CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-972/S-001

Administrative/Correspondence Documents

SUSTIVA™ CAPSULES
(efavirenz)
PATENT INFORMATION

NEW DRUG APPLICATION
The DuPont Merck Pharmaceutical Company
Wilmington, DE 19805

1) Trade Name of Drug Product	SUSTIVA™
2) Active Ingredient(s)	Efavirenz (chemical name is (S)6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3, 1-benzoxazin-2-one)
3) Strength(s)	50mg, 75mg, 100mg, 150mg, 200mg
4) Dosage Form	Capsule
Route of Administration	Oral
5) Name of Applicant	The DuPont Merck Pharmaceutical Company
6) NDA Number	20972
7) Applicable Patent Numbers and Expiration Date of Each	
Type of Patent	5, 519, 021 expires: May 21, 2013** Covers compound and pharmaceutical composition
Name of Patent Owner	Merck & Co., Inc., licensed to The DuPont Merck Pharmaceutical Company
Type of Patent	5,663,169 expires: Sept. 2, 2014** Covers method of use
Name of Patent Owner	Merck & Co., Inc., licensed to The DuPont Merck Pharmaceutical Company

**This date does not include any extension under 35 USC 156.

SUSTIVA™ CAPSULES
(efavirenz)
PATENT INFORMATION

NEW DRUG APPLICATION
The DuPont Merck Pharmaceutical Company
Wilmington, DE 19805

Pursuant to the provisions of Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act [21 USC 355(b)(1)] submitted herewith please find the patent information for the above identified application.

The undersigned declares that U.S. Patent No. 5,519,021 covers the efavirenz compound and pharmaceutical compositions containing efavirenz (SUSTIVA™), which is the subject of this application for which approval is being sought.

The undersigned declares that U.S. Patent No. 5,663,169 covers the method of use of efavirenz (SUSTIVA™) for the treatment of HIV infection, which is the subject of this application for which approval is being sought.

A claim of patent infringement could be asserted if a person not licensed by the owner of U.S. Patent No. 5,519,021 engaged in the manufacture, use or sale of efavirenz (SUSTIVA™).

A claim of patent infringement could be asserted if a person not licensed by the owner of U.S. Patent No. 5,663,169 engaged in the manufacture, use or sale of efavirenz (SUSTIVA™) for the treatment of HIV infection.

By: _____

Blair Q. Ferguson, Ph.D., J.D.
Associate General Counsel
The DuPont Merck Pharmaceutical Company

SUSTIVA™ CAPSULES
(efavirenz)
PATENT INFORMATION

NEW DRUG APPLICATION
The DuPont Merck Pharmaceutical Company
Wilmington, DE 19805

The following patent applications for SUSTIVA™ have been filed and are pending:

Title: Benzoxazinones as Inhibitors of HIV Reverse Transcriptase.

U.S. Patent Application No. 08/815,780, filed August 7, 1992.

Title: Formulation of Fast-Dissolving Efavirenz Capsules or Tablets.

U.S. Provisional Patent Application, Attorney Docket No. DM-6884-P1, filed April 7, 1998.

Title: Oral Liquid Formulations of Benzoxazinone HIV Reverse Transcriptase Inhibitor.

U.S. Provisional Patent Application, Attorney Docket No. DM-6971-P1, filed February 17, 1998.

EXCLUSIVITY SUMMARY FOR NDA # 20-972

Trade Name: **SUSTIVA** Generic Name: **efavirenz**
Applicant Name: DuPont **Pharmaceuticals Company** HFD # **530**
Approval Date: December , 1998

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /___/ NO /_X_/

b) Is it an effectiveness supplement?

YES /_X__/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE7

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no").

YES /_X_/ NO /__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /__X__/ NO /__/

If the answer to (d) is "yes", how many years of exclusivity did the applicant request?

5 1/2 years with the accelerated approval application

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES /__X__/ NO /___/

If yes, NDA # 20-972 Drug Name: efavirenz

IF THE ANSWER TO QUESTION 2 IS "YES", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__X__/

IF THE ANSWER TO QUESTION 3 IS "YES", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes", identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one-never-before-approved active moiety and one previously approved active moiety, answer "yes". (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved).

YES /__/ NO /___/

If "yes", identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES", GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant". This section should be completed only if the answer to PART II, Question 1 or 2 was "yes".

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies). If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes", then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__/ NO /__/

If "no", state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__/ NO /__/

(1) If the answer to 2(b) is "yes", do you personally know of any reason to disagree with the applicant's conclusion?

YES /__/ NO /__/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no", are you aware of published studies not conducted or sponsored by the applicant or other publicly available date that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /__/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no", identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval", has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no").

Investigation #1 YES /__/ NO /__/

Investigation #2 YES /__/ NO /__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /__/ NO /__/

Investigation #2 YES /__/ NO /__/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are "no", identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /__/ NO /__/ Explain: _____

_____

Investigation #2

IND # _____ YES /__/ NO /__/ Explain: _____

_____

b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /__/ Explain _____ NO /__/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /__/ Explain _____ NO /__/ Explain _____

_____ _____

_____ _____

(c) Not withstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest)

YES /__/ NO /__/

If yes, explain: _____

_____

/S/ 12-1-99
Signature of Project Manager Date

/S/ 2/7/00
Signature of Division Director Date

cc: Orig NDA Div File HFD-85

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-972 Supplement # 001 Circle one: SE1 SE2 SE3 SE4 SE5 SE6 (SE7)

HFD-530 Trade and generic names/dosage form: Sustiva (efavirenz capsules) 50mg, 100mg, 200mg
Action: (AP) AE NA

Applicant DuPont Pharmaceuticals Therapeutic Class 7030240 NNRTI

Indication(s) previously approved Treatment of HIV-1 infection in combination with other antiretrovirals

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate X

Indication in this application Treatment of HIV-1 infection in combination with other antiretrovirals (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

X 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

X c. The applicant has committed to doing such studies as will be required.
- X (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- X (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

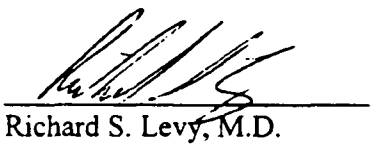
/S/ 12/1/99

Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 20-972
Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

Item 16. Debarment Certification (FDC Act 306(k)(1))

In compliance with Section 306(k)(1) of the Federal Food, Drug, and Cosmetic Act 21 USC335a(k)(1), the undersigned certifies that to the best of their knowledge and belief, DuPont Pharmaceuticals Company did not and will not use in any capacity the services of any persons debarred under subsections (a) or (b) (Sections 306(a) or (b)), in connection with this application for approval of Sustiva™ Capsules.



5/17/99

Richard S. Levy, M.D. Date
Vice President, Worldwide Regulatory Affairs and Pharmacovigilance
DuPont Pharmaceuticals Company

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	DMP 266-006	SEE ATTACHED
	DMP 266-020	SEE ATTACHED

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached. ACTG 364 (see attached)

NAME	TITLE
Edward C. Bradley, M.D.	Executive Vice President, Worldwide Science and Development
FIRM/ORGANIZATION: DuPont Pharmaceuticals Company	
SIGNATURE: Edward C. Bradley	DATE: 5/24/99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Created by Electronic Document Services/USDHHS: (301) 443-2454 EF

Redacted 11

pages of trade secret and/or confidential commercial information

FORM FDA 3454 Attachment – Study ACTG 364

At the time of this submission, no financial disclosure information is available for investigators and other qualifying individuals under CFR 54.4 for Study ACTG 364. Our current understanding, based on information received from the Division of AIDS (DAIDS), the sponsor of the study, is that the Division has not adopted a policy of obtaining financial disclosure information from its investigators.

While it may be possible to obtain such information in the future, The DuPont Pharmaceuticals Company requests a waiver from providing financial disclosure information for ACTG 364 on the following grounds:

1. The sponsor of the study (DAIDS) has not provided financial disclosure information to the applicant, and has not requested this information from study investigators.

2. The sponsor of the study is a government institution. The ACTG investigators cannot hold an equity interest in the sponsor, nor do they receive any payment from DAIDS that could influence the outcome of the study. No ACTG investigators hold patent rights to efavirenz.

3. The clinical portion of ACTG 364 was completed prior to February 2, 1999, the date that the Financial Disclosure Rule went into effect.

Taken together, these points clearly establish that the integrity and reliability of ACTG 364 data has not been influenced by any financial stake that the investigators might have in the sponsor of the study.

ACTG 364 - LIST OF PRINCIPAL INVESTIGATORS (Page 1 of 5)

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ACTG 364 - LIST OF PRINCIPAL INVESTIGATORS (Page 4 of 5)

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ACTG 364 - LIST OF PRINCIPAL INVESTIGATORS (Page 5 of 5)

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Group Leader's Memorandum

NDA:	**20-972/001**
Drug and Indication:	**Sustiva™ (efavirenz capsules) for the treatment of HIV-1 infection in combination with other antiretroviral agents**
Dose:	**600 mg once daily**
Applicant:	**DuPont Pharmaceuticals Company**
Submission received:	**May 26, 1999**
Date of MO review:	**January 31, 2000**
Date of Memorandum:	**January 31, 2000**

DuPont Pharmaceuticals has requested traditional approval for Susiva™ (efavirenz capsules), a non-nucleoside reverse transcriptase inhibitor, for the treatment of HIV-1 infection when used in combination with other antiretroviral agents. This indication is based on treatment-induced changes in plasma HIV RNA levels in controlled studies of 48 weeks duration. The original New Drug Application for Sustiva was submitted on June 11, 1998 and was approved on September 17, 1998 under accelerated approval regulations, 21 CFR 314 subpart H.

To fulfill the post-marketing commitments of accelerated approval, the applicant has conducted two controlled clinical trials, 006 and ACTG 364, to support traditional approval and provide evidence of clinical benefit for HIV-1 infected patients. Together, these two studies randomized 1462 patients. The data from one 24-week controlled clinical trial in 327 NRTI-experienced patients, safety data from five additional smaller clinical trials and an expanded access program serve as a supporting evidence of safety and efficacy.

In the two principal trials, the primary efficacy analysis was time to treatment failure (TTF). Plasma HIV-1 RNA levels were measured using the approved Amplicor HIV-1 RNA Monitor™ assay with the limit of quantification of 400 copies/mL in study 006 and 500 copies/mL in ACTG 364. In the TTF analysis, patients who were randomized but never received treatment or never achieved viral load below the assay limit of quantification were considered to have TTF of zero days. For patients who achieved viral load below the assay limit, TTF was measured from the onset of treatment to the first of a confirmed HIV RNA above the assay limit, an AIDS-defining event, or discontinuation of study treatment for any reason. Sustained suppression in plasma HIV-1 RNA levels

has been accepted as a surrogate endpoint that is reasonably likely to predict clinical benefit. This correlation between plasma HIV-1 RNA levels and clinical outcomes was discussed at the Antivirals Advisory Committee Meeting held in July of 1997. Clinical considerations for accelerated and traditional approval of antiretroviral drugs using plasma HIV RNA measurements was published in the Federal Register in August of 1999, as the Guidance for Industry draft document.

In study 006, 760 of 1266 patients reached a treatment outcome at week 112 and in ACTG 364, 146 of 196 reached a treatment outcome at week 72. The TTF analyses based on Kaplan-Meier estimates accounted for patients who were responders but have not reached 112 or 72 weeks of follow-up in study 006 or ACTG 364, respectively. Therefore, this approach allowed for data beyond 48 weeks to be included in the analysis of duration of response.

The secondary efficacy analyses included the proportion of patients with HIV-1 RNA below the assay limit (Roche Amplicor HIV-1 Monitor and Ultrasensitive assay), mean changes from baseline in CD4 cell count, duration of HIV RNA suppression, MOS Quality of Life Index, and new onset of AIDS-defining events. A virologic response in the non-completer equals failure (NC=F) analysis included all patients who had at least 48 weeks of follow-up. Patients were assigned as failures for every scheduled visit subsequent to having dropped out of study for any reason, if a missed visit was surrounded on either side by HIV RNA measurement greater than the lower limit of quantification (HIV RNA $\geq$400copies/mL), or developed an AIDS-defining event.

In principal trials, 006 and ACTG 364, efavirenz was studied in combination with nucleoside reverse transcriptase inhibitors (NRTIs) and/or protease inhibitors. Reduction in viral load below the assay limit and increase in CD4 cell counts was demonstrated in both, treatment-naïve and NRTI-experienced patients who received efavirenz. The efficacy of efavirenz was demonstrated in the TTF analysis. At each time point through 112 or 72 weeks for 006 and ACTG 364 trials, respectively, a higher fraction of patients treated with efavirenz compared to control had not reached the treatment failure endpoint.

The treatment effect was also demonstrated in subgroup analysis of patients with HIV-1 RNA levels >30,000 or $\geq$ 100,000 copies/ml at baseline for ACTG 364 or 006 study, respectively. In the third supportive trial, in NRTI-experienced patients, there was no significant difference between treatment regimens through 24 weeks of treatment, though a numerical advantage was seen for efavirenz.

This application does not provide sufficient information about the efficacy of efavirenz in patients with advanced HIV-infection (CD4 <50 cells/m^3) or in patients who previously failed NNRTIs or protease inhibitor containing regimens. The number of AIDS-defining events or deaths was too small to allow for reasonable conclusions about the effect of efavirenz on clinical progression or survival.

Approximately 9200 patients received efavirenz at various doses across all studies and an expanded access program. In three controlled clinical trials, 1,134 patients received

600 mg once daily, a marketed dose of efavirenz. The adverse events of primary concern were psychiatric, nervous system symptoms, and rash, already discussed in the current package insert for efavirenz.

Serious psychiatric/nervous system symptoms included manic and paranoid reactions, aggressive behavior, depression, suicidal ideation/attempts and successful suicides. Patients with prior psychiatric history appear to be at greater risk for developing these serious adverse events. Other nervous system symptoms were dizziness, insomnia, impaired concentration, somnolence, abnormal dreams, and hallucinations. These symptoms usually begin during the first or second day of therapy and generally resolve after two to four weeks. Dosing at bedtime improved the tolerability of these symptoms.

Skin rash was reported by 26% (266/1008) of patients who received 600 mg of efavirenz in clinical trials. Severe rash that included erythema multiforme and Stevens-Johnson syndrome was reported in less than 1% of patients.

Detailed discussion of efavirenz safety and efficacy is provided in the joint medical and statistical review of this supplemental application. I am in agreement with the conclusions of the primary reviewers that this supplemental application should be approved. The efficacy of efavirenz in combination with other antiretroviral agents for the treatment of HIV-1 infection was demonstrated in studies of longer then 48 weeks duration, which included treatment naïve and NRTI-experienced patients. The available safety information does not alter the overall understanding of the efavirenz safety profile.

Labeling discussions were focused on:

a. Provision of balanced information in the Warning Section of the package insert about serious psychiatric adverse events that occurred during efavirenz treatment and clearly separating them from more frequent nervous system symptoms.
b. Description of nervous system symptoms in the Warning Section of the labeling for efavirenz.
c. Inclusion of Post-Marketing safety data.
d. Presentation of the efficacy data; addition of TTF analyses as Kaplan-Meier estimates that will account for patients who are responders but have not reached 112 or 72 weeks of follow-up in study 006 and ACTG 364, respectively.
e. Presentation of HIV-RNA data for both approved Amplicor HIV-1 Monitor and Ultrasensitive assay.

I am in agreement with the proposed Phase IV commitments included in the approval letter for efavirenz.

/S/

Stanka Kukich, M.D.
Medical Team Leader, HFD-530

cc:
NDA 20-972
HFD-530/HJolson/HHaverkos/SKukich

VIA FEDERAL EXPRESS

DuPont Pharmaceuticals Company

Desk copy: C. Kelly
(HFD-530)

February 7, 2000

Heidi Jolson, M.D., Director
Division of Antiviral Drug Products (HFD-530)
Center for Drug Evaluation and research
Food and Drug Administration
9201 Corporate Blvd
Rockville, MD 20850

RE: NDA No. 20-972; SUSTIVA™ (efavirenz)
Phase 4 Commitments and Traditional Approval Labeling

Dear Dr. Jolson,

The DuPont Pharmaceuticals Company agrees to the following Phase 4 commitments as set forth in the Agency's facsimile correspondence of February 7, 2000:

1. [redacted]

2. Continue to study and define the resistance profile of efavirenz at the 600 mg dose and correlated 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 006 until at least all treatment arms reach the median TTF 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.

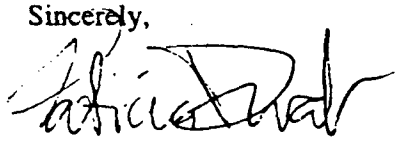
8. Conduct and submit results of a multiple dose pharmacokinetic study in patients with hepatic impairment.

9. Complete the ongoing carcinogenicity studies with efavirenz and submit the data in a timely fashion.

A clean copy of the proposed label as submitted on February 1, 2000, is provided as both paper copy and in WORD format on diskette (LABEL18.doc). A copy of the proposed Patient Package Insert, with the revisions as discussed during the December 10, 1999 teleconference, is also provided as paper copy and electronically (Qa_ppi10c.doc).

Please contact me if you have any questions.

Sincerely,



Patricia Dewalt, Ph.D.
Director, Regulatory Affairs
(302) 992-5440

Submitted in Triplicate

Attachments:
Diskette
Proposed Labeling
Proposed Patient Package Insert

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: February 7, 2000

To: Patricia G. Dewalt, Ph.D.

Address: DuPont Pharmaceuticals
Fax- (302) 892-0712

From: Christine Kelly, RN, MS, MBA, Project Manager

Through: Stanka Kukich, M.D., Medical Team Leader, HFD-530 2/7/00
Harry Haverkos, M.D., Medical Officer, HFD-530 2/7/00
Sandra Suarez, Ph.D., Pharmacokinetics Reviewer, HFD-530 2/7/00
Kellie Reynolds, Pharm. D., Pharmacokinetics Team Leader, HFD-530 2-7-20

NDA: 20-972

Subject: *Pharmacokinetic comments on IND submission
*Phase 4 commitment proposal
*Labeling comments on supplemental application for traditional approval (SE7-001)

Pharmacokinetic Comments-

The following comments pertain to serial number 041, which was submitted to IND 49,465 on November 39, 1999, "A Phase 1, Open-label, Single-Center Study to Evaluate the Pharmacokinetics of DMP 266 in Subjects with Chronic Liver Disease".

1. The data presented in this study report are not adequate to conclude that efavirenz 600-mg is the appropriate dose for patients with chronic liver disease.

2. Because efavirenz follows non-linear PK, PK data following administration of multiple doses are needed in order to make dosing recommendations for patients with liver impairment. To provide appropriate dosing recommendations across the entire spectrum of hepatic impairment, the study should include patients with mild, moderate, and severe liver impairment (Child-Pugh, A, B, and C, respectively) as well as a healthy control group. Data should be provided for at least six subjects in each arm of the study.

3. Please note that a Phase 4 commitment for the above study has been included below.

Proposed Phase 4 Commitments

Please review the following outstanding Phase 4 commitments. If you accept them as stated, please make a formal submission to the NDA including these commitments.

1. [

]

2. Continue to study and define the resistance profile of efavirenz at the 600 mg dose and correlated 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 006 until at least all treatment arms reach the median TTF 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.

Labeling Comments

We have accepted your label as submitted in the February 1, 2000 general correspondence to the NDA. Please submit the February 1 label (alone, not in a side by side format) as a formal amendment to the traditional approval supplement; please include a paper copy and an electronic copy in MS Word.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

S

Christine Kelly, RN, MS, MBA
Regulatory Health Project Manager
Division of Antiviral Drug Products

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: Pat Dewalt

Fax Number: (302) 892-0712

Date: January 28, 2000

Company: DuPont Pharmaceuticals Company

No. of pages (excluding cover): 3

Message: This is a facsimile containing FDA comments on the draft package insert.

From: Christine Kelly, RN, MS, MBA

Telephone: (301) 827- 2335

Fax Number: (301) 827-2510

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

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: January 28, 2000

To: Patricia G. Dewalt, Ph.D.

Address: DuPont Pharmaceuticals
Fax- (302) 892-0712

From: Christine Kelly, RN, MS, MBA, Project Manager

Through: Stanka Kukich, M.D., Medical Team Leader, HFD-530
Harry Haverkos, M.D., Medical Officer, HFD-530

NDA: 20-972

Subject: Clinical comments on Supplemental Application for Traditional Approval (SE7-001)

Clinical Comments

Please include the following statement under the Precautions section in compliance with the Geriatric Use ruling:

Clinical studies of SUSTIVA did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Christine Kelly, RN, MS, MBA
Regulatory Health Project Manager
Division of Antiviral Drug Products

cc:
NDA 20-972

Division File 20-972
HFD-530/TL/Kukich
HFD-530/MO/Haverkos

Facsimile

KE114

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: December 15, 1999

To: Patricia G. Dewalt, Ph.D.

Address: DuPont Pharmaceuticals
Fax- (302) 892-0712

From: Christine Kelly, RN, MS, MBA, Project Manager

Through: Stanka Kukich, M.D., Medical Team Leader, HFD-530 SK 12/15/99
Harry Haverkos, M.D., Medical Officer, HFD-530
Mike Elashoff, Ph.D., Statistical Reviewer, HFD-725

NDA: 20-972

Subject: Phase IV- Clinical and Statistical Comments on Supplemental Application for Traditional Approval (SE7-001)

Clinical and Statistical Comments

1. [

]

2. Resistance data – To continue to study and define the resistance profile of efavirenz at the 600 mg dose and correlated resistance with plasma viral RNA.

3. Methadone interaction – To conduct a drug interaction study of efavirenz with methadone.

4. Carcinogenicity studies – To complete the ongoing carcinogenicity studies with efavirenz and submit the data in a timely fashion.

5. Chemistry, Manufacturing and Controls – To revisit the specification limits for drug substance and tightening, if possible, to ——— once the first ten scale up batches have been accomplished.

6. Nervous system and psychiatric adverse events – To review clinical trial data and evaluate the association between the use of efavirenz and potential risk factors for the development of nervous system and psychiatric adverse events.

7. Lipid profile studies – 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 among patients receiving efavirenz, the incidence of these events, 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.

8. The sponsor will continue to submit efficacy data from 006 until at least all treatment arms reach the median TTF and present such median results for inclusion in the label.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Christine Kelly, RN, MS, MBA
Regulatory Health Project Manager
Division of Antiviral Drug Products

cc:
NDA 20-972
Division File 20-972
HFD-530/TL/Kukich
HFD-530/MO/Haverkos 12/15/99
HFD-725/Stat/Breazna
HFD-725/Stat/Elashoff MRE 12/14/99
HFD-530/PM/Kelly
Facsimile

OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA #20-972 Drug Sustiva (efavirenz) DATE 12-1-99

Applicant DuPont Pharmaceuticals CSO Christine Kelly Phone 301-827-2335

User Fee Goal Date: March 26, 2000

Arrange package in the following order:	Check or Comment
1. ACTION LETTER with supervisory signatures Are there any Phase 4 commitments?	AP ✓ AE ____ NA ____ Yes ✓ No ____
2. Have all disciplines completed their reviews? If no, what review(s) is/are still pending?	Yes ✓ No ____
3. Completed copy of this CHECKLIST in package	Chem/Ther Types ____
4. LABELING (package insert and carton and container labels). (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)	Draft ✓ Revised Draft ____ Final ____
5. PATENT INFORMATION	✓
6. EXCLUSIVITY CHECKLIST	✓
7. PEDIATRIC PAGE	✓
8. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992).	✓
9. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status. If no audits were requested, include a memo expaining why.	NA
10. REVIEWS:	
DIVISION DIRECTOR'S MEMO (If more than 1 review for any discipline, separate reviews with a sheet of colored paper. Any conflicts between reviews must have resolution documented)	NA
GROUP LEADER'S MEMO	✓
MEDICAL REVIEW	✓
SAFETY UPDATE REVIEW	
STATISTICAL REVIEW	✓
BIOPHARMACEUTICS REVIEW	NA
PHARMACOLOGY REVIEW (Include pertinent IND reviews)	✓
Statistical Review of Carcinogenicity Study(ies)	NA
CAC Report/Minutes	NA
CHEMISTRY REVIEW	NA
Labeling and Nomenclature Committee Review Memorandum	NA
Date EER completed ____ (attach signed form or CIRTS printout) FUR needed ____ FUR requested ____	OK NA No ____
Have the methods been validated?	Yes (attach) NA No ____
Environmental Assessment Review / FONSI	Review NA FONSI ____
MICROBIOLOGY REVIEW	✓
What is the status of the monograph?	NA
11. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes	✓
12. MINUTES OF MEETINGS Date of End-of-Phase 2 Meeting 45 day filing meeting minutes Date of pre-NDA Meeting NA	✓
13. ADVISORY COMMITTEE MEETING MINUTES or, if not available, 48-Hour Info Alert or pertinent section of transcript.	N/A Minutes ____ Info Alert ____ Transcript ____ No mtg ____
14. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS	NA
15. If approval letter, has ADVERTISING MATERIAL been reviewed? If no and this is an AP with draft labeling letter, has advertising material already been requested?	Yes ____ No ____ Yes, documentation attached ____ No, included in AP ltr ✓

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

Record of Teleconference

NDA: **20-972**

Date: **November 19, 1999**

Drug: **Sustiva (efavirenz)**

Sponsor: **DuPont**

BETWEEN: **Representatives of DuPont**
Pat Dewalt, Regulatory Affairs
Richard Levy, Clinical
Laura Bessen, M.D., Clinical
Tom Donnelley, Regulatory Affairs
Ed Bradley, VP, Medical Science and Development
Don Labrink

AND: **Representatives of DAVDP**
Stanka Kukich, M.D., Medical Team Leader
Mike Elashoff, Ph.D., Statistical Reviewer
Andrei Breazna, Ph.D. Statistical Reviewer
Christine Kelly, RN, MS, MBA, Project Manager

SUBJECT: Traditional Approval Supplement-Labeling

Background: This teleconference was requested by the Medical Team Leader (11/16/99) to discuss DuPont's labeling for their traditional approval supplement in response to the fax sent in by the sponsor November 17, 1999 (please see attached).

Discussion

1. On page 5 of the fax, the sponsor will delete the following sentence from the WARNINGS
2. Under ADVERSE REACTIONS section, " will be deleted.
3. On page 10 of the fax, " will be replaced with "suicide", and the following will "and in 6% of patients treated with control" will be added at the end of the following sentence," As symptomatic...SUSTIVA.

4. On page 12, line 100, The sponsor will added a sentence addressing aggressive reactions. It was also recommended to the sponsor that they add a statement about aggressive reaction in the PPI.

5. The sponsor will include a curve out to 48 weeks with the lower limit of quantification.

Action

1. The sponsor will make the above labeling changes.

2. The sponsor will submit an outcomes table and a new graph.

Concurrence:

HFD-530/MO TL/Kukich 11-24-99

cc:
NDA 20-972
Division File 20,972
HFD-530/TL/Kukich
HFD-530/MO/Haverkos
HFD-725/Stat/Breazna
HFD-520/CSO/Kelly

Record of Teleconference

Telefax

DuPont Pharmaceuticals Company
Centre Road, Wilmington DE 19805
Phone (302) 992-5440 FAX (302) 992-3011

Date: 17 November 1999

To: Chris Kelly DAVDP **301.827.2523 (fax)**
301.827.2335 (ph)

From: Patricia Dewalt, PhD
Director Regulatory Affairs

Total Pages: 14

Re: NDA No. 20-972; SUSTIVA™ (efavirenz)

Chris,

In follow-up to our teleconference of 11/12/99, we are submitting revised labeling proposals for the Warnings and Precautions sections of the Sustiva Package Insert and corresponding rationale for your review. The attached proposal also includes the parallel changes to the Information for Patients and Adverse Reactions, as well as a revised Patient Package Insert.

I will be contacting you to set up another teleconference with the medical and Statistical reviewers with the goal of coming to final agreement on the safety language The Clinical Trial Descriptions are in preparation and will be forwarded as soon as possible.

Warnings - Psychiatric Symptoms

Based on our teleconference with the Division on Nov. 12, 1999 we have proposed revised warning sections on psychiatric symptoms and nervous system symptoms. In drafting the proposed warning on psychiatric symptoms we considered several factors important to the FDA and several factors important to DuPont.

Our understanding of FDA's position is that although the controlled clinical trials show approximately equal rates of specific serious psychiatric symptoms in the Sustiva and control groups, the FDA believes that some of these symptoms are related to the use of efavirenz. We understand that this suspicion is based largely on the higher rate of post marketing reporting of serious psychiatric symptoms with Sustiva than with other anti-retroviral agents and may also based on the known association of Sustiva with nervous system symptoms such as dizziness. We understand that despite the inability of the data to demonstrate that these psychiatric symptoms are related to the use of Sustiva, the FDA needs to warn patients about these symptoms because if they are related to use of Sustiva, prompt discontinuation of Sustiva may be very important to patient safety. We also understand, but do not agree with, FDA's belief that presenting the similar event rates in the control group trivializes the warning.

Our view is that while the nervous system symptoms such as dizziness are definitely related to the use of Sustiva, it is not at all clear that serious psychiatric symptoms such as severe depression and suicidal behavior are related. We believe that controlled clinical trials are the best way to determine association, and the controlled trials do not support an association, acknowledging that the studies were not powered to test this hypothesis. We do not believe it is appropriate to base the assessment of causality largely on the post-marketing experience with Sustiva in comparison to the post marketing experience with other drugs. From the time the drug was launched, the accelerated approval labeling for Sustiva noted that severe acute depression, suicidal behavior, delusions and inappropriate behavior had been reported. Coupled with our competitors making frequent note of this to physicians, it is not surprising that the rate of post-marketing reports is far higher with our drug than with other drugs where these events undoubtedly occur (as they did in the control arm of our controlled studies) but are not suspected to be related to the use of other drugs.

Despite this, we accept that even if the possibility of these events being related to use of Sustiva is relatively small, patients should be warned about these potential events so that they can be quickly evaluated to determine if an individual patient's symptoms might be related to the use of Sustiva, and if so, to determine whether treatment with Sustiva should be discontinued. We cannot accept, however, misrepresenting the data by excluding rates in the control group from the warning to make it appear more likely that these events are related to Sustiva. While it is never appropriate to misrepresent data, there are additional reasons to include the control rates in the warning that may not be apparent to FDA. First, in order for a physician to decide whether to discontinue Sustiva, for which the patient may not have an adequate therapeutic alternative, he or she should have the data which indicate that the association with use of Sustiva is not certain.

Second, if the rates in the control groups are not provided, our competitors will be able to distort the data, convincing physicians to use less effective alternatives, which is not in the best interest of patients. These critical treatment decisions need to be based on the facts. Third, if we were to misrepresent the data in a way that made it seem more likely that these events are related to the use of Sustiva than the data support, we would not be able to properly defend ourselves in liability claims.

We believe that the proposed wording of the warning section is the best way to meet FDA's and our own needs, and more importantly the needs of health care providers and patients. The fact that a warning appears in labeling indicates to all that this is not a trivial issue. The first sentence indicates that serious psychiatric events have been reported in patients treated with Sustiva. This first sentence does not include any statement about similar rates in patients treated with control regimens and will lead health care providers and patients to read the entire warning. The next sentence provides the data without bias or interpretation. The following sentence indicates that patients with a prior history of psychiatric disorders appear to be a higher risk, and gives the approximate frequency in the group treated with Sustiva, but does not mention that the rates are similarly increased in the control group. The next sentence provides full disclosure about the other serious psychiatric adverse experiences in the post marketing reports. The final sentence makes several important points including that any patient's symptoms may be related to the use of Sustiva, that patients should seek immediate medical evaluation, and that discontinuation of Sustiva may be required based both on the assessment of causality and risk-benefit. We can accept alternate wording, but we cannot accept any wording designed to make the association seem stronger than the data support.

Warnings - Nervous System Symptoms

In addition to the warning on psychiatric symptoms, the precaution on nervous system symptoms has been moved to warnings. We have deleted the statement that nervous system symptoms are not related to psychiatric symptoms, but have included the important statement that nervous system symptoms do not predict subsequent onset of psychiatric symptoms.

Information for Patients

We have created statements to mirror the WARNINGS section. We choose to speak of the nervous system symptoms first in this section because information given to patients before starting Sustiva needs to emphasize the nervous system symptoms that they are likely to experience within days of starting Sustiva and to emphasize that these symptoms are likely to improve with continued therapy. In the statement about psychiatric symptoms, we don't provide control data because patients should not be asked to interpret data. However, we do indicate both that it is not certain whether the symptoms are related but that they should seek immediate medical evaluation. We believe this wording maximizes the chances that patients will seek medical evaluation.

Adverse Reactions

We start with nervous system symptoms because they are common and clearly related to the use of Sustiva. In order to avoid confusion between nervous system symptoms and psychiatric symptoms, we now specifically list each of the nervous system symptoms that were pooled. In the table on the frequency and severity of nervous system symptoms we have deleted the line FDA asked us to add on serious symptoms because serious symptoms do not refer to NSS but to psychiatric symptoms which are addressed separately.

Under Psychiatric Symptoms we have repeated the first two sentences of the warning and referred to the warning itself. In addition, we have added information any other new-onset psychiatric events that occurred at a frequency of greater than 2% in the ISS database (600 mg QD and controls).

In the table of adverse experiences we have moved several adverse reaction terms from the psychiatric body system to the central and peripheral nervous system. This is done to present adverse reactions in a manner consistent with the psychiatric and nervous system warnings. Several of the pooled nervous system symptoms are coded under the psychiatric body system by WHOART, and this will only cause confusion. Therefore, we believe to maximize clarity, we should override the body system classification created by WHOART.

We have also created a new body system list of adverse reactions based on post market reports. These lists are based on the four periodic reports that have been submitted to FDA covering the first one-year on the U.S. market. The body system list does not include events that are already mentioned or discussed under ADVERSE REACTIONS, but does capture events that are included under WARNINGS or PRECAUTIONS. We are currently preparing a cumulative listing of these reports to aid your review. This will be forwarded under separate cover in the near future.

Specific Proposals for revised wording of the safety information follow. As in the proposal transmitted via fax on November 9, 1999, all line numbers refer to the Agency's proposed draft package insert received via fax on October 29, 1999. Underlining (additions) or strikethrough (deletion) indicates changes from the Agency's language or previous draft language proposed by DuPont. In cases where sections have been revised extensively, the new language has not been marked up.

9 pages redacted from this section of the approval package consisted of draft labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

Record of Teleconference

NDA: **20-972**

Date: **November 17, 1999**

Drug: **Sustiva (efavirenz)**

Sponsor: **DuPont**

BETWEEN: **Representatives of DuPont**
Pat Dewalt, Director Regulatory Affairs
Ken Abremski, Director Bioinformatics
Lee Bachelor, Senior Investigator, Virology
Dominic Labriola, Senior Director, CNS/Virology/Inflammation (Biometrics)
Sue Erickson-Viitanen, Senior Director, Virology
Brian Waters, Biometrics

AND: **Representatives of DAVDP**
Mike Elashoff, Ph.D., Statistical Reviewer
Andrei Breazna, Ph.D. Statistical Reviewer
Lauren Iacono-Connors, Ph.D., Microbiology Team Leader
Christine Kelly, RN, MS, MBA, Project Manager

SUBJECT: Microbiology-Assay Data

Background: This teleconference was requested by FDA (11/15/99) to discuss the microbiology assay data that the sponsor has available.

Discussion

1. The sponsor clarified that clinical studies 003, 004, and 005 uses clonal based sequencing. Study 024 uses population-based sequencing.

2. The sponsor stated that they have RNA and genotype data at baseline and at failure. At FDA's request, they will look for a relationship between the 103 mutation and the loss of reponse.

Action

1. The sponsor will submit treatment time points, approximately one month from now. The sponsor will include a table including clone data by patient, trial number, treatment failure day, and number of clones.

2. The requested information will be submitted in an excel format.

/S/

Concurrence:
HFD-530/Micro TL/Connors 01/06/00

cc:
NDA 20-972
Division File 20,972
HFD-530/TL/Kukich
HFD-530/MO/Haverkos
HFD-725/Stat/Breazna

Record of Teleconference

HFD-530

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

Kelly

Record of Teleconference

NDA: **20-972**

Date: **November 12, 1999**

Drug: **Sustiva (efavirenz)**

Sponsor: **DuPont**

BETWEEN: **Representatives of DuPont**
Pat Dewalt, Regulatory Affairs
Richard Levy, Clinical
Doug Mannan
Dominic Labriola, Statistics
Laura Bessen, M.D., Clinical
Tom Donnelley, Regulatory Affairs
Rob Krupp, Clinical

AND: **Representatives of DAVDP**
Heidi Jolson, M.D., M.P.H., Director
Stanka Kukich, M.D., Medical Team Leader
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Lauren Iacono-Connors, Ph.D., Microbiology Team Leader
Girish Aras, Ph.D., Statistical Team Leader
Christine Kelly, RN, MS, MBA, Project Manager

SUBJECT: Traditional Approval Supplement-Labeling

Background: This teleconference was requested by the Medical officer (10/29/99) to discuss DuPont's labeling for their traditional approval supplement in response to the fax sent in by the sponsor November 9, 1999 (please see attached).

Discussion

FDA agreed to the following:

1. It would be acceptable to put serious psychiatric adverse events in a second paragraph of the warning section. CNS adverse events may also be in another part of the warning section.

2. Adverse events may be identified by where they occurred, i.e. in clinical trials or during the post-marketing period.

3. The sponsor will re-send a proposal based on Table 4. Seizures and convulsions will be dealt with separately.

4. In the WARNINGS section, Under Nervous System Symptoms, in the following sentence, "These common nervous...symptoms", the sponsor will replace "related" with "predictive"

Actions:

1. The sponsor will resubmit the label early next week.

2. A teleconference will be set up next week to discuss assay data that the sponsor has available.

Concurrence:

HFD-530/MO TL/Kukich 11-13-99

cc:
HFD-530 Div. File
HFD-530/PM/Kelly

Record of Teleconference

11:50 AM

Telefax

DuPont Pharmaceuticals Company
Centre Road, Wilmington DE 19805
Phone (302) 992-5440 FAX (302) 992-3011

Resending Fax

Date: 9 November 1999

To: Chris Kelly DAVDP 301.827.2523 (fax) 301.827.2335 (ph)

10:30 AM Nov 10

From: Patricia Dewalt, PhD
Director Regulatory Affairs

Total Pages: 6

Re: NDA No. 20-972; SUSTIVA™ (efavirenz)

Chris,

Our labeling proposals for Psychiatric & Nervous System Warnings and Precautions, and corresponding rationale are attached for your consideration. We would like to focus the Friday Nov 12 teleconference on resolution of these issues. Following agreement on the philosophy and language for these sections, the corresponding changes to the Information for Patients, Adverse Reactions, and Patient Package Insert should be largely derivative.

The TTF graphs for Studies 006 and ACTG 364, which were sent to you FedEx on 11/8 will be incorporated in to the label. Following resolution of the safety issues identified above, a complete package insert will be prepared and submitted as soon as possible in order to ratify any outstanding items that we have not yet discussed.

Response to Agency's Suggested Safety and Precautions Changes

In the response (submitted September 13, 1999) to the Agency's August 12, 1999 request for additional information on serious neurologic and psychiatric events, the data was summarized differently in the responses to Question 1 and Question 7. As we stated in the response, the response to Question 1 was based on review of individual case narratives to determine the true frequency of specific adverse experiences. The response to Question 7 was based on the database, which was not changed based on the few discrepancies found during the review for Question 1. In the response to the August 12 request, the statistical analyses were based on the uncorrected database.

For the purpose of labeling, we have redone the relevant analyses for Question 7 based on the corrected data. A summary of these new analyses is provided below as a basis for labeling discussions.

[

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4 pages redacted from this section of the approval package consisted of draft labeling

HFD-530

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

KELLY

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

45 DAY FILING MEETING MINUTES

NDA: 20-972/SE7-001

DATE: 8 July 1999

DRUG: Sustiva (efavirenz)

SPONSOR: DuPont

PARTICIPANTS: Heidi Jolson, M.D., M.P.H., Division Director
Walla Dempsey, Ph.D., Associate Director
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Jim Farrelly, Ph.D., Pharmacology/Toxicology Team Leader
Girish Aras, Ph.D., Statistical Team Leader
Mike Elashoff. Ph.D., Statistical Reviewer
Vanitha Sekar, Ph.D., Biopharmaceutical Reviewer
Dan Boring, Ph.D., Chemistry Reviewer
Lauren Connors, Ph.D., Microbiology Team Leader
Leslie Stephens, RN, MSN, Regulatory Management Officer
Christine Kelly, RN, MS, MBA, Project Manager

BACKGROUND: DuPont submitted this supplemental application on May 26, 1999. It has a filing date of July 25, 1999 and a user fee date of November 22, 1999. This meeting was held to determine if the application is fileable. This supplement provides for a traditional approval.

PHARMACOLOGY/TOXICOLOGY: Acceptable for filing.

CHEMISTRY: Acceptable for filing.

MICROBIOLOGY: Acceptable for filing.

STATISTICS: Acceptable for filing.

Action: Phase 2 efficacy data and the expanded access safety data base will be requested from the sponsor.

BIOPHARMACEUTICS: There are no filing issues.

CLINICAL: Acceptable for filing.

CONCURRENCE:
HFD-530/MO/Haverkos 7/8/99
HFD-530/MO TL/Kukich 8/2/99

cc:

NDA 20-228/20-779
Division File
HFD-530/TL /Kukich
HFD-530/MO/Haverkos
HFD-530/Chem/ Boring
HFD-530/Pharm/Yuen
HFD-530/Micro/Connors
HFD-530/Biopharm/Sekar
HFD-530/Stat/Elashoff
HFD-530/CSO/Kelly

45 Day Filing Meeting