, 1998	August 28, 1998
October 23, 1998	November 17, 1998	November 23, 1998 (2)
November 30, 1998	December 3, 1998	

This new drug application provides for the use of Epivir-HBV (lamivudine) Tablets for the treatment of chronic hepatitis B associated with evidence of hepatitis B viral replication and active liver inflammation.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

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We remind you of your Phase 4 commitments specified in your submission dated December 3, 1998 and as discussed during telephone conversations on December 7, 1998 and December 8, 1998. These commitments, along with any completion dates agreed upon, are listed below.

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Validation of the regulatory methods has not been completed. At the 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 problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

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Sincerely,

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