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APPLICATION NUMBER: 21-360

MEDICAL REVIEW(S)

NDA 21-360
Original Application

Medical Officer's Review

Date Submitted: March 30, 2001
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Review completed: July 26, 2001
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Final food study report from sponsor: November 12, 2001
Review completed: January 30, 2002

Applicant:		DuPont Pharmaceutical Company Chestnut Run Plaza 974 Centre Road Wilmington, DE 19805
Drug:	Chemical:	(S)6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4- (trifluoromethyl)-2H-3,1-benzpxazin-2-one
	Generic:	Efavirenz
	Trade:	SUSTIVA®
Route:		Oral
Dosage Form:		300 mg and 600 mg tablets
Proposed Indication:		Treatment of HIV-1 infection in combination with other antiretroviral agents
Related INDs:		[redacted]
Related NDAs:		20-972 (capsules)

NDA ——

1. Resume

Sustiva® capsules were granted traditional approval on February 9, 2000, and is available as 50-, 100-, and 200-mg hard gelatin capsules. In this application the applicant requests approval for Sustiva® tablets, a non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of HIV-1 infection, when used in combination with other antiretroviral agents. This indication is based on pharmacokinetic studies demonstrating bioequivalence between the approved capsule and two tablet strengths that are the subject of this application. Recommended dose of Sustiva® is 600mg once daily.

In support of the request for approval for Sustiva® tablets, the applicant has submitted chemistry, manufacturing, and pharmacokinetic data. In addition, the applicant has safety data from three bioavailability studies in healthy volunteers. No efficacy data were required and none was submitted.

Bioequivalence between tablets and capsules was defined as 90% confidence intervals within —— for the log transformation parameters, C_{max}, AUC, and AUCT.

There is a significant food effect with efavirenz Co-administration of a single dose of efavirenz tablet formulation with food was associated with statistically significant increases in efavirenz mean C_{max} (79%) and mean AUC (28%) compared to when taken fasted.

2. Regulatory history

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The applicant returned to FDA for an End-of-Phase 2 meeting on December 1, 1997 and a Pre-NDA meeting on December 17, 1997. A rolling submission of the results of phase 1 and 2 studies was initiated in March 1998. ——

—→ On June 11, 1998, the NDA package for accelerated approval was submitted and was approved on September 17, 1998. On May 26, 1999, the NDA package for traditional approval was submitted and was approved on February 9, 2000. ——

— On March 30, 2001, the NDA package for efavirenz tablets was submitted. On November 12, 2001 the sponsor submitted food-effect study results.

3. Summary of NDA clinical section

The clinical section of this application includes safety reports from three bioavailability trials in healthy volunteers, and the safety results of the food-effect study.

NDA ——

Study DMP 266-054

Title: A phase I, open-label, single-dose, two period crossover pilot bioavailability study in healthy volunteers comparing efavirenz tablets (formulation ————) to efavirenz capsules.

This was a pilot, open-label, single-dose crossover study to compare the rate and extent of absorption of a 300 mg strength tablet formulation of efavirenz with that of the 200 mg strength commercial capsule formulation.

Fourteen Caucasian healthy subjects received two different 600-mg doses of efavirenz separated by at least 14 days. Serial blood collections for pharmacokinetic analysis were obtained over a 14-day interval after each dose and safety assessments were obtained during the first day (confinement period) and during outpatient visits on days 2, 3, 4, 5, 7, 10 and 14 after dosing.

Table 1. Descriptive statistics of efavirenz pharmacokinetic parameters

Pk parameter		Tablet 2 x 300 mg N=12	Capsule 3 x 200 mg N=12
Cmax, µM	Mean	8.19	8.34
	SD	2.15	2.63
	%CV	26.3	31.5
Tmax, h	Median	3.0	4.0
	Range	——	——
AUC , µM*h	Mean	317.9	329.4
	SD	91.4	86.2
	%CV	28.8	26.2
T½, h	Mean	73.9	82.0
	SD	36.4	33.2
	%CV	49.2	40.5
Clo, L/h	Mean	6.47	6.14
	SD	1.89	1.55
	%CV	29.3	25.2

AUC : Area under the plasma concentration-time curve from time zero until time infinity; calculated as AUCT+Clast/ n where Clast is the last quantifiable concentration.
No statistically significant differences were found between tablet and capsule.
Data Source: Table 6.1, Item 6, Volume 1, page 100

Table 2. Geometric mean ratios of efavirenz 300-mg tablet to efavirenz 200-mg capsule for Study DMP 266-054 (N=12)

Pk parameter	Geometric mean ratio (%)	90% confidence intervals
Cmax	99.70	84.68, 117.38
AUC	96.31	88.74, 104.53
AUC	95.70	89.21, 102.67

Source: Table 6, IND —— serial number 454, page 14, submitted December 27, 2000.

Conclusion: Bioequivalence was established when 300-mg tablets and 200-mg commercial capsules were compared.

SAFETY
Fourteen subjects were enrolled and received at least one dose of medication. Two patients discontinued prematurely, one after receiving capsules and one after tablets. Therefore, 12 of the subjects completed the sequence of study medications as specified in the protocol and represent the study group.

Brief narratives on the two subjects who discontinued prematurely follows:

Subject 111 developed headache, mild back pain and coughing on Day 10 after receiving one dose of efavirenz capsules. He received approval to take ibuprofen/pseudoephedrine HCL through day 13. On day 13 he took unapproved medications (chlorpheniramine/phenylpropanolamine and pseudoephedrine/doxylamine/ dextromethorphan/acetaminophen/alcohol). He discontinued from the study on day 15 because he had coughing, headache, and back pain on presentation for efavirenz tablets and because of a protocol violation, uses of unapproved medications.

Subject 112 developed mild diarrhea on day 6 after receiving efavirenz tablets. The diarrhea persisted for more than 10 days and the patient discontinued study on Day 18 because of diarrhea without receiving efavirenz capsules.

No adverse events of moderate or severe intensity were reported during the study.

The following table list new-onset adverse events by formulation.

Table 3. New-onset adverse experiences by formulation in two or more subjects

Adverse experience	EFV tablet (N=13)	EFV capsule (N=13)
Headache	2	4
Dizziness	3	4
Nausea	0	2
Impaired concentration	1	2
Coughing	0	2
Total number of subjects with any adverse event	4	5

Source: Table 7.1, Item 6, Volume 1, page 105

Assessment: No significant differences in pharmacokinetic parameters or adverse events were noted comparing tablets and capsules.

Study DMP 266-058
Title: A phase 1, open-label, single dose, three-period crossover, bioavailability study in healthy volunteers comparing 300 mg —— and 600 mg —— efavirenz tablets to commercial efavirenz capsules.

NDA —

This was an single-center, open-label, randomized three-period, crossover study to compare the rate and extent of absorption of a single 600 mg doses of efavirenz as three 200 mg commercial capsules, two 300 mg tablets, or one 600 mg tablet in one of six treatment sequences. There was a minimum 28-day washout period between doses. Subjects received the study medication in a fasted state. Subjects were admitted to the clinical study unit on day 0 of each study period and remained confined until at least 24 hours after dose administration. Blood samples were collected at scheduled times during each study period.

Thirty healthy subjects were enrolled, 28 completed all three periods of study. One subject withdrew before dosing, another withdrew consent after period 1 (300 mg tablets) because of job-related issues. The 29 study subjects who received at least one dose were predominantly male (79%) and white (66%). The mean age was 28.9 years.

Table 4. Descriptive statistics of efavirenz pharmacokinetic parameters

Pk parameter		300 mg Tablet (N=28)	600 mg Table (N=28)	200 mg Capsule (N=28)
Cmax, μM	Mean	9.51*	9.17*	7.58
	SD	2.21	2.63	2.21
	%CV	23.3	28.7	29.2
Tmax, h	Median	4.0	3.5	4.0
	Range	—	—	—
AUC , μM*h	Mean	427.64*	419.01*	387.45
	SD	165.87	176.84	172.52
	%CV	38.8	42.2	44.5
T½, h	Mean	85.56	84.44	86.32
	SD	32.42	29.34	30.86
	%CV	37.9	34.7	35.8
Clo, L/h	Mean	4.74*	4.86*	5.20
	SD	1.87	1.76	1.91
	%CV	39.5	36.2	36.7

* Statistically significant differences ($P<0.05$) were found between efavirenz tablets and capsules.

AUC : Area under the plasma concentration-time curve from time zero until time infinity; calculated as AUCT+Clast/ n where Clast is the last quantifiable concentration.

Data Source: Table 6.1, Item 6, Volume 3, page 50 (vol. 8/13, page 49).

Table 5. Geometric mean ratios (GMR) of efavirenz 300-mg and 600-mg tablets to efavirenz 200-mg capsule for study DMP266-058 (N=28)

Pk Parameter	300-mg tablet GMR (%)	90% confidence interval	600-mg tablet GMR (%)	90% confidence interval
Cmax	123.35	113.38, 134.21	118.38	108.80, 128.79
AUC	110.97	105.64, 116.56	107.62	102.46, 113.05
AUC	109.82	104.94, 114.92	106.61	101.88, 111.57

Source: Table 8, IND — serial number 454, page 15, submitted December 27, 2000.

NDA —

Neither the 300-mg or 600-mg tablets evaluated in Study 266-058 demonstrated bioequivalence with respect to Cmax. The 90% confidence interval for Cmax was 113-134% and 109-129% for the 300-mg and 600-mg tablets, respectively, which were outside the ——— , range required to demonstrate bioequivalence.

Conclusion: Bioequivalence was not demonstrated between capsules and tablets in this study.

SAFETY

Twenty-eight of the subjects completed the sequence of study medications as specified in the protocol; 29 subjects received at least one dose.

One of 29 patients who received at least one dose discontinued the study prematurely due to job-related issues.

No deaths were reported. One subject reported a severe headache, but was considered unrelated to study medication. Seven patients, most frequently headache (3) or syncope (2) reported one or more adverse experiences of moderate intensity.

The following table list new-onset adverse events by formulation.

Table 6. New-onset adverse experiences by formulation in three or more subjects

Adverse experience	300 mg tablet (N=29)	600 mg tablet (N=28)	200 mg capsule (N=28)
Dizziness	117	11	10
Headache	3	5	3
Euphoria	3	0	1
Pain	0	1	2
Reaction unclassified	2	0	2
Diarrhea	1	2	0
Vomiting	2	1	0
Nausea	3	0	0
Confusion	0	1	2
Total number of subjects with an AE	15	18	17

Source: Table 7.1, Item 6, Volume 3, page 56 (Volume 8/13, page 55)

Assessment: The tablets and capsules were not bioequivalent. Modification of the tablet formulation was warranted.

NDA —

Study DMP 266-108

Title: A phase 1, open-label, single-dose, three-period crossover bioavailability study in healthy volunteers comparing 300 mg (formulation ——————— and 600 mg (formulation ——————— efavirenz tablets to efavirenz capsules.

This was an single-center, open-label, randomized three-period, crossover study to compare the rate and extent of absorption of a single 600 mg doses of efavirenz as three 200 mg commercial capsules, two 300 mg tablets, or one 600 mg tablet in one of six treatment sequences. There was a minimum 28-day washout period between doses. Subjects received the study medication in a fasted state. Subjects were admitted to the clinical study unit on day –1 of each study period and remained confined until at least 24 hours after dose administration. Blood samples were collected over a 21-day period after each dose.

Twenty-seven healthy subjects were enrolled, 21 completed all three periods of study. Three subjects withdrew consent, two discontinued because of adverse events (one for vomiting and one for acute mononucleosis with lymphadenopathy), and one failed to return to the clinical study unit.

The 27 study subjects were all white, 24 males and 3 females. The mean age was 27.4 years.

Table 7. Descriptive statistics of efavirenz pharmacokinetic parameters

Pk parameter		300 mg Tablet (N=21)	600 mg Table (N=21)	200 mg Capsule (N=21)
Cmax, μM	Mean	7.62	8.06	7.50
	SD	2.26	1.95	2.81
	%CV	29.6	24.2	37.4
Tmax, h	Median	3.00	4.00	4.00
	Range	—	—	—
AUC , μM*h	Mean	332.57	338.77	326.97
	SD	116.92	111.37	112.47
	%CV	35.2	32.9	34.4
T½, h	Mean	76.03	78.21	75.81
	SD	28.46	27.74	29.56
	%CV	37.4	35.5	39.0
Clo, L/h	Mean	5.78	5.59	5.88
	SD	1.80	1.74	2.07
	%CV	31.2	31.0	35.2

AUC : Area under the plasma concentration-time curve from time zero until time infinity; calculated as AUCT+Clast/ n where Clast is the last quantifiable concentration.
No statistically significant differences were found between tablet and capsule formulations.
Data Source: Table 6.1, Item 6, Volume 6, page 51 (vol. 11/13, page 50).

Table 8. Geometric mean ratios (GMR) of efavirenz 300-mg and 600-mg tablets to efavirenz 200-mg capsule for study DMP 266-108 (N=21)

Pk parameter	300-mg tablet GMR (%)	90% confidence interval	600-mg tablet GMR (%)	90% confidence interval
Cmax	103	93, 115	110	99, 123
AUC	102	96, 109	102	96, 109
AUC	102	96, 108	103	97, 109

Source: Table 10, IND —— serial number 454, page 16, submitted December 27, 2000.

Conclusion: Because bioequivalence between tablets and capsules of efavirenz was not demonstrated in study DMP 266-058, formulation for efavirenz tablets was modified for this study. Bioequivalence between 600 mg doses (300 and 600 mg tablets) and 600 mg dose (200 mg capsules) was demonstrated in Study DMP 266-108.

SAFETY

Twenty-one of the subjects completed the sequence of study medications as specified in the protocol. All 27 subjects received at least one dose.

Six patients discontinued prematurely, three withdrew consent (one following a death in the family, one because of relocation, one because of an illness), two patients discontinued due to adverse events (see below), and one patient failed to return for follow-up.

Subject 102, a 22 year-old male, developed acute mononucleosis with lymphadenopathy (moderate severity) and discontinued study on day 19 of period 2 (300 mg tablets).

Subject 121, a 23 year-old male, developed mild vomiting on study day 1 of period 1 and (capsules).

No adverse events of severe intensity were reported during the study.

Laboratory studies. No clinical laboratory results were reported as adverse events during the study. Statistically significant changes from baseline were noted for several laboratory results but none of the changes were clinically meaningful. For example, mean hemoglobin decreased from 14.97 gm/dl on period 1, day 1 to 14.42 gm/dl on period 3, day 15. Although statistically significant this difference is not clinically significant and probably reflects phlebotomy hemoglobin losses during the study.

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The following table list new-onset adverse events by formulation.

Table 9. New-onset adverse experiences by formulation in three or more subjects

Adverse experience	300 mg tablet (N=24)	600 mg tablet (N=24)	200 mg capsule (N=24)
Dizziness	7	8	7
Headache	6	3	3
Nausea	3	2	3
Impaired concentration	1	2	2
Influenza-like symptoms	2	0	1
Euphoria	1	0	1
Total number of subjects with any adverse event	14	14	15

Source: Table 7.1, Item 6, Volume 6, page 57 (Volume 11/13, page 56)

Assessment: No significant differences in pharmacokinetic parameters or adverse events were noted when 300 mg and 600 mg tablets and 200 mg capsules of efavirenz were compared. No new safety concerns were identified.

Food effect study submitted November 12, 2001

Study DMP 266-110

Title: A phase 1, open-label, single-dose, randomized, two-period crossover study in healthy volunteers to determine the effect of food on the bioavailability of efavirenz tablets.

This was an single-center, open-label, randomized two-period, crossover study with one group of healthy volunteers who were randomly assigned to one of two treatment sequences. The subjects received a single 600-mg tablet orally under fasted conditions in one study period and a single 600-mg tablet orally under fed conditions (standard high-fat/high-calorie breakfast meal) in the other study period. There was a minimum 28-day washout period between doses. Blood samples were collected over a 21-day period after each dose.

Twenty-four healthy subjects were enrolled, 22 completed both periods of study. Two subjects discontinued; one due to vomiting and one due to protocol violation.

The 24 study subjects included 23 males and one female, 20 whites, 3 Blacks and one other. The mean age was 26.7 years.

Table 10. Descriptive statistics of efavirenz pharmacokinetic parameters

Pk parameter		Fed - High fat/ High -calorie meal (N=22)	Fasted (N=221)
Cmax, μM	Mean SD	12.25 * 3.23	6.90 2.10
C24. μM	Mean SD	3.38* 1.08	2.94 1.11
Tmax, h	Median Range	4.00 —	4.00 —
AUC∞, μM•h	Mean SD	369.71* 91.55	289.14 82.32
AUC, μM•h	Mean SD	396.70* 94.21	312.85 82.54
T½, h	Mean SD	61.21 25.44	62.60 25.29
Clo, L/h	Mean SD	5.05* 1.16	6.48 1.62

Data Source: Table 6.1, Volume 1, page 48, November 12, 2001 submission.

Conclusion: Statistically significant differences were observed between fed and fasted states after administration of the efavirenz tablet for Cmax, C24, AUC∞, AUC, and CLo.

SAFETY

Twenty-two of the subjects completed the sequence of study medications as specified in the protocol. All 24 subjects received at least one dose.

Two patients discontinued prematurely, one due to an adverse event (vomiting) and one due to protocol violation (positive urine drug screen) after completing the first treatment sequence.

No severe adverse events were reported during the study.

The following table list new-onset adverse events by fasted and fed states and frequency of occurrence.

Table 11. New-onset adverse experiences by state in two or more subjects

Adverse experience	Fasted (N=23)	Fed (N=23)
Dizziness	10	16
Headache	4	7
Impaired concentration	4	6
Nausea	2	3
Euphoria	1	2
Abnormal Gait	1	2
Hypoesthesia	0	2
Vomiting	1	1
Abdominal pain	0	2
Coughing	1	1
Rhinitis	1	2
Total number of subjects with any adverse event	17	21

Source: Table 7.1, page 56, Volume 1, November 12, 2001 submission.

Laboratory abnormalities. No clinical laboratory results were reported as adverse events during the study. Although a few changes in mean laboratory values were noted from beginning to end of the study, none were determined to be clinically significant.

Assessment: Co-administration of a single dose of efavirenz with was associated with statistically significant increases in efavirenz mean Cmax (79%) and mean AUC (28%). Most subjects reported an adverse event during the study; nervous system symptoms were most common. A higher incidence of adverse events was reported when efavirenz was taken with food compared to the fasted state.

Financial Disclosure

Pursuant to 21 CFR 54.2(e) the financial certification statement provided by the applicant was reviewed. There were 5 investigators listed for Study DMP 266-058 and five for Study DMP 266-108. The applicant certified that each listed clinical investigator required to disclose to the sponsor whether he/she had a proprietary interest in the product or a significant equity in the sponsor did not disclose any such interests. The applicant further certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

NDA ——

Assessment: The tablet formulation appears to be similar to the capsule formulation in terms of bioavailability and safety. There were two issues that required negotiation during the label writing process; the presence of a food effect on plasma levels of the drug, and the potential effect of increased plasma levels on the rates of adverse events. Dosing on an empty stomach preferably at bedtime was recommended.

Regulatory Action: NDA 21-360 should be approved. The negotiated label was acceptable.

Harry W. Haverkos, M.D.
Medical Officer, DAVDP

Concurrence:
HFD-530/ActDivDir/Murray
HFD-530/TL/Kukich

CC: HFD-530/NDA 21-360
HFD-530/Div file
HFD-530/CSO/Yoerg
HFD-530/DivDir/Birnkrant
HFD-530/Pharm/Reynolds
HFD-530/Pharm/DiGiacinto
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HFZ-827/Stats/Soon
HFD-530/MO/Haverkos

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