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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-972/S-001

Approval Letter(s)

NDA 20-972/S-001

DuPont Pharmaceuticals Company
Attention: Patricia Dewalt
Director, Regulatory Affairs
Chestnut Run Plaza
MR 2136
974 Centre Road
Wilmington, DE 19805

Dear Dr. Dewalt:

Please refer to your supplemental new drug application dated May 26, 1999, received May 26, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sustiva™ (efavirenz), 50mg, 100mg, and 200mg capsules.

We acknowledge receipt of your submissions dated:

March 16, 1998	September 13, 1999	November 24, 1999
April 4, 1998	November 15, 1999	February 7, 2000
August 20, 1999	November 23, 1999	

This supplemental application provides information to fulfill the accelerated approval commitments as required under 21 CFR 314.510. Specifically, this new drug application provides for the use of Sustiva™ in combination with other antiretroviral agents, for the treatment of HIV-1 infection.

We have completed the review of this supplemental application 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 draft labeling submitted on February 7, 2000. Accordingly, this supplemental application is approved effective on the date of this letter. Approval of this supplement fulfills your commitments made under 21 CFR 314.510.

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 supplement NDA 20-972/001." In addition, please submit an electronic copy of the label in MS Word. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your outstanding Phase 4 commitments specified in your submission dated February 7, 2000. These commitments are listed below.

The DuPont Pharmaceuticals Company agrees to the following:

1. Continue with the development of a pediatric program, with emphasis on developing a liquid formulation along with obtaining safety, tolerability, pharmacokinetic and antiviral activity data. Additionally, we refer to our Pediatric Written Request letter.
2. Continue to study and define the resistance profile of efavirenz at the 600 mg dose and correlate resistance with plasma viral RNA.
3. Review clinical trial data and evaluate the association between potential risk factors and development of nervous system and psychiatric adverse events.
4. Submit efficacy data from trial 006 until at least all treatment arms reach the median to time treatment failure and present such median results for inclusion in the label.
5. Evaluate the safety, tolerability, and efficacy of efavirenz-containing regimens in patients who have failed non-efavirenz containing regimens.
6. Conduct a drug interaction study of efavirenz with methadone.
7. Investigate lipid metabolic pathways through in vitro studies. The applicant also agrees to continue monitoring fat distribution, changes in lipid profiles and lipid disorders in ongoing and future clinical trials.
8. Conduct and submit results of a multiple dose pharmacokinetic study in patients with hepatic impairment.
9. Complete the ongoing carcinogenicity studies with efavirenz and submit the data in a timely fashion.

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

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Be advised that, 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 you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until September 30, 2001. Additionally, please refer to our Pediatric Written Request letter dated September 17, 1998.

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).

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 Christine Kelly, RN, MS, MBA, Regulatory Health Project Manager, at (301) 827-2335.

Sincerely,



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

Concurrence:

HFD-530/Stat/Elashoff
HFD-530/Stat/Breazna
HFD-503/Stat/Aras 02-08-00
HFD-530/Micro/Connors
HFD-530/BP/Reynolds
HFD-530/MO/Haverkos 02-08-00
HFD-530/MO TL/Kukich 02-08-00
HFD-530/CPM/DeCicco
HFD-530/DD/Birnkrant

4/12/99
2-9-2000
2-9-00
2/9/00

cc:

Archival NDA 20-972
HFD-530/Div. Files
HFD-530/PM/Kelly
HFD-530/MO TL/Kukich
HFD-530/MO/Haverkos
HFD-530/Stat/Elashoff
HFD-530/Stat/Breazna
HFD-530/Micro/Connors
HFD-530/BP/Reynolds
HFD-530/Chem/Boring
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-104/ADRA (with labeling)
HFD-104/Peds/V.Kao (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - for drug discussed at advisory committee meeting.
HFD-095/DDMS-IMT (with labeling)
HFD-830/DNDC Division Director
DISTRICT OFFICE

Drafted by: cmk/December 1, 1999
Filename: v: davdp/kelly/nda/20-972/letters

APPROVAL (AP)