CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-360

ADMINISTRATIVE DOCUMENTS

DFS 2/1/02

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : NDA 21-360 Supplement Type (e.g. SE5): _____ Supplement Number:_____

Stamp Date: April 2, 2001 Action Date: February 1, 2002

HFD-530 Trade and generic names/dosage form: Sustiva® (efavirenz) 300 mg and 600 mg tablets

Applicant: Bristol-Myers Squibb Pharma Company Therapeutic Class: systemic antiretroviral

Indication(s) previously approved: capsules for the treatment of HIV-1 infection in combination with other antiretroviral agents.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: treatment of HIV-1 infection in combination with other antiretroviral agents.

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ✓ **No: Please check all that apply: X Partial Waiver __Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr. 3 and up Tanner Stage_____
Max_____ kg_____ mo._____ yr. N/A Tanner Stage_____

Reason(s) for partial waiver:

- ✓ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

***Please note*:** _____ **currently being tested in clinical trial ACTG 382. Due date for studies outlined in the Written Request is June 30, 2002.**

Date studies are due (mm/dd/yy): **June 30, 2003**

This page was completed by:

{See appended electronic signature page}

/S/

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1 APPLICANT'S NAME AND ADDRESS

DuPont Pharmaceuticals Company
974 Centre Road
Wilmington, DE 19805

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 02 2001
CDR

3. PRODUCT NAME
SUSTIVA™ (efavirenz)

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW.

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____
(APPLICATION NO. CONTAINING THE DATA)

2. TELEPHONE NUMBER *(Include Area Code)*
(302) 892-7099

5 USER FEE I.D. NUMBER
4100

6. LICENSE NUMBER / NDA NUMBER
21-360

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug and Cosmetic Act
(See item 7 reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
/S/	Robert W. Babilon Associate Director, Regulatory Affairs	March 28, 2001

FORM FDA 3397 (5/98)

16. DEBARMENT CERTIFICATION (FDC Act 306(k)(l)

RE: SUSTIVA™ (efavirenz) Tablets

In compliance with Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act 21 USC 335a(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™ (efavirenz) Tablets.

21MAR01

Max W. Talbott, Ph.D.
Senior Vice President, Worldwide Regulatory Affairs
& Pharmacovigilance
DuPont Pharmaceuticals Company

Date

APPEARS THIS WAY
ON ORIGINAL

SUSTIVA™ TABLETS **(efavirenz tablets)** **PATENT INFORMATION**	**NEW DRUG APPLICATION** **DuPont Pharmaceuticals Company** **Wilmington, DE 19805**

1) Trade Name of Drug Product	SUSTIVA™
2) Active Ingredient(s)	Efavirenz (chemical name: (S)6-chloro-4-(cyclopropylethynyl)-1,4-dihydo-4-(trifluoromethyl)-2H-3, 1-benzoxazin-2-one)
3) Strength(s)	300mg, 600mg
4) Dosage Form	Tablet
Route of Administration	Oral
5) Name of Applicant	DuPont Pharmaceuticals Company
6) NDA Number	21-360
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 DuPont Pharmaceuticals Company
Type of Patent	5,663,169 Expires: September 2, 2014* Covers method of use; cover use for the treatment of HIV infection
Name of Patent Owner	Merck & Co., Inc., licensed to DuPont Pharmaceuticals Company

SUSTIVA™ TABLETS (efavirenz tablets) PATENT INFORMATION	NEW DRUG APPLICATION DuPont Pharmaceuticals Company Wilmington, DE 19805
Type of Patent	5,811,423 Expires: August 7, 2012* Covers method of use; covers use in the treatment of HIV infection in combination with one or more additional HIV antiviral agents
Name of Patent Owner	Merck & Co., Inc., licensed to DuPont Pharmaceuticals Company

* This date does not include any extension under 35 USC 156 or extension based upon Pediatric Exclusivity.

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 (NDA 21-360).

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 (NDA 21-360) for which approval is being sought.

The undersigned declares that U.S. Patent No. 5,663,169 covers the use of efavirenz (SUSTIVA™) for the treatment of HIV infection, which is the subject of this application (NDA 21-360) for which approval is being sought.

The undersigned declares that U.S. Patent No. 5,811,423 covers the method of use of efavirenz (SUSTIVA™) for the treatment of HIV infection in combination with one or more additional HIV antiviral agents, which is the subject of this application (NDA 21-360) for which approval is being sought.

SUSTIVA™ TABLETS
(efavirenz tablets)
PATENT INFORMATION

NEW DRUG APPLICATION
DuPont Pharmaceuticals Company
Wilmington, DE 19805

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™), which is the subject of this application (NDA 21-360).

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, which is the subject of this application (NDA 21-360).

A claim of patent infringement could be asserted if a person not licensed by the owner of U.S. Patent No. 5,811,423 engaged in the manufacture, use or sale of efavirenz (SUSTIVA™) for the treatment of HIV infection, which is the subject of this application (NDA 21-360).

By: _____

Blair Q. Ferguson, Ph.D., J.D.
Vice President and Chief Intellectual Property Counsel
DuPont Pharmacueticals Company

APPEARS THIS WAY
ON ORIGINAL

DFS'd 2/1/2002

EXCLUSIVITY SUMMARY for NDA # 21-360
Trade Name Sustiva® **Generic Name efavirenz**
Applicant Name Bristol-Myers Squibb Company **HFD- 530**
Approval Date February 1, 2002

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 questions about the submission.

   a) Is it an original NDA? YES /✓/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /✓/

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

   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 /___/ 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.

      The currently marketed formulation and strengths of Sustiva are 50, 100, and 200 mg capsules. The bioequivalence studies for 300 and 600 mg tablets were submitted for this NDA.

      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 /___/ NO /✓/

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

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /✓/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 # 20-972 Sustiva capsules

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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 9:**

_____

_____

(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? If not applicable, answer NO.

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 data 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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /___/

Investigation #3 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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

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 the 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 the 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) Notwithstanding 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/

Signature of Preparer

Jan. 25, 2002
Date

Title: Regulatory Project Manager

/S/ for D. BIRNKRANT

Signature of Office or Division Director

2/01/02
Date

DFS
2/1/02

cc:
Archival NDA
HFD-530/Division File
HFD-530/Yoerg
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

WITHHOLD 63 PAGE (S)

Draft

Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: S. Beam c/o Mary Dempsey at CDER/ORM/DDREII/OPDRA HFD-440			FROM(*Division/Office*) Virginia L. Yoerg, Regulatory Project Manager Division of Antiviral Drug Products HFD-530	
DATE: 6/5/01	IND NO.	NDA NO. 21-360	TYPE OF DOCUMENT: New NDA (new formulation/strength)	DATE OF DOCUMENT: March 30, 2001
NAME OF DRUG: Sustiva (evafirenz) tablets	PRIORITY CONSIDERATION: None		CLASSIFICATION OF DRUG: Treatment of HIV	DESIRED COMPLETION DATE: January 3, 2002

NAME OF FIRM: DuPont Pharmaceuticals Company

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*: New NDA for approved drug- new formulation and strength (300 and 600 mg tablets)

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

The PDUFA date for this NDA is February 2, 2002. Please take a look at the labeling and the proposed packaging. Do you have comments to the applicant that need to be coordinated? If you have any comments or questions, please call Harry Haverkos, M.D. at (301) 827-2368/haverkosh@cder.fda.gov or me at (301) 827-2419/email yoergv@cder.fda.gov. This consult sent via email and courier (with Volume 1 of NDA).

Many thanks,

Virginia L. Yoerg

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 6/7/01	DUE DATE: 11/21/01	OPDRA CONSULT: 01-0121

TO:

Debra Birnkrant, M.D.
(Acting) Director, Division of Antiviral Drug Products
HFD-530

THROUGH:

Virginia L. Yoerg
Project Manager, Division of Antiviral Drug Products
HFD-530

PRODUCT NAME:	**MANUFACTURER:** DuPont Pharmaceuticals Company/Bristol-Myers Squibb Company
Sustiva (efavirenz) Tablets 300 mg and 600 mg **NDA #:** 21-360	

SAFETY EVALUATOR: Jennifer Fan, Pharm.D.

SUMMARY: In response to a consult from the Division of Antiviral Drug Products (HFD-530), OPDRA conducted a review of the proposed labels and package insert for the new higher strengths of Sustiva.

OPDRA RECOMMENDATION: Please see review for OPDRA recommendations.

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: 301-827-3246
Fax: 301-443-5161

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 16, 2001

NDA NUMBER: 21-360

NAME OF DRUG: Sustiva (efavirenz) Tablets, 300 mg and 600 mg

NDA HOLDER: DuPont Pharmaceuticals Company/Bristol-Myers Squibb Company

I. INTRODUCTION:

This consult was written in response to a request from the Division of Antiviral Drug Products (HFD-530) for assessment of the proposed labeling and package insert for the new higher strengths, 300 mg and 600 mg, of *Sustiva*.

PRODUCT INFORMATION

Sustiva (efavirenz) has been in the U.S. market since September 1998 and is currently available as a 50 mg, 100 mg, and 200 mg capsule. Efavirenz is a non-nucleoside reverse transcriptase (RT) inhibitor of human immunodeficiency virus type 1 (HIV-1). Its activity is mediated predominantly by non-competitive inhibition of HIV-1 RT. *Sustiva* in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. The recommended dosage for *Sustiva* is 600 mg orally, once a day in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs).

II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

A. CONTAINER LABEL (300 mg: —tablet bottle; 600 mg: 30 tablet bottle)

1. We recommend that the Usual Dosage statement be revised to state "Usual Dosage: 600 mg once a day. See package insert."
2. The "Rx only" should be relocated to the main panel of the label.
3. The strength color on the label should be different from the strength color of the 50 mg, 100 mg, and 200 mg labels.
4. The net quantity should not be so prominently displayed. For example, it can be moved to the bottom of the label.
5. OPDRA believes that a boxed alert about drug-drug interactions would be more instructive if the specific drugs were mentioned. In this regard, we suggest:

> CAUTION: DO NOT take SUSTIVA with astemizole, cisapride, midazolam, triazolam, or ergot derivatives.

6. The sponsor has proposed to label the product as a ———— . Since the tablet formulation has never been approved, we believe that ———— is not appropriate.
7. We note that the sponsor has proposed no imprint code on these tablets, except for the "Sustiva" name on both strengths. The capsules contain both the strength and the *Sustiva* name, which allows easier identification of the capsules. We would recommend that the firm adopt a similar strategy with these two strengths of the tablet.

B. UNIT DOSE (300 mg and 600 mg)

1. Since *Sustiva* is available in multiple strengths, the strengths should be differentiated by highlighting and/or outlining the strength in different colors or borders, corresponding to the strength presentation on the bottle.
2. The bar code should be revised so that each blister package would have its own bar code, not shared between two individual blister packages. There should be white space on all four sides of the bar code for accurate scanning.

B. CARTON LABELING (300 mg and 600 mg)

See comments under CONTAINER LABEL, as appropriate.

C. PACKAGE INSERT

See comment above concerning the imprint codes.

III. RECOMMENDATIONS:

OPDRA recommends the above labeling revisions to encourage the safest possible use of the product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, R.Ph. at 301-827-3231.

Jennifer Fan, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

APPEARS THIS WAY
ON ORIGINAL

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jennifer Fan
11/29/01 12:57:43 PM
PHARMACIST

Jerry Phillips
11/29/01 01:00:37 PM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Rebecca Redman at CDER/OMP/DDMAC HFD-42	FROM*(Division/Office)* Virginia L. Yoerg, Regulatory Project Manager Division of Antiviral Drug Products HFD-530

DATE: 6/5/01	IND NO.	NDA NO. 21-360	TYPE OF DOCUMENT: New NDA (new formulation/strengths)	DATE OF DOCUMENT: March 30, 2001

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Sustiva (evafirenz) tablets	None	Treatment of HIV	January 3, 2002

NAME OF FIRM: DuPont Pharmaceuticals Company

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☒ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☒ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: New NDA for approved drug- new formulation and strengths (300 and 600 mg tablets)

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

The PDUFA date for this NDA is February 2, 2002. Please take a look at the labeling and the proposed packaging. Do you have comments to the applicant that need to be coordinated? If you have any comments or questions, please call Harry Haverkos, M.D. at (301) 827-2368/haverkosh@cder.fda.gov or me at (301) 827-2419/email yoergv@cder.fda.gov. This consult sent via email and courier (with Volume 1 of NDA).

Many thanks,

Virginia L. Yoerg

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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Draft

Labeling

Team Leader's Memorandum

NDA:	**21-360**
Drug and Indication:	**Sustiva® (efavirenz) tablets for the treatment of HIV-1 infection in combination with other antiretroviral agents**
Dose:	**600 mg once daily**
Submission received:	**April 2, 2001**
Date of MO review:	**January 10, 2002**
Date of Memorandum:	**January 15, 2002**

DuPont Pharmaceuticals has submitted a New Drug Application (NDA), requesting approval for Sustiva (efavirenz) 300 mg and 600 mg film-coated tablets in addition to the already approved Sustiva capsules for the treatment of HIV-1 infection, when used in combination with other antiretroviral agents. At present, Sustiva is available as 50 mg, 100 mg, and 200 mg gelatin capsules and the recommended dosage of Sustiva for adults is 600 mg once daily. The primary support for approval of the new tablet formulation was based on demonstration of bioequivalence between the 300 mg and 600 mg tablets and the currently marketed 200 mg capsule. Bioequivalence was defined as a 90% confidence interval (CI) within ——— for the log transformation parameters Cmax, AUC, and AUCT. No efficacy data were required for this New Drug Application.

In support of the request for approval of the new tablet formulation, the applicant has submitted the results of one principal and two supportive pharmacokinetic studies of efavirenz in healthy subjects. The objectives of these trials were to establish bioequivalence between the 300 mg and 600 mg tablets and the already approved 200 mg capsule formulation of Sustiva. A first bioeqivalence trial compared the 300 mg tablet to 200 mg commercially available capsule. A second study compared both the 300 mg and 600 mg tablets to the 200 mg capsule. However, the results of this second study did not satisfy the terms of bioequivalence because the 90% CI for Cmax was above —— for both the 300 mg and 600 mg tablet strengths. Consequently, the tablet was reformulated ——————————————— and a third pivotal trial was conducted.

The pivotal bioequivalence study was designed as a single-center, open-label, randomized, three-period crossover trial and enrolled 27 healthy subjects. The study results (shown in the table below) demonstrated that the 300 mg and 600 mg tablets,

given as 2 x 300mg or 1 x 600 mg, were bioequivalent to 200 mg commercially available capsules (given as 3 x 200 mg).

Geometric Mean Ratios (GMRs) of efavirenz 300 mg and 600 mg tablets to efavirenz 200 mg capsule:

Parameter	300-mg Tablet GMR (%)	90% CI	600-mg Tablet GMR (%)	90% CI
Cmax	103	93, 115	110	99, 123
AUCT	102	96, 109	102	96, 109
AUC	102	96, 108	103	97, 109

Data source: Table 12, Item 3, and Vol.1

During the review process the applicant has also submitted the results from a food-effect study. This study was a single-center, open-label, randomized, two-period crossover design that enrolled 24 healthy subjects. A single 600 mg tablet of efavirenz was given to subjects under fasted and fed conditions during two study periods separated by a minimum of 28 days. The objectives of this study were to compare the rate and extent of absorption of efavirenz 600 mg tablet under fasted and fed (1000 kcal with 60 grams of fat) conditions. Statistically significant differences were found between the fed and fasted state for Cmax, C24, AUCT, and AUC. The geometric mean ratios (high fat/high calorie meal/fasted) were 179%, 129%, and 128% for Cmax, AUCT, and AUC, respectively. The means and 90% CI for Cmax, AUC, and AUCT were all above the upper limit for the standard bioequivalence range.

Detailed discussion of pharmacokinetic and safety data is provided in the biopharmaceutics and medical reviews. I am in agreement with the conclusions of the primary reviewers that this application should be approved. Bioequivalence was demonstrated between the to be marketed tablet formulation (300 mg and 600 mg) and the commercially available 200 mg Sustiva capsules. The 300 mg and 600 mg film-coated tablets may provide the advantage of a lower pill burden to adults, and therefore, may improve compliance with antiretroviral therapy.

Approximately 70 healthy subjects received efavirenz tablets across all three studies. A higher number of subjects who received efavirenz under fed conditions reported new-onset adverse events (91%) compared to subjects who received efavirenz under fasted conditions (74%). Some of these adverse events were dizziness, headache, impaired concentration, euphoria, abnormal gait, hypoaesthesia, purpura, abdominal pain, and nausea. However, safety information provided in this NDA did not alter the overall understanding of the efavirenz safety profile.

The labeling discussions were focused on:

1. Recommendation for Sustiva to be taken on an empty stomach. When compared to a fasted state, a significant increase in efavirenz exposure was demonstrated after a single dose of efavirenz was co-administered with food to healthy subjects. In

addition, a higher number of subjects reported adverse events when efavirenz was taken with food then when it was taken under fasted conditions.

2. Revising the recommendation of bedtime dosing for efavirenz from "during the first two to four weeks of therapy and in patients who continue to experience these symptoms" to a bedtime dosing throughout therapy (whenever possible) in order to improve the tolerability of central nervous system side effects.

Phase IV commitments outlined in the Traditional Approval letter of February 9, 2000 should be referenced in the approval letter for the 300 mg and 600 mg Sustiva tablets. At present, outstanding Phase IV commitments that the applicant should address are as follows:

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 at the time when all treatment arms reach the median time to treatment failure.

5. Evaluate the safety, tolerability and efficacy of efavirenz-containing regimens in patients who have failed non-efavirenz containing regimens.

6. Investigate lipid metabolic pathways, monitor fat distribution, changes in lipid profiles and lipid disorders.

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

The ownership of this drug was transferred from DuPont Pharmaceuticals to Bristol-Myers Squibb Company during the review process. The Bristol-Myers Squibb Company decided ——————— at this time.

Stanka Kukich, M.D.
Medical Team Leader, DAVDP

Concurrence:
HFD-530/Div.Director/DBirnkrant

cc:NDA 21-360
HFD-530/MO/HHaverkos

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Stanka Kukich
2/4/02 09:01:01 AM
MEDICAL OFFICER

Jeffrey Murray
2/6/02 04:51:21 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON CRIGINAL