CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-977 + 20-978

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-977
NDA 20-978

DEC 17 1998

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 June 24, 1998, new drug applications, NDA 20-977 and NDA 20-978 submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Ziagen™ (abacavir sulfate), 300mg Tablets and 20mg/mL Oral Solution.

We acknowledge receipt of your submissions dated:

March 27, 1998
April 15, 1998
April 28, 1998
May 18, 1998
June 3, 1998
July 10, 1998
August 7, 1998
August 28, 1998
August 31, 1998
September 15, 1998
October 1, 1998
October 2, 1998
October 8, 1998
October 9, 1998 (2)
October 12, 1998
October 13, 1998
October 15, 1998 (2)
October 16, 1998
October 20, 1998
October 28, 1998
October 29, 1998
October 30, 1998 (2)
November 4, 1998
November 9, 1998
November 10, 1998
November 12, 1998
November 13, 1998
December 1, 1998 (2)
December 3, 1998
December 4, 1998
December 10, 1998
December 14, 1998
December 15, 1998
December 16, 1998
December 17, 1998

These new drug applications provide for the use of Ziagen (abacavir sulfate), in combination with other antiretroviral agents, for the treatment of HIV-1 infection.

We have completed the review of these applications, as amended, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to approve Ziagen (abacavir sulfate) 300mg tablets and 20mg/mL oral solution for use as recommended in the draft label dated December 17, 1998. Accordingly, these applications are approved under 21 CFR 314 Subpart H. Approval is effective on the date of this letter. Marketing of these drug products 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 enclosed labeling (text for the package insert, text for the medication guide and text for the warning card). 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 sixteen 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 copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-977 and approved NDA 20-978. Approval of this submission by FDA is not required before the labeling is used.

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 as specified in your submission dated December 15, 1998, in which you agreed to submit the results of three 48-week studies of the safety and efficacy of abacavir sulfate to support traditional approval. Two of these studies are currently underway: study CNAA3006, a 48 week study in therapy-experienced pediatric patients, and study CNAAB3005, a 48-week equivalence study in treatment-naïve adults. Additionally, in response to comments raised at the November 2, 1998 Advisory Committee meeting regarding the adequacy of your traditional approval package, we acknowledge your November 4, 1998, commitment to conduct a third study to support traditional approval of abacavir sulfate. We further acknowledge your submission of December 15, 1998, which confirms that a draft protocol for this third study will be submitted by the end of March 1999 with the intention to initiate the study in the second quarter of 1999.

Final study reports should be submitted to this NDA as a supplemental application. For administrative purposes, all submissions relating to the Subpart H commitment must be clearly designated "Subpart H ".

In addition, we note the following Phase 4 commitments, specified in your submission dated December 17, 1998. These commitments, along with any completion dates agreed upon, include:

1. Glaxo Wellcome (GW) agrees to provide a proposal for a comprehensive plan to study abacavir sulfate hypersensitivity reactions. GW commits to provide plans with the following components, within the timeframes specified below.

    a. Prior to accelerated approval, GW agrees to the inclusion of a toll-free 1-800 number in the abacavir sulfate physician's labeling to facilitate reporting of post-marketing hypersensitivity reactions.
    b. As an ongoing effort beginning immediately after accelerated approval, GW agrees to conduct a review of the safety-related information in the professional labeling, Medication Guide, and Warning Card in order to assure that such labeling remains current and effectively conveys the importance of the warnings.
    c. Within 45 days after accelerated approval, GW agrees to submit a draft protocol for a prospective, population-based epidemiologic study to evaluate abacavir hypersensitivity reactions. GW additionally agrees to continue to collect and describe abacavir hypersensitivity reactions occurring in ongoing clinical trials.
    d. Within 60 days after accelerated approval, GW agrees to submit a proposal for the study of the biologic mechanism/immunologic basis of hypersensitivity reactions to abacavir sulfate.

e. Within 60 days after accelerated approval, GW agrees to submit a concept sheet for a labeling comprehension study for subjects reading the Medication Guide and Warning Card. Following consultation with experts, Glaxo Wellcome will submit a complete protocol for this study under [redacted].

2. Glaxo Wellcome agrees to continue to study and submit reports on the following:

   a. The safety and efficacy of abacavir sulfate used in combination with other antiretroviral agents.
   b. The role of abacavir sulfate in therapy experienced patients.
   c. The available information on the management of rash developing in patients who are being treated with multiple antiretroviral agents (including protease inhibitors and non-nucleoside reverse transcriptase inhibitors) and other commonly used drugs (e.g. TMP/SMX) that may cause rash.

3. Glaxo Wellcome agrees to conduct the following pharmacokinetic studies and submit the resulting reports:

   a. Evaluation of abacavir in neonates. Please note that this Phase 4 commitment does not constitute a Pediatric Written Request.
   b. Evaluation of abacavir in adults with hepatic impairment.
   c. Evaluation of abacavir in adolescent patients.

4. Glaxo Wellcome agrees to include with the submission for traditional approval of abacavir sulfate an evaluation of safety, efficacy and pharmacokinetics of abacavir in women and minorities.

5. Glaxo Wellcome agrees to complete and submit the results of resistance and cross-resistance assessments from ongoing GW-sponsored clinical studies.

6. Glaxo Wellcome agrees to complete the ongoing carcinogenicity studies and submit reports of the studies in a timely manner.

7. Glaxo Wellcome agrees to submit biannual reports on the rate of clinical endpoints by treatment group from ongoing clinical trials.

In addition to the reports of studies conducted in support of traditional approval, GW agrees that the traditional approval package for Ziagen will include final reports of completed studies and reports of the status of ongoing studies for all trials referenced in the Phase 4 commitments numbers 1-7 above. Study results that become available before the traditional approval submission may be submitted individually, and the traditional approval package may incorporate by reference any complete study reports already submitted.

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."

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 the drug when it is available.

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 Health Manager, at (301) 827-2335.

Sincerely yours,

/S/

M. Dianne Murphy, M.D.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD

To: Martha Anne Moore, R.Ph.

Fax Number: (919) 483-5756

Date: 12-17-98

Company: Glaxo Wellcome, Inc.

No. of pages (including cover): 5

Message: Martha Anne,

Congratulations!!!!! Happy birthday to Ziagen a mighty fine day to be approved.

Melissa

From: Melissa M. Truffa, R.Ph. /S/

Telephone: (301) 827- 2418

Fax Number: (301) 827-2471

Mail:
Division of Antiviral Drug Products
5600 Fishers Lane (HFD-530)
Rockville, Maryland 20857

Courier:
Division of Antiviral Drug Products
HFD-530
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

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Division of Antiviral Drug Products
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Concurrence:
HFD-530/Dir/Jolson 12/17/98
HFD-530/DepDir/Birnkrant 12/17/98
HFD-530/SMO/Kukich 12/16/98
HFD-530/MD/Cvetkovich 12/16/98
HFD-530/MicroTL/Connors 12/14/98
HFD-530/Micro/Mishra 12/15/98
HFD-530/PharmTL/Farrelly 12/15/98
HFD-590/Pharm/McMaster 12/14/98
HFD-530/ChemTL/Miller 12/14/98
HFD-530/Chem/Kambhampati 12/16/98
HFD-830/CChen 12/15/98
HFD-530/BiopharmTL/Reynolds 12.14.98
HFD-530/Biopharm/Rajagopalan 12-16-98
HFD-530/SCSO/DeCicco 12/14/98
HFD-530/CSO/Truffa 12/14/98
HFD-104/Kweder
HFD-104/Hassall
HFD-530/Dpty Dir/Dempsey 12/16/98

cc:
Original NDA 20-977 and NDA 20-978
Division File
HF-2/MedWatch (with draft/final labeling)
HF-2/Lumpkin
HFD-104 (with draft/final labeling)
OFFICE FILE (with draft/final labeling)
HFD-40 (with draft/final labeling)
HFD-613 (with draft/final labeling)
District Office
HFD-830/CChen
HFD-530/Cvetkovich
HFD-530/Kukich
HFD-530/Jolson
HFD-530/Rajagopalan
HFD-530/Mishra
HFD-590/McMaster
HFD-530/Elashoff
HFD-530/Truffa

Drafted by: Truffa/December 1, 1998
Initialed by:
final:

APPROVAL under Subpart H (AP) (Subpart H Phase 4 Commitments)

Approved labeling accurately reflects study results.
Concurrence:
HFD-725/StatTL/Flyer JF 12/16/98
HFD-725/Stat/Elashoff MRE 12/16/98