# CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-007
21-039

## APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-007
NDA 21-039

APR 15 1999

Glaxo Wellcome Inc.
Attention: Robert Watson
Antiviral Group- Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

Dear Mr. Watson:

Please refer to your October 15, 1998 new drug application, NDA 21-007, for Agenerase™ (amprenavir), 50mg and 150mg Capsules and to your December 7, 1998 new drug application, NDA 21-039, for Agenerase™ (amprenavir) 15mg/mL Oral Solution submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act.

We acknowledge receipt of your submissions dated:

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|---|---|---|---|
| May 29, 1998 | November 23, 1998 | January 15, 1999 | March 16, 1999 |
| June 15, 1998 | November 24, 1998 | January 18, 1999 | March 18, 1999 (2) |
| July 27, 1998 | December 2, 1998 | January 26, 1999 | March 24, 1999 |
| August 31, 1998 (2) | December 4, 1998 | January 28, 1999 (2) | March 26, 1999 |
| September 28, 1998 | December 7, 1998 | February 1, 1999 (2) | March 29, 1999 |
| October 1, 1998 | December 9, 1998 (2) | February 2, 1999 | March 30, 1999 |
| October 12, 1998 | December 11, 1998 | February 15, 1999 | March 31, 1999 |
| October 28, 1998 | December 15, 1998 | February 18, 1999 | April 1, 1999 |
| November 12, 1998 | December 16, 1998 | February 22, 1999 (2) | April 2, 1999 |
| November 16, 1998 | December 22, 1998 (2) | February 26, 1999 | April 5, 1999 |
| November 19, 1998 | January 11, 1999 | March 3, 1999 | April 6, 1999 |
| November 20, 1998 | January 13, 1999 (2) | March 5, 1999 | |

These new drug applications provide for the use of Agenerase™ (amprenavir), 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 Agenerase (amprenavir) 50mg capsules, 150mg capsules, and 15mg/mL oral solution for use as recommended in the draft label dated April 15, 1999. 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 and text for the patient package insert). 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 paper copies and one diskette that includes a WORD version of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten paper copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 21-007 and approved NDA 21-039. 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 February 18, 1999, in which you agreed to submit the results of two 48-week Phase 3 studies of the safety and efficacy of amprenavir to support traditional approval. Study PROAB3001, a 48 week study in therapy-naïve adults, and study PROAB3006, a 48-week equivalence study in treatment-experienced adults are currently underway.

Final study reports should be submitted to these NDAs 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 April 13, 1999. These commitments include:

1. The applicant will continue to study and report the safety and efficacy of amprenavir used in combination with other antiretroviral agents to demonstrate the utility of amprenavir in various patient populations, including protease-inhibitor experienced and advanced HIV-infected (salvage) patients, by initiating or completing the following clinical trials:

    - ACTG 398 Phase 2 randomized trial of amprenavir in combination with abacavir, efavirenz, and
    - ACTG 400 Phase 2 open-label trial of antiviral therapy (efavirenz plus two nucleoside reverse transcriptase inhibitors plus at least one new protease inhibitor) for nelfinavir failures,
    - PRO20005 Phase 2 open-label trial for treatment of HIV infection in subjects who have failed initial combination therapy with regimens containing indinavir or nelfinavir. This study assesses combination therapy with amprenavir, lamivudine, and abacavir plus either nelfinavir or indinavir for 48 weeks,
    - CNAA2007: A Phase 2 study evaluating the safety and antiviral activity of combination therapy with amprenavir, abacavir, and efavirenz in HIV-1 infected subjects with detectable plasma HIV-1 RNA despite treatment with a protease inhibitor-containing regimen for 48 weeks, and

- Safety data for patients with CD4 cell count < 100 at entry will be provided from ACTG398, ACTG400, PRO20005, CNAA2007, and the Agenerase Early Access program. In addition, the applicant agrees to submit a plan for review by the Division of Antiviral Drug Products (DAVDP) for studying patients with advanced HIV infection.

2. The applicant agrees to prepare and submit a supplemental NDA for traditional approval of Agenerase products. This application will include exploration of any gender-related differences in safety and efficacy outcome measures.

3. The applicant agrees to provide data on HIV-infected pediatric patients as agreed to in the Written Request dated April 7, 1999. In addition, the applicant agrees to further discussions with DAVDP of appropriate pre-clinical toxicology evaluations that would support the administration of amprenavir to neonates.

4. The applicant agrees to propose and conduct a study of a) the tolerability of amprenavir in patients with a known sulfonamide allergy, and b) the tolerability of sulfonamide therapy after patients have been treated with amprenavir.

5. The applicant agrees to propose and conduct an evaluation of the safety of chronic, high-dose Vitamin E administration in adults and pediatric patients receiving amprenavir, including the evaluation of vitamin E levels.

6. The applicant agrees to submit reports of completed carcinogenicity studies in a timely manner.

7. The applicant agrees to initiate or complete drug-drug interaction studies of amprenavir with ritonavir, efavirenz, nevirapine, methadone, and a representative female hormonal contraceptive product.

8. The applicant agrees to evaluate resistance to amprenavir and cross-resistance to other protease inhibitors in sequential HIV isolates from patients maintained on amprenavir in clinical trials, including:

   a. determination of *in vitro* susceptibility of HIV isolates to amprenavir,
   b. assessment of the genotypic basis of drug susceptibility attributable to the viral target genes and extragenic sites, such as the protease cleavage sites, and
   c. assessment of cross-resistance of amprenavir-resistant variants to other protease inhibitors and vice versa.

9. The applicant will investigate lipid metabolic pathways through *in vitro* studies. The applicant also agrees to investigate the possible mechanisms for the development of fat redistribution in patients receiving protease inhibitors, the incidence of this event, and the potential for long-term consequences. In addition, ongoing and future clinical trials should provide appropriate monitoring for these events and for any lipid-related disorders.

10. The applicant agrees to complete and submit a report of the results of the experiments

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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 capsules and the oral solution 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 not fulfilled all the requirements of 21 CFR 314.55. We are deferring submission of reports of additional pediatric studies in patients less than four years of age, including neonates, until December 31, 2003. Additionally, we refer to our Pediatric Written Request letter dated April 7, 1999.

We also remind you that 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).

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,

/S/

Sandra L. Kweder, M.D.
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Concurrence:
HFD-530/Dir/Jolson /S/
HFD-530/DepDir/Birnkrant OB 4/14/99
HFD-530/TLMO/Cvetkovich TC 4/13/99
HFD-530/MO/Martin JM 14 Apr 99
HFD-530/MicroTL/Battula NB 4/9/99
HFD-530/Micro/Mishra LM 4/8/99
HFD-530/PharmTL/Farrelly JDF 4/8/99
HFD-590/Pharm/McMaster JJM for OMM 4/8/99 4/14/99
HFD-540/PharmTL/A. Jacobs Review by ODE 5 Pharmacology/Toxicology aj 4/8/99 - complete
HFD-530/ChemTL/Miller
HFD-530/Chem/Lunn
HFD-830/CChen
HFD-530/Stat/Soon G.S 4/11/99
HFD-530/StatTL/Flyer OF 4/15/99
HFD-530/BiopharmTL/Reynolds KSR 4/8/99
HFD-530/Biopharm/Rajagopalan RB 4/9/99
HFD-530/SCSO/DeCicco D 4-12-99
HFD-530/CSO/Truffa MT 4/1/99
HFD-104/Hassall TH 4-15-99
HFD-530/ Biopharm/Tammara KSR for VT 4/8/99

SEE 2nd sheet For signitures. From ONDC III

cc:
Original NDA 21-007 and NDA 21-039
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/Martin
HFD-530/Jolson
HFD-530/Rajagopalan
HFD-530/Reynolds
HFD-530/Mishra
HFD-590/McMaster
HFD-530/Soon
HFD-530/Truffa

Drafted by: Truffa/March 25, 1999
APPROVAL under Subpart H (AP) (Subpart H Phase 4 Commitments)

[redacted]