IND 49,465
NDA 20-972

SEP 17 1998

DuPont Pharmaceuticals Company
Attention: Mark Taisey
Chestnut Run Plaza
974 Centre Road
Wilmington, DE 19805

Dear Mr. Taisey:

To obtain needed pediatric information on Sustiva ™ (efavirenz), the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A(a) of the Federal Food, Drug, and Cosmetic Act, that you submit information from the following:

Type of studies:
An open-label, 48-week study to determine the pharmacokinetics, safety, and antiretroviral activity of efavirenz administered orally in combination with other antiretroviral therapy in HIV infected pediatric patients.

Objectives/rationale:
1. Determine the dosing regimen based on pharmacokinetic profile of efavirenz and tolerability in the pediatric population.
2. To assess safety and antiretroviral activity of efavirenz in combination with nelfinavir.

Indication to be studied:
HIV-1 infection.

Study design:
A 48 week, open-label, AUC controlled, multicenter study to determine the pharmacokinetics, safety, and antiviral activity of efavirenz in combination with nelfinavir in HIV-1 infected children between the ages of 3 months and 16 years. All of the patients have the option of concomitant use of nucleoside reverse transcriptase inhibitors. Efavirenz dosage is adjusted based on targeted efavirenz plasma concentrations and safety at 2 weeks of therapy.

Age group in which study(ies) will be performed:
Children between the ages of 3 months and 16 years will be studied:

Number of patients to be studied or power of study to be achieved:
A number of completed subjects to adequately characterize pharmacokinetics for each of the age groups, 3-24 months, 2-5 years, 6-12 years, and 13-16 years.

Entry criteria:
HIV-1 infected pediatric patients.

Clinical endpoints:
1. Pharmacokinetic parameters will be assessed (see Study Evaluations below).
2. Proportion of patients with HIV-RNA < 400 copies/ml by Roche Amplicor™ assay will be measured at 48 weeks of therapy. Mean change in CD4 count at 48 weeks will be a secondary endpoint.
3. Clinical and Laboratory safety assessments during 48 weeks of therapy.

Study evaluations:
1. Reports of C_{max}, T_{max}, AUC, C_{min}, CLo. AUC and CLo should be evaluated versus age as a continuous variable.
2. Safety and antiviral activity assessments through week 48.

Drug information:
- Dosage form: liquid formulation and 50mg, 75 mg, 100mg, 150mg, and 200 mg capsules
- Route of administration: oral
- Formulation: an appropriate formulation for the pediatric population

Safety concerns:
CNS symptoms, rash, hepatotoxicity

Statistical information:
Descriptive statistics will be provided.

Labeling that may result from the studies:
Information regarding dosing and safety in HIV-1 infected patients ages 3 months to 16 years.

Format of reports to be submitted:
Full study reports or analyses addressing the issues outlined in this request with full analysis, assessment, and interpretation for the study. Include other information as appropriate.

Timeframe for submitting reports of the studies:
On or before August 1, 1999.

Reports of these studies should be submitted as supplements to your approved NDA or as an amendment to your pending application with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports of these pediatric studies, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of

your submission, via fax (301-594-0183) or messenger to the Director Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, please contact Terrie L. Crescenzi, R.Ph., Regulatory Management Officer, at (301) 827-2335.

Sincerely yours,

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

Concurrence:
HFD-530/Dir/Jolson H Jolson 9/4/98
HFD-530/DepDir/Birnkrant 9/4/98
HFD-530/SCSO/DeCicco 8.26.98
HFD-530/AMOTL/Kukich SK 8/26/98
HFD-530/MO/Haverkos 8/24/98
HFD-530/BiopharmTL/Reynolds KSR 8/26/98
HFD-530/Biopharm/Sekar VJS 8/26/98
HFD-530/CSO/Crescenzi 8/26/98
HFD-104/T. Hassell

cc:
Original NDA 20-972
HFD-530/Div. Files
HFD 530/CSO/Crescenzi
HFD-530/Haverkos
HFD-530/Kukich
HFD-530/Jolson
HFD-104/DMurphy
HFD-600/Office of Generic Drugs
HFD-2/MLumpkin
HFD-6/Kroberts

Drafted by: HH/August 19, 1998, TLC/August 21, 1998 Final:
Edited: TLC/August 26, 1998
Edited:

PEDIATRIC WRITTEN REQUEST LETTER (PWR)