CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-972 / S-022
21-360 / S-006

Trade Name: Sustiva

Generic Name: (efavirenz)

Sponsor: Bristol Myers Squibb

Approval Date: August 13, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-972 / S-022
21-360 / S-006

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-972 / S-022
21-360 / S-006

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-972, S-022
NDA 21-360, S-006

Bristol-Myers Squibb
Attn: Crystina Cupp, Ph.D.
Manager, Global Regulatory Science
P.O. Box 5100
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Cupp:

Please refer to your supplemental new drug applications dated October 10, 2003, received October 14, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SUSTIVA® (efavirenz) Capsules and SUSTIVA® (efavirenz) Tablets.

We acknowledge receipt of your submission(s) dated November 11, 2003, November 14, 2003, January 7, 2004, April 5, 2004, April 14, 2004, May 3, 2004, May 17, 2004, June 11, 2004, June 16, 2004, July 23, 2004, July 29, 2004, August 5, 2004, August 6, 2004, and August 12, 2004.

These supplemental new drug applications provide for the inclusion of safety and efficacy data through 168 weeks of therapy from study AI266006 to the SUSTIVA® (efavirenz) Capsules and SUSTIVA® (efavirenz) Tablets package inserts.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert submitted August 12, 2004, patient package insert submitted August 12, 2004.)

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-972, S-022, NDA 21-360, S-006." Approval of these submissions by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages three months to 16 years until October 31, 2005.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. This commitment is listed below:

> Continue with the development of a pediatric program, with emphasis on developing a liquid formulation along with obtaining safety, tolerability, pharmacokinetic and antiviral activity data. Additionally, we refer to our Pediatric Written Request letter.

Additionally, we remind you of your outstanding postmarketing commitments listed in the approval letter for NDA 20-972 for SUSTIVA® (efavirenz) Capsules dated February 9, 2000, numbers two, three, five, seven, and eight.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Destry M. Sillivan, M.S., Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

Debra Birnkrant
8/13/04 04:08:12 PM
NDA 21-360, 20-972

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-972 / S-022
21-360 / S-006

APPROVED LABELING

SUSTIVA®

(efavirenz) capsules and tablets

Rx only

DESCRIPTION

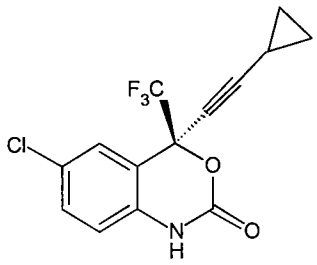
SUSTIVA® (efavirenz) is a human immunodeficiency virus type 1 (HIV-1) specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI).

Capsules: SUSTIVA is available as capsules for oral administration containing either 50 mg, 100 mg, or 200 mg of efavirenz and the following inactive ingredients: lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and sodium starch glycolate. The capsule shell contains the following inactive ingredients and dyes: gelatin, sodium lauryl sulfate, titanium dioxide, and/or yellow iron oxide. The capsule shells may also contain silicon dioxide. The capsules are printed with ink containing carmine 40 blue, FD&C Blue No. 2, and titanium dioxide.

Tablets: SUSTIVA is available as film-coated tablets for oral administration containing 600 mg of efavirenz and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The film coating contains Opadry® Yellow and Opadry® Clear. The tablets are polished with carnauba wax and printed with purple ink, Opacode® WB.

Efavirenz is chemically described as (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one.

Its empirical formula is $C_{14}H_9ClF_3NO_2$ and its structural formula is:



Efavirenz is a white to slightly pink crystalline powder with a molecular mass of 315.68. It is practically insoluble in water (<10 µg/mL).

MICROBIOLOGY

Mechanism of Action

Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). EFV activity is mediated predominantly by noncompetitive inhibition of HIV-1 reverse transcriptase (RT). HIV-2 RT and human cellular DNA polymerases α, β, γ, and δ are not inhibited by EFV.

Antiviral Activity *In vitro*

The concentration of EFV inhibiting *in vitro* replication of wild-type laboratory adapted strains and clinical isolates by 90-95% (IC_{90-95}) ranged from 1.7 to 25 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs), and macrophage/monocyte cultures. EFV demonstrated antiviral activity against most non-clade B isolates (subtypes A, AE, AG, C, D, F, G, J, N), but had reduced antiviral activity against group O viruses. EFV demonstrated additive antiviral activity without cytotoxicity against HIV-1 in cell culture when combined with the NNRTIs delavirdine (DLV) and nevirapine (NVP), NRTIs (abacavir, didanosine, emtricitabine, lamivudine [LAM], stavudine, tenofovir, zalcitabine, zidovudine [ZDV]), PIs (amprenavir, indinavir [IDV], lopinavir, nelfinavir, ritonavir, saquinavir), and the fusion inhibitor enfuvirtide. EFV demonstrated additive to antagonistic antiviral activity *in vitro* with atazanavir. EFV was not antagonistic with adefovir, used for the treatment of hepatitis B virus infection, or ribavirin, used in combination with interferon for the treatment of hepatitis C virus infection.

Resistance

In vitro: HIV-1 isolates with reduced susceptibility to EFV (>380-fold increase in IC_{90} value) emerged rapidly under *in vitro* selection. Genotypic characterization of these viruses identified mutations resulting in single amino acid substitutions L100I or V179D, double substitutions L100I/V108I, and triple substitutions L100I/V179D/ Y181C in RT.

Clinical studies: Clinical isolates with reduced susceptibility *in vitro* to EFV have been obtained. One or more RT substitutions at amino acid positions 98, 100, 101, 103, 106, 108, 188, 190, 225, and 227 were observed in patients failing treatment with EFV in combination with IDV, or with ZDV plus LAM. The mutation K103N was the most frequently observed. Long-term resistance surveillance (average 52 weeks, range 4-106 weeks) analyzed 28 matching baseline and virologic failure isolates. Sixty-one percent (17/28) of these failure isolates had decreased EFV susceptibility *in vitro* with a median 88-fold change in EFV susceptibility (IC_{50} value) from reference. The most frequent NNRTI mutation to develop in these patient isolates was K103N (54%). Other NNRTI mutations that

developed included L100I (7%), K101E/Q/R (14%), V108I (11%), G190S/T/A (7%), P225H (18%), and M230I/L (11%).

Cross-Resistance

Cross-resistance among NNRTIs has been observed. Clinical isolates previously characterized as EFV-resistant were also phenotypically resistant *in vitro* to DLV and NVP compared to baseline. DLV- and/or NVP-resistant clinical viral isolates with NNRTI resistance-associated substitutions (A98G, L100I, K101E/P, K103N/S, V106A, Y181X, Y188X, G190X, P225H, F227L, or M230L) showed reduced susceptibility to EFV *in vitro*. Greater than 90% of NRTI-resistant clinical isolates tested *in vitro* retained susceptibility to EFV.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption: Peak efavirenz plasma concentrations of 1.6-9.1 μM were attained by 5 hours following single oral doses of 100 mg to 1600 mg administered to uninfected volunteers. Dose-related increases in C_{max} and AUC were seen for doses up to 1600 mg; the increases were less than proportional suggesting diminished absorption at higher doses.

In HIV-infected patients at steady state, mean C_{max}, mean C_{min}, and mean AUC were dose proportional following 200-mg, 400-mg, and 600-mg daily doses. Time-to-peak plasma concentrations were approximately 3-5 hours and steady-state plasma concentrations were reached in 6-10 days. In 35 patients receiving SUSTIVA 600 mg once daily, steady-state C_{max} was 12.9 ± 3.7 μM (mean ± SD), steady-state C_{min} was 5.6 ± 3.2 μM, and AUC was 184 ± 73 μM•h.

Effect of Food on Oral Absorption:

Capsules—Administration of a single 600-mg dose of efavirenz capsules with a high-fat/high-caloric meal (894 kcal, 54 g fat, 54% calories from fat) or a reduced-fat/normal-caloric meal (440 kcal, 2 g fat, 4% calories from fat) was associated with a mean increase of 22% and 17% in efavirenz AUC_{∞} and a mean increase of 39% and 51% in efavirenz C_{max}, respectively, relative to the exposures achieved when given under fasted conditions. (See **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS: Information for Patients.**)

Tablets—Administration of a single 600-mg efavirenz tablet with a high-fat/high-caloric meal (approximately 1000 kcal, 500-600 kcal from fat) was associated with a 28% increase in mean AUC_{∞} of efavirenz and a 79% increase in mean C_{max} of efavirenz relative to the exposures achieved under

fasted conditions. (See **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS: Information for Patients**.)

Distribution: Efavirenz is highly bound (approximately 99.5-99.75%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients (n=9) who received SUSTIVA 200 to 600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0.26 to 1.19% (mean 0.69%) of the corresponding plasma concentration. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Metabolism: Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that efavirenz is principally metabolized by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The *in vitro* studies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism.

Efavirenz has been shown to induce P450 enzymes, resulting in the induction of its own metabolism. Multiple doses of 200-400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22-42% lower) and a shorter terminal half-life of 40-55 hours (single dose half-life 52-76 hours).

Elimination: Efavirenz has a terminal half-life of 52-76 hours after single doses and 40-55 hours after multiple doses. A one-month mass balance/excretion study was conducted using 400 mg per day with a ^{14}C-labeled dose administered on Day 8. Approximately 14-34% of the radiolabel was recovered in the urine and 16-61% was recovered in the feces. Nearly all of the urinary excretion of the radiolabeled drug was in the form of metabolites. Efavirenz accounted for the majority of the total radioactivity measured in feces.

Special Populations

Hepatic Impairment: The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment (see **PRECAUTIONS: General**).

Renal Impairment: The pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency; however, less than 1% of efavirenz is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal.

Gender and Race: The pharmacokinetics of efavirenz in patients appear to be similar between men and women and among the racial groups studied.

Geriatric: see **PRECAUTIONS: Geriatric Use**

Pediatrics: see **PRECAUTIONS: Pediatric Use**

Drug Interactions (see also CONTRAINDICATIONS and PRECAUTIONS: Drug Interactions)

Efavirenz has been shown *in vivo* to cause hepatic enzyme induction, thus increasing the biotransformation of some drugs metabolized by CYP3A4. *In vitro* studies have shown that efavirenz inhibited P450 isozymes 2C9, 2C19, and 3A4 with K_i values (8.5-17 μM) in the range of observed efavirenz plasma concentrations. In *in vitro* studies, efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 (K_i values 82-160 μM) only at concentrations well above those achieved clinically. The effects on CYP3A4 activity are expected to be similar between 200-mg, 400-mg, and 600-mg doses of efavirenz. Coadministration of efavirenz with drugs primarily metabolized by 2C9, 2C19, and 3A4 isozymes may result in altered plasma concentrations of the coadministered drug. Drugs which induce CYP3A4 activity would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.

Drug interaction studies were performed with efavirenz and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interaction. The effects of coadministration of efavirenz on the AUC and C_{max} are summarized in Table 1 (effect of efavirenz on other drugs) and Table 2 (effect of other drugs on efavirenz). For information regarding clinical recommendations see **PRECAUTIONS: Drug Interactions**.

Table 1: Effect of Efavirenz on Coadministered Drug Plasma C_{max} and AUC

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (% change) C_{max} (mean [90% CI])	Coadministered Drug (% change) AUC (mean [90% CI])
Atazanavir	400 mg qd with a light meal d 1-20	600 mg qd with a light meal d 7-20	27	↓ (59%) [49-67%]	↓ (74%) [68-78%]
	400 mg qd d 1-6, then 300 mg qd d 7-20 with ritonavir 100 mg qd and a light meal	600 mg qd 2 h after atazanavir and ritonavir d 7-20	13	↑ (14%)[a] [↓ 17-↑ 58%]	↑ (39%)[a] [2-88%]
Indinavir	1000 mg q8h x 10 days	600 mg x 10 days	20		
	After morning dose			↔[b]	↓ (33%)[b] [26-39%]
	After afternoon dose			↔[b]	↓ (37%)[b] [26-46%]

Table 1: Effect of Efavirenz on Coadministered Drug Plasma C_{max} and AUC

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (% change) C_{max} (mean [90% CI])	Coadministered Drug (% change) AUC (mean [90% CI])
	After evening dose			↓ (29%)b [11-43%]	↓ (46%)[b] [37-54%]
Lopinavir/ ritonavir	400/100 mg q12h x 9 days	600 mg x 9 days	11,7[c]	↔[d]	↓ (19%)[d] [↓ 36-↑ 3%]
Nelfinavir	750 mg q8h x 7 days	600 mg x 7 days	10	↑ (21%) [10-33%]	↑ (20%) [8-34%]
Metabolite AG-1402				↓ (40%) [30-48%]	↓ (37%) [25-48%]
Ritonavir	500 mg q12h x 8 days	600 mg x 10 days	11		
After AM dose				↑ (24%) [12-38%]	↑ (18%) [6-33%]
After PM dose				↔	↔
Saquinavir SGC[e]	1200 mg q8h x 10 days	600 mg x 10 days	12	↓ (50%) [28-66%]	↓ (62%) [45-74%]
Lamivudine	150 mg q12h x 14 days	600 mg x 14 days	9	↔	↔
Zidovudine	300 mg q12h x 14 days	600 mg x 14 days	9	↔	↔
Azithromycin	600 mg single dose	400 mg x 7 days	14	↑ (22%) [4-42%]	↔
Clarithromycin	500 mg q12h x 7 days	400 mg x 7 days	11	↓ (26%) [15-35%]	↓ (39%) [30-46%]
14-OH metabolite				↑ (49%) [32-69%]	↑ (34%) [18-53%]
Fluconazole	200 mg x 7 days	400 mg x 7 days	10	↔	↔
Rifabutin	300 mg qd x 14 days	600 mg x 14 days	9	↓ (32%) [15-46%]	↓ (38%) [28-47%]
Cetirizine	10 mg single dose	600 mg x 10 days	11	↓ (24%) [18-30%]	↔
Ethinyl estradiol	50 µg single dose	400 mg x 10 days	13	↔	↑ (37%) [25-51%]
Lorazepam	2 mg single dose	600 mg x 10 days	12	↑ (16%) [2-32%]	↑ (7%) [1-14%]
Methadone	Stable maintenance 35-100 mg daily	600 mg x 14-21 days	11	↓ (45%) [25-59%]	↓ (52%) [33-66%]
Paroxetine	20 mg qd x 14 days	600 mg x 14 days	16	↔	↔
Sertraline	50 mg qd x 14 days	600 mg x 14 days	13	↓ (29%) [15-40%]	↓ (39%) [27-50%]
Voriconazole	400 mg po q12h x 1 day then 200 mg po q12h	400 mg x 9 days	—	↓ (61%)[f]	↓ (77%)[f]

Table 1: Effect of Efavirenz on Coadministered Drug Plasma C_{max} and AUC

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (% change) C_{max} (mean [90% CI])	Coadministered Drug (% change) AUC (mean [90% CI])
	x 8 days				

↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change

[a] Compared with atazanavir 400 mg qd alone.

[b] Comparator dose of indinavir was 800 mg q8h x 10 days. Mean decreases in the C_{min} of indinavir ranged from 39 to 57%.

[c] Parallel-group design; n for efavirenz + lopinavir/ritonavir, n for lopinavir/ritonavir alone.

[d] C_{min} of lopinavir was significantly decreased by 39%. The pharmacokinetics of ritonavir 100 mg q12h are unaffected by concurrent efavirenz.

[e] Soft Gelatin Capsule.

[f] 90% CI not available.

Table 2: Effect of Coadministered Drug on Efavirenz Plasma C_{max} and AUC

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (% change) C_{max} (mean [90% CI])	Efavirenz (% change) AUC (mean [90% CI])
Indinavir	800 mg q8h x 14 days	200 mg x 14 days	11	↔	↔
Lopinavir/ ritonavir	400/100 mg q12h x 9 days	600 mg x 9 days	11,12[a]	↔	↓ (16%) [↓ 38-↑ 15%]
Nelfinavir	750 mg q8h x 7 days	600 mg x 7 days	10	↔	↔
Ritonavir	500 mg q12h x 8 days	600 mg x 10 days	9	↑ (14%) [4-26%]	↑ (21%) [10-34%]
Saquinavir SGC[b]	1200 mg q8h x 10 days	600 mg x 10 days	13	↓ (13%) [5-20%]	↓ (12%) [4-19%]
Azithromycin	600 mg single dose	400 mg x 7 days	14	↔	↔
Clarithromycin	500 mg q12h x 7 days	400 mg x 7 days	12	↑ (11%) [3-19%]	↔
Fluconazole	200 mg x 7 days	400 mg x 7 days	10	↔	↑ (16%) [6-26%]
Rifabutin	300 mg qd x 14 days	600 mg x 14 days	11	↔	↔
Rifampin	600 mg x 7 days	600 mg x 7 days	12	↓ (20%) [11-28%]	↓ (26%) [15-36%]
Aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, plus simethicone 40 mg	30 mL single dose	400 mg single dose	17	↔	↔
Cetirizine	10 mg single dose	600 mg x 10 days	11	↔	↓ (8%) [4-11%]
Ethinyl estradiol	50 µg single dose	400 mg x 10 days	13	↔	↔
Famotidine	40 mg single dose	400 mg single dose	17	↔	↔
Paroxetine	20 mg qd x 14 days	600 mg x 14 days	12	↔	↔
Sertraline	50 mg qd x 14 days	600 mg x 14 days	13	↑ (11%) [6-16%]	↔
Voriconazole	400 mg po q12h x 1 day then 200 mg po q12h x 8 days	400 mg x 9 days	—	↑ (38%)[c]	↑ (44%)[c]

↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change

[a] Parallel-group design; n for efavirenz + lopinavir/ritonavir, n for efavirenz alone.

[b] Soft Gelatin Capsule.

[c] 90% CI not available.

INDICATIONS AND USAGE

SUSTIVA (efavirenz) in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. This indication is based on two clinical trials of at least one year duration that demonstrated prolonged suppression of HIV RNA.

Description of Studies

Study 006, a randomized, open-label trial, compared SUSTIVA (600 mg once daily) + zidovudine (ZDV, 300 mg q12h) + lamivudine (LAM, 150 mg q12h) or SUSTIVA (600 mg once daily) + indinavir (IDV, 1000 mg q8h) with indinavir (800 mg q8h) + zidovudine (300 mg q12h) + lamivudine (150 mg q12h). Twelve hundred sixty-six patients (mean age 36.5 years [range 18-81], 60% Caucasian, 83% male) were enrolled. All patients were efavirenz-, lamivudine-, NNRTI-, and PI-naive at study entry. The median baseline CD4+ cell count was 320 cells/mm^3 and the median baseline HIV-1 RNA level was 4.8 $\log_{10}$ copies/mL. Treatment outcomes with standard assay (assay limit 400 copies/mL) through 48 and 168 weeks are shown in Table 3. Plasma HIV RNA levels were quantified with standard (assay limit 400 copies/mL) and ultrasensitive (assay limit 50 copies/mL) versions of the AMPLICOR HIV-1 MONITOR® assay. During the study, version 1.5 of the assay was introduced in Europe to enhance detection of non-clade B virus.

Table 3: Outcomes of Randomized Treatment Through 48 and 168 Weeks, Study 006

	SUSTIVA + ZDV + LAM		SUSTIVA + IDV		IDV + ZDV + LAM	
	n=422		n=429		n=415	
Outcome	Week 48	Week 168	Week 48	Week 168	Week 48	Week 168
Responder[a]	69%	48%	57%	40%	50%	29%
Virologic failure[b]	6%	12%	15%	20%	13%	19%
Discontinued for adverse events	7%	8%	6%	8%	16%	20%
Discontinued for other reasons[c]	17%	31%	22%	32%	21%	32%
CD4+ cell count (cells/mm^3)						
Observed subjects (n)	(279)	(205)	(256)	(158)	(228)	(129)
Mean change from baseline	190	329	191	319	180	329

[a] Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48 or Week 168.

[b] Includes patients who rebounded, patients who were on study at Week 48 and failed to achieve confirmed HIV-1 RNA <400 copies/mL at time of discontinuation, and patients who discontinued due to lack of efficacy.

[c] Includes consent withdrawn, lost to follow-up, noncompliance, never treated, missing data, protocol violation, death, and other reasons. Patients with HIV-1 RNA levels <400 copies/mL who chose not to continue in the voluntary extension phases of the study were censored at date of last dose of study medication.

For patients treated with SUSTIVA + zidovudine + lamivudine, SUSTIVA + indinavir, or indinavir + zidovudine + lamivudine, the percentage of responders with HIV-1 RNA <50 copies/mL was 65%, 50%, and 45%, respectively, through 48 weeks, and 43%, 31%, and 23%, respectively, through 168 weeks. A Kaplan-Meier analysis of time to loss of virologic response (HIV RNA <400 copies/mL) suggests that both the trends of virologic response and differences in response continue through 4 years.

ACTG 364 is a randomized, double-blind, placebo-controlled, 48-week study in NRTI-experienced patients who had completed two prior ACTG studies. One-hundred ninety-six patients (mean age 41 years [range 18-76], 74% Caucasian, 88% male) received NRTIs in combination with SUSTIVA (efavirenz) (600 mg once daily), or nelfinavir (NFV, 750 mg TID), or SUSTIVA (600 mg once daily) + nelfinavir in a randomized, double-blinded manner. The mean baseline CD4+ cell count was 389 cells/mm^3 and mean baseline HIV-1 RNA level was 8130 copies/mL. Upon entry into the study, all patients were assigned a new open-label NRTI regimen, which was dependent on their previous NRTI treatment experience. There was no significant difference in the mean CD4+ cell count among treatment groups; the overall mean increase was approximately 100 cells at 48 weeks among patients who continued on study regimens. Treatment outcomes are shown in Table 4. Plasma HIV RNA levels

were quantified with the AMPLICOR HIV-1 MONITOR® assay using a lower limit of quantification of 500 copies/mL.

Table 4: Outcomes of Randomized Treatment Through 48 Weeks, Study ACTG 364*

Outcome	SUSTIVA + NFV + NRTIs n=65	SUSTIVA + NRTIs n=65	NFV + NRTIs n=66
HIV-1 RNA <500 copies/mL[a]	71%	63%	41%
HIV-1 RNA ≥500 copies/mL[b]	17%	34%	54%
CDC Category C Event	2%	0%	0%
Discontinuations for adverse events[c]	3%	3%	5%
Discontinuations for other reasons[d]	8%	0%	0%

* For some patients, Week 56 data were used to confirm the status at Week 48.

[a] Subjects achieved virologic response (two consecutive viral loads <500 copies/mL) and maintained it through Week 48.

[b] Includes viral rebound and failure to achieve confirmed <500 copies/mL by Week 48.

[c] See **ADVERSE REACTIONS** for a safety profile of these regimens.

[d] Includes loss to follow-up, consent withdrawn, noncompliance.

A Kaplan-Meier analysis of time to treatment failure through 72 weeks demonstrates a longer duration of virologic suppression (HIV RNA <500 copies/mL) in the SUSTIVA-containing treatment arms.

CONTRAINDICATIONS

SUSTIVA (efavirenz) is contraindicated in patients with clinically significant hypersensitivity to any of its components.

SUSTIVA should not be administered concurrently with astemizole, cisapride, midazolam, triazolam, or ergot derivatives because competition for CYP3A4 by efavirenz could result in inhibition of metabolism of these drugs and create the potential for serious and/or life-threatening adverse events (eg, cardiac arrhythmias, prolonged sedation, or respiratory depression). SUSTIVA should not be administered concurrently with voriconazole because SUSTIVA significantly decreases voriconazole plasma concentrations (see **CLINICAL PHARMACOLOGY**, Tables 1 and 2).

WARNINGS

ALERT: Find out about medicines that should NOT be taken with SUSTIVA. This statement is also included on the product's bottle labels. (See **CONTRAINDICATIONS** and **PRECAUTIONS: Drug Interactions**.)

SUSTIVA must not be used as a single agent to treat HIV-1 infection or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors, resistant virus emerges rapidly when efavirenz is administered as monotherapy. The choice of new antiretroviral agents to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance.

Psychiatric Symptoms: Serious psychiatric adverse experiences have been reported in patients treated with SUSTIVA. In controlled trials of 1008 patients treated with regimens containing SUSTIVA for a mean of 2.1 years and 635 patients treated with control regimens for a mean of 1.5 years, the frequency of specific serious psychiatric events among patients who received SUSTIVA or control regimens, respectively, were: severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonfatal suicide attempts (0.5%, 0), aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.2%, 0.3%). When psychiatric symptoms similar to those noted above were combined and evaluated as a group in a multifactorial analysis of data from Study 006, treatment with efavirenz was associated with an increase in the occurrence of these selected psychiatric symptoms. Other factors associated with an increase in the occurrence of these psychiatric symptoms were history of injection drug use, psychiatric history, and receipt of psychiatric medication at study entry; similar associations were observed in both the SUSTIVA and control treatment groups. In Study 006, onset of new serious psychiatric symptoms occurred throughout the study for both SUSTIVA-treated and control-treated patients. One percent of SUSTIVA-treated patients discontinued or interrupted treatment because of one or more of these selected psychiatric symptoms. There have also been occasional postmarketing reports of death by suicide, delusions, and psychosis-like behavior, although a causal relationship to the use of SUSTIVA cannot be determined from these reports. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of SUSTIVA, and if so, to determine whether the risks of continued therapy outweigh the benefits (see **ADVERSE REACTIONS**).

Nervous System Symptoms: Fifty-three percent of patients receiving SUSTIVA in controlled trials reported central nervous system symptoms compared to 25% of patients receiving control regimens. These symptoms included, but were not limited to, dizziness (28.1%), insomnia (16.3%), impaired concentration (8.3%), somnolence (7.0%), abnormal dreams (6.2%), and hallucinations (1.2%). These symptoms were severe in 2.0% of patients, and 2.1% of patients discontinued therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2-4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5 to 9% in patients treated with regimens containing SUSTIVA and from 3 to 5% in patients treated with a control regimen. Patients should be informed that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms (see **WARNINGS:**

Psychiatric Symptoms). Dosing at bedtime may improve the tolerability of these nervous system symptoms (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Analysis of long-term data from Study 006 (median follow-up 180 weeks, 102 weeks, and 76 weeks for patients treated with SUSTIVA + zidovudine + lamivudine, SUSTIVA + indinavir, and indinavir + zidovudine + lamivudine, respectively) showed that, beyond 24 weeks of therapy, the incidences of new-onset nervous system symptoms among SUSTIVA-treated patients were generally similar to those in the indinavir-containing control arm.

Patients receiving SUSTIVA should be alerted to the potential for additive central nervous system effects when SUSTIVA is used concomitantly with alcohol or psychoactive drugs.

Patients who experience central nervous system symptoms such as dizziness, impaired concentration, and/or drowsiness should avoid potentially hazardous tasks such as driving or operating machinery.

Drug Interactions: Concomitant use of SUSTIVA and St. John's wort (*hypericum perforatum*) or St. John's wort-containing products is not recommended. Coadministration of non-nucleoside reverse transcriptase inhibitors (NNRTIs), including SUSTIVA, with St. John's wort is expected to substantially decrease NNRTI concentrations and may result in suboptimal levels of efavirenz and lead to loss of virologic response and possible resistance to efavirenz or to the class of NNRTIs.

Reproductive Risk Potential: Malformations have been observed in fetuses from efavirenz-treated monkeys that received doses which resulted in plasma drug concentrations similar to those in humans given 600 mg/day (see **PRECAUTIONS: Pregnancy**); therefore, pregnancy should be avoided in women receiving SUSTIVA. Barrier contraception should always be used in combination with other methods of contraception (eg, oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing prior to initiation of SUSTIVA.

PRECAUTIONS

General

Skin Rash: In controlled clinical trials, 26% (266/1008) of patients treated with 600 mg SUSTIVA experienced new-onset skin rash compared with 17% (111/635) of patients treated in control groups. Rash associated with blistering, moist desquamation, or ulceration occurred in 0.9% (9/1008) of patients treated with SUSTIVA. The incidence of Grade 4 rash (eg, erythema multiforme, Stevens-Johnson syndrome) in patients treated with SUSTIVA in all studies and expanded access was 0.1%. The median time to onset of rash in adults was 11 days and the median duration, 16 days. The discontinuation rate for rash in clinical trials was 1.7% (17/1008). SUSTIVA should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or

fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash.

Rash was reported in 26 of 57 pediatric patients (46%) treated with SUSTIVA capsules. One pediatric patient experienced Grade 3 rash (confluent rash with fever), and two patients had Grade 4 rash (erythema multiforme). The median time to onset of rash in pediatric patients was 8 days. Prophylaxis with appropriate antihistamines prior to initiating therapy with SUSTIVA in pediatric patients should be considered (see **ADVERSE REACTIONS**).

Liver Enzymes: In patients with known or suspected history of hepatitis B or C infection and in patients treated with other medications associated with liver toxicity, monitoring of liver enzymes is recommended. In patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range, the benefit of continued therapy with SUSTIVA (efavirenz) needs to be weighed against the unknown risks of significant liver toxicity (see **ADVERSE REACTIONS: Laboratory Abnormalities**).

Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering SUSTIVA to these patients.

Convulsions: Convulsions have been observed infrequently in patients receiving efavirenz, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medications primarily metabolized by the liver, such as phenytoin, carbamazepine, and phenobarbital, may require periodic monitoring of plasma levels. Caution must be taken in any patient with a history of seizures.

Animal toxicology: Nonsustained convulsions were observed in 6 of 20 monkeys receiving efavirenz at doses yielding plasma AUC values 4- to 13-fold greater than those in humans given the recommended dose.

Cholesterol: Monitoring of cholesterol and triglycerides should be considered in patients treated with SUSTIVA (see **ADVERSE REACTIONS**).

Fat Redistribution: Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including SUSTIVA. During the initial phase

of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis carinii* pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.

Information for Patients

A statement to patients and healthcare providers is included on the product's bottle labels: **ALERT: Find out about medicines that should NOT be taken with SUSTIVA.** A Patient Package Insert (PPI) for SUSTIVA is available for patient information.

Patients should be informed that SUSTIVA is not a cure for HIV-1 infection and that they may continue to develop opportunistic infections and other complications associated with HIV-1 disease. Patients should be told that there are currently no data demonstrating that SUSTIVA therapy can reduce the risk of transmitting HIV to others through sexual contact or blood contamination.

Patients should be advised to take SUSTIVA every day as prescribed. SUSTIVA must always be used in combination with other antiretroviral drugs. Patients should be advised to take SUSTIVA on an empty stomach, preferably at bedtime. Taking SUSTIVA with food increases efavirenz concentrations and may increase the frequency of adverse events. Dosing at bedtime may improve the tolerability of nervous system symptoms (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**). Patients should remain under the care of a physician while taking SUSTIVA.

Patients should be informed that central nervous system symptoms including dizziness, insomnia, impaired concentration, drowsiness, and abnormal dreams are commonly reported during the first weeks of therapy with SUSTIVA. Dosing at bedtime may improve the tolerability of these symptoms, and these symptoms are likely to improve with continued therapy. Patients should be alerted to the potential for additive central nervous system effects when SUSTIVA is used concomitantly with alcohol or psychoactive drugs. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery (see **WARNINGS: Nervous System Symptoms**). In clinical trials, patients who develop central nervous system symptoms were not more likely to subsequently develop psychiatric symptoms (see **WARNINGS: Psychiatric Symptoms**).

Patients should also be informed that serious psychiatric symptoms including severe depression, suicide attempts, aggressive behavior, delusions, paranoia, and psychosis-like symptoms have also been infrequently reported in patients receiving SUSTIVA. Patients should be informed that if they experience severe psychiatric adverse experiences they should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of SUSTIVA, and if so, to determine

whether discontinuation of SUSTIVA may be required. Patients should also inform their physician of any history of mental illness or substance abuse (see **WARNINGS: Psychiatric Symptoms**).

Patients should be informed that another common side effect is rash. These rashes usually go away without any change in treatment. In a small number of patients, rash may be serious. Patients should be advised that they should contact their physician promptly if they develop a rash.

Because malformations have been observed in fetuses from efavirenz-treated animals, instructions should be given to avoid pregnancy in women receiving SUSTIVA. Women should be advised to notify their physician if they become pregnant while taking SUSTIVA. A reliable form of barrier contraception should always be used in combination with other methods of contraception, including oral or other hormonal contraception, because the effects of efavirenz on hormonal contraceptives are not fully characterized.

SUSTIVA may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, nonprescription medication or herbal products, particularly St. John's wort.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Drug Interactions (see also CONTRAINDICATIONS and CLINICAL PHARMACOLOGY: Drug Interactions)

Efavirenz has been shown *in vivo* to induce CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when coadministered with SUSTIVA. *In vitro* studies have demonstrated that efavirenz inhibits 2C9, 2C19, and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Coadministration of efavirenz with drugs primarily metabolized by these isozymes may result in altered plasma concentrations of the coadministered drug. Therefore, appropriate dose adjustments may be necessary for these drugs.

Drugs which induce CYP3A4 activity (eg, phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations. Drug interactions with SUSTIVA are summarized in Table 5.

Table 5[a]

Drugs That Should Not Be Coadministered With SUSTIVA	
Drug Class	**Drugs Within Class Not To Be Coadministered With SUSTIVA**
Antihistamines	Astemizole
Benzodiazepines	midazolam, triazolam
GI Motility Agents	Cisapride
Anti-Migraine	ergot derivatives
Antifungal	Voriconazole

Established Drug Interactions

Drug Name	Effect	Clinical Comment
Atazanavir	↓ atazanavir	When coadministered with SUSTIVA in treatment-naive patients, the recommended dose of atazanavir is 300 mg with ritonavir 100 mg and SUSTIVA 600 mg (all once daily). Dosing recommendations for SUSTIVA and atazanavir in treatment-experienced patients have not been established.
Clarithromycin	↓ clarithromycin concentration ↑ 14-OH metabolite concentration	Plasma concentrations decreased by SUSTIVA; clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving SUSTIVA and clarithromycin. No dose adjustment of SUSTIVA is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered (see **Other Drugs,** following table). Other macrolide antibiotics, such as erythromycin, have not been studied in combination with SUSTIVA.
Indinavir	↓ indinavir concentration	The optimal dose of indinavir, when given in combination with SUSTIVA, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to SUSTIVA. When indinavir at an increased dose (1000 mg every 8 hours) was given with SUSTIVA (600 mg once daily), the indinavir AUC and C_{min} were decreased on average by 33-46% and 39-57%, respectively, compared to when indinavir (800 mg every 8 hours) was given alone.
Lopinavir/ritonavir	↓ lopinavir concentration	A dose increase of lopinavir/ritonavir to 533/133 mg (4 capsules or 6.5 mL) twice daily taken with food is recommended when used in combination with SUSTIVA.
Methadone	↓ methadone concentration	Coadministration in HIV-infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

Established Drug Interactions

Drug Name	Effect	Clinical Comment
Ethinyl estradiol	↑ ethinyl estradiol concentration	Plasma concentrations increased by SUSTIVA; clinical significance unknown. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterized, a reliable method of barrier contraception should be used in addition to oral contraceptives.
Rifabutin	↓ rifabutin concentration	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Rifampin	↓ efavirenz concentration	Clinical significance of reduced efavirenz concentrations unknown.
Ritonavir	↑ ritonavir concentration ↑ efavirenz concentration	Combination was associated with a higher frequency of adverse clinical experiences (eg, dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when SUSTIVA is used in combination with ritonavir.
Saquinavir	↓ saquinavir concentration	Should not be used as sole protease inhibitor in combination with SUSTIVA.
Sertraline	↓ sertraline concentration	Increases in sertraline dose should be guided by clinical response.

Other Potentially Clinically Significant Drug or Herbal Product Interactions With SUSTIVA[b]

Anticoagulants: Warfarin	Plasma concentrations and effects potentially increased or decreased by SUSTIVA.
Anticonvulsants: Phenytoin Phenobarbital Carbamazepine	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antifungals: Itraconazole Ketoconazole	Drug interaction studies with SUSTIVA and these imidazole and triazole antifungals have not been conducted. SUSTIVA has the potential to decrease plasma concentrations of itraconazole and ketoconazole.
Anti-HIV protease inhibitors:	
Saquinavir/ritonavir combination	No pharmacokinetic data are available.
Amprenavir	SUSTIVA has the potential to decrease serum concentrations of amprenavir.
Non-nucleoside reverse transcriptase inhibitors	No studies have been performed with other NNRTIs.
St. John's wort (*Hypericum perforatum*)	Expected to substantially decrease plasma levels of efavirenz; has not been studied in combination with SUSTIVA.

[a] See Tables 1 and 2.

[b] This table is not all-inclusive.

Other Drugs: Based on the results of drug interaction studies (see Tables 1 and 2), no dosage adjustment is recommended when SUSTIVA is given with the following: aluminum/magnesium hydroxide antacids, azithromycin, cetirizine, famotidine, fluconazole, lamivudine, lorazepam, nelfinavir, paroxetine, and zidovudine.

Specific drug interaction studies have not been performed with SUSTIVA and NRTIs other than lamivudine and zidovudine. Clinically significant interactions would not be expected since the NRTIs are metabolized via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term carcinogenicity studies in mice and rats were carried out with efavirenz. Mice were dosed with 0, 25, 75, 150, or 300 mg/kg/day for 2 years. Incidences of hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas were increased above background in females. No increases in tumor incidence above background were seen in males. In studies in which rats were administered efavirenz at doses of 0, 25, 50, or 100 mg/kg/day for 2 years, no increases in tumor incidence above background were observed. The systemic exposure (based on AUCs) in mice was approximately 1.7-fold that in humans receiving the 600-mg/day dose. The exposure in rats was lower than that in humans. The mechanism of the carcinogenic potential is unknown. However, in genetic toxicology assays, efavirenz showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. These included bacterial mutation assays in *S. typhimurium* and *E. coli*, mammalian mutation assays in Chinese hamster ovary cells, chromosome aberration assays in human peripheral blood lymphocytes or Chinese hamster ovary cells, and an *in vivo* mouse bone marrow micronucleus assay. Given the lack of genotoxic activity of efavirenz, the relevance to humans of neoplasms in efavirenz-treated mice is not known.

Efavirenz did not impair mating or fertility of male or female rats, and did not affect sperm of treated male rats. The reproductive performance of offspring born to female rats given efavirenz was not affected. As a result of the rapid clearance of efavirenz in rats, systemic drug exposures achieved in these studies were equivalent to or below those achieved in humans given therapeutic doses of efavirenz.

Pregnancy

Pregnancy Category C: Pregnancy should be avoided in women receiving SUSTIVA. Barrier contraception should always be used in combination with other methods of contraception (eg, oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing prior to initiation of SUSTIVA (see **WARNINGS: Reproductive Risk Potential**).

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to SUSTIVA, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling (800) 258-4263.

There are no adequate and well-controlled studies in pregnant women. SUSTIVA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options. As of July 2003, the Antiretroviral Pregnancy Registry has received reports of 165 pregnancies exposed to efavirenz-containing regimens, the majority of which were first-trimester exposures (160 pregnancies). Birth defects occurred in 4 of 142 live births (first-trimester exposure) and 0 of 11 live births (second-/third-trimester exposure). In addition, there has been one report of multiple defects including abnormalities consistent with Dandy-Walker syndrome in a fetus from a spontaneous abortion, one report of neural tube defect in a fetus from a pregnancy electively terminated in the second trimester, and one report of meningomyelocele in an infant. All three mothers were exposed to efavirenz-containing regimens in the first trimester. A causal relationship of these events to the use of SUSTIVA cannot be established.

Malformations have been observed in 3 of 20 fetuses/infants from efavirenz-treated cynomolgus monkeys (versus 0 of 20 concomitant controls) in a developmental toxicity study. The pregnant monkeys were dosed throughout pregnancy (postcoital days 20-150) with efavirenz 60 mg/kg daily, a dose which resulted in plasma drug concentrations similar to those in humans given 600 mg/day of SUSTIVA. Anencephaly and unilateral anophthalmia were observed in one fetus, microophthalmia was observed in another fetus, and cleft palate was observed in a third fetus. Efavirenz crosses the placenta in cynomolgus monkeys and produces fetal blood concentrations similar to maternal blood concentrations. Efavirenz has been shown to cross the placenta in rats and rabbits and produces fetal blood concentrations of efavirenz similar to maternal concentrations. An increase in fetal resorptions was observed in rats at efavirenz doses that produced peak plasma concentrations and AUC values in female rats equivalent to or lower than those achieved in humans given 600 mg once daily of SUSTIVA. Efavirenz produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to and AUC values approximately half of those achieved in humans given 600 mg once daily of SUSTIVA.

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Although it is not known if efavirenz is secreted in human milk, efavirenz is secreted into the milk of lactating rats. Because of the potential for HIV transmission and the potential for serious adverse effects in nursing infants, **mothers should be instructed not to breast-feed if they are receiving SUSTIVA.**

Pediatric Use

ACTG 382 is an ongoing, open-label study in 57 NRTI-experienced pediatric patients to characterize the safety, pharmacokinetics, and antiviral activity of SUSTIVA in combination with nelfinavir (20-30 mg/kg TID) and NRTIs. Mean age was 8 years (range 3-16). SUSTIVA has not been studied in pediatric patients below 3 years of age or who weigh less than 13 kg. At 48 weeks, the type and frequency of adverse experiences was generally similar to that of adult patients with the exception of a higher incidence of rash, which was reported in 46% (26/57) of pediatric patients compared to 26% of adults, and a higher frequency of Grade 3 or 4 rash reported in 5% (3/57) of pediatric patients compared to 0.9% of adults (see **ADVERSE REACTIONS,** Table 7).

The starting dose of SUSTIVA was 600 mg once daily adjusted to body size, based on weight, targeting AUC levels in the range of 190-380 μM•h. The pharmacokinetics of efavirenz in pediatric patients were similar to the pharmacokinetics in adults who received 600-mg daily doses of SUSTIVA. In 48 pediatric patients receiving the equivalent of a 600-mg dose of SUSTIVA, steady-state C_{max} was 14.2 ± 5.8 μM (mean ± SD), steady-state C_{min} was 5.6 ± 4.1 μM, and AUC was 218 ± 104 μM•h.

Geriatric Use

Clinical studies of SUSTIVA did not include sufficient numbers of subjects aged 65 years 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 therapy.

ADVERSE REACTIONS

The most significant adverse events observed in patients treated with SUSTIVA are nervous system symptoms, psychiatric symptoms, and rash. Unless otherwise specified, the analyses described below included 1008 patients treated with regimens containing SUSTIVA and 635 patients treated with a control regimen in controlled trials.

Nervous System Symptoms: Fifty-three percent of patients receiving SUSTIVA reported central nervous system symptoms (see **WARNINGS: Nervous System Symptoms**). Table 6 lists the frequency of the symptoms of different degrees of severity and gives the discontinuation rates in clinical trials for one or more of the following nervous system symptoms: dizziness, insomnia, impaired concentration, somnolence, abnormal dreaming, euphoria, confusion, agitation, amnesia, hallucinations, stupor, abnormal thinking, and depersonalization. The frequencies of specific central and peripheral nervous system symptoms are provided in Table 8.

Table 6: Percent of Patients with One or More Selected Nervous System Symptoms[a,b]

Percent of Patients with:	SUSTIVA 600 mg Once Daily (n=1008) %	Control Groups (n=635) %
Symptoms of any severity	52.7	24.6
Mild symptoms[c]	33.3	15.6
Moderate symptoms[d]	17.4	7.7
Severe symptoms[e]	2.0	1.3
Treatment discontinuation as a result of symptoms	2.1	1.1

[a] Includes events reported regardless of causality.

[b] Data from Study 006 and three Phase 2/3 studies.

[c] "Mild" = Symptoms which do not interfere with patient's daily activities.

[d] "Moderate" = Symptoms which may interfere with daily activities.

[e] "Severe" = Events which interrupt patient's usual daily activities.

Psychiatric Symptoms: Serious psychiatric adverse experiences have been reported in patients treated with SUSTIVA. In controlled trials, the frequency of specific serious psychiatric symptoms among patients who received SUSTIVA or control regimens, respectively, were severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonfatal suicide attempts (0.5%, 0), aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.2%, 0.3%) (see **WARNINGS: Psychiatric Symptoms**). Additional psychiatric symptoms observed at a frequency of >2% among patients treated with SUSTIVA or control regimens, respectively, in controlled clinical trials were depression (19%, 16%), anxiety (13%, 9%), and nervousness (7%, 2%).

Skin Rash: Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with SUSTIVA. In most patients, rash resolves with continuing SUSTIVA therapy within one month. SUSTIVA can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids may be considered when SUSTIVA is restarted. SUSTIVA should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. The frequency of rash by NCI grade and the discontinuation rates as a result of rash are provided in Table 7.

Table 7: Percent of Patients with Treatment-Emergent Rash[a,b]

Percent of Patients with:	Description of Rash Grade[c]	SUSTIVA 600 mg Once Daily Adults (n=1008)	SUSTIVA Pediatric Patients (n=57)	Control Groups Adults (n= 635)
		%	%	%
Rash of any grade	—	26.3	45.6	17.5
Grade 1 rash	Erythema, pruritus	10.7	8.8	9.8
Grade 2 rash	Diffuse maculopapular rash, dry desquamation	14.7	31.6	7.4
Grade 3 rash	Vesiculation, moist desquamation, ulceration	0.8	1.8	0.3
Grade 4 rash	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, necrosis requiring surgery, exfoliative dermatitis	0.1	3.5	0.0
Treatment discontinuation as a result of rash	—	1.7	8.8	0.3

[a] Includes events reported regardless of causality.

[b] Data from Study 006 and three Phase 2/3 studies.

[c] NCI Grading System.

As seen in Table 7, rash is more common in pediatric patients and more often of higher grade (ie, more severe) (see **PRECAUTIONS: General**).

Experience with SUSTIVA (efavirenz) in patients who discontinued other antiretroviral agents of the NNRTI class is limited. Nineteen patients who discontinued nevirapine because of rash have been treated with SUSTIVA. Nine of these patients developed mild-to-moderate rash while receiving therapy with SUSTIVA, and two of these patients discontinued because of rash.

A few cases of pancreatitis have been described, although a causal relationship with efavirenz has not been established. Asymptomatic increases in serum amylase levels were observed in a significantly higher number of patients treated with efavirenz 600 mg than in control patients (see **ADVERSE REACTIONS: Laboratory Abnormalities**).

Selected clinical adverse experiences of moderate or severe intensity observed in ≥2% of SUSTIVA-treated patients in two controlled clinical trials are presented in Table 8.

Table 8: Selected Treatment-Emergent[a] Adverse Events of Moderate or Severe Intensity Reported in ≥2% of SUSTIVA-Treated Patients in Studies 006 and ACTG 364

Adverse Events	Study 006 LAM-, NNRTI-, and Protease Inhibitor-Naive Patients			Study ACTG 364 NRTI-experienced, NNRTI- and Protease Inhibitor-Naive Patients		
	SUSTIVA[b] + ZDV/LAM (n=412) 180 weeks[c]	SUSTIVA[b] + Indinavir (n=415) 102 weeks[c]	Indinavir + ZDV/LAM (n=401) 76 weeks[c]	SUSTIVA[b] + Nelfinavir + NRTIs (n=64) 71.1 weeks[c]	SUSTIVA[b] + NRTIs (n=65) 70.9 weeks[c]	Nelfinavir + NRTIs (n=66) 62.7 weeks[c]
Body as a Whole						
Fatigue	8%	5%	9%	0	2%	3%
Pain	1%	2%	8%	13%	6%	17%
Central and Peripheral Nervous System						
Dizziness	9%	9%	2%	2%	6%	6%
Headache	8%	5%	3%	5%	2%	3%
Insomnia	7%	7%	2%	0	0	2%
Concentration impaired	5%	3%	<1%	0	0	0
Abnormal dreams	3%	1%	0	—	—	—
Somnolence	2%	2%	<1%	0	0	0
Anorexia	1%	<1%	<1%	0	2%	2%
Gastrointestinal						
Nausea	10%	6%	24%	3%	2%	2%
Vomiting	6%	3%	14%	—	—	—
Diarrhea	3%	5%	6%	14%	3%	9%
Dyspepsia	4%	4%	6%	0	0	2%
Abdominal pain	2%	2%	5%	3%	3%	3%
Psychiatric						
Anxiety	2%	4%	<1%	—	—	—
Depression	5%	4%	<1%	3%	0	5%
Nervousness	2%	2%	0	2%	0	2%
Skin & Appendages						
Rash	11%	16%	5%	9%	5%	9%
Pruritus	<1%	1%	1%	9%	5%	9%

[a] Includes adverse events at least possibly related to study drug or of unknown relationship for Study 006. Includes all adverse events regardless of relationship to study drug for Study ACTG 364.

[b] SUSTIVA provided as 600 mg once daily.

[c] Median duration of treatment.

— = Not Specified.
ZDV = zidovudine, LAM=lamivudine.

Clinical adverse experiences observed in ≥10% of 57 pediatric patients aged 3 to 16 years who received SUSTIVA capsules, nelfinavir, and one or more NRTIs were: rash (46%), diarrhea/loose stools (39%), fever (21%), cough (16%), dizziness/lightheaded/fainting (16%), ache/pain/discomfort

(14%), nausea/vomiting (12%), and headache (11%). The incidence of nervous system symptoms was 18% (10/57). One patient experienced Grade 3 rash, two patients had Grade 4 rash, and five patients (9%) discontinued because of rash (see also **PRECAUTIONS: Skin Rash** and **Pediatric Use**).

Postmarketing Experience

Body as a Whole: allergic reactions, asthenia, redistribution/accumulation of body fat (see **PRECAUTIONS: Fat Redistribution**)

Central and Peripheral Nervous System: abnormal coordination, ataxia, convulsions, hypoesthesia, paresthesia, neuropathy, tremor

Endocrine: gynecomastia

Gastrointestinal: constipation, malabsorption

Cardiovascular: flushing, palpitations

Liver and Biliary System: hepatic enzyme increase, hepatic failure, hepatitis

Metabolic and Nutritional: hypercholesterolemia, hypertriglyceridemia

Musculoskeletal: arthralgia, myalgia, myopathy

Psychiatric: aggressive reactions, agitation, delusions, emotional lability, mania, neurosis, paranoia, psychosis, suicide

Respiratory: dyspnea

Skin and Appendages: erythema multiforme, nail disorders, skin discoloration, Stevens-Johnson syndrome

Special Senses: abnormal vision, tinnitus

Laboratory Abnormalities

Selected Grade 3-4 laboratory abnormalities reported in ≥2% of SUSTIVA-treated patients in two clinical trials are presented in Table 9.

Table 9: Selected Grade 3-4 Laboratory Abnormalities Reported in ≥2% of SUSTIVA-Treated Patients in Studies 006 and ACTG 364

		Study 006 LAM-, NNRTI-, and Protease Inhibitor-Naive Patients			Study ACTG 364 NRTI-experienced, NNRTI- and Protease Inhibitor-Naive Patients		
Variable	Limit	SUSTIVA[a] + ZDV/LAM (n=412) 180 weeks[b]	SUSTIVA[a] + Indinavir (n=415) 102 weeks[b]	Indinavir + ZDV/LAM (n=401) 76 weeks[b]	SUSTIVA[a] + Nelfinavir + NRTIs (n=64) 71.1 weeks[b]	SUSTIVA[a] + NRTIs (n=65) 70.9 weeks[b]	Nelfinavir + NRTIs (n=66) 62.7 weeks[b]
Chemistry							
ALT	>5 x ULN	5%	8%	5%	2%	6%	3%
AST	>5 x ULN	5%	6%	5%	6%	8%	8%
GGT[c]	>5 x ULN	8%	7%	3%	5%	0	5%
Amylase	>2 x ULN	4%	4%	1%	0	6%	2%
Glucose	>250 mg/dL	3%	3%	3%	5%	2%	3%
Triglycerides[d]	≥751 mg/dL	9%	6%	6%	11%	8%	17%
Hematology							
Neutrophils	<750/mm^3	10%	3%	5%	2%	3%	2%

[a] SUSTIVA provided as 600 mg once daily.

[b] Median duration of treatment.

[c] Isolated elevations of GGT in patients receiving SUSTIVA may reflect enzyme induction not associated with liver toxicity.

[d] Nonfasting.

ZDV = zidovudine, LAM = lamivudine. ULN = Upper limit of normal. ALT = alanine aminotransferase. AST = aspartate aminotransferase. GGT = gamma-glutamyltransferase.

Liver function tests should be monitored in patients with a history of hepatitis B and/or C. In the long-term data set from Study 006, 137 patients treated with SUSTIVA-containing regimens (median duration of therapy, 68 weeks) and 84 treated with a control regimen (median duration, 56 weeks) were seropositive at screening for hepatitis B (surface antigen positive) and/or C (hepatitis C antibody positive). Among these co-infected patients, elevations in AST to greater than five times ULN developed in 13% of patients in the SUSTIVA arms and 7% of those in the control arm, and elevations in ALT to greater than five times ULN developed in 20% of patients in the SUSTIVA arms and 7% of patients in the control arm. Among co-infected patients, 3% of those treated with SUSTIVA-containing regimens and 2% in the control arm discontinued from the study because of liver or biliary system disorders (see **PRECAUTIONS: General**).

Lipids: Increases from baseline in total cholesterol of 10-20% have been observed in some uninfected volunteers receiving SUSTIVA. In patients treated with SUSTIVA + zidovudine + lamivudine,

increases from baseline in nonfasting total cholesterol and HDL of approximately 20% and 25%, respectively, were observed. In patients treated with SUSTIVA + indinavir, increases from baseline in nonfasting cholesterol and HDL of approximately 40% and 35%, respectively, were observed. Nonfasting total cholesterol levels ≥240 mg/dL and ≥300 mg/dL were reported in 34% and 9%, respectively, of patients treated with SUSTIVA + zidovudine + lamivudine, 54% and 20%, respectively, of patients treated with SUSTIVA + indinavir, and 28% and 4%, respectively, of patients treated with indinavir + zidovudine + lamivudine. The effects of SUSTIVA on triglycerides and LDL were not well characterized since samples were taken from nonfasting patients. The clinical significance of these findings is unknown (see **PRECAUTIONS: General**).

Cannabinoid Test Interaction: Efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results have been observed in non-HIV-infected volunteers receiving SUSTIVA when the Microgenics CEDIA® DAU Multi-Level THC assay was used for screening. Negative results were obtained when more specific confirmatory testing was performed with gas chromatography/mass spectrometry.

Of the three assays analyzed (Microgenics CEDIA DAU Multi-Level THC assay, Cannabinoid Enzyme Immunoassay [Diagnostic Reagents, Inc], and AxSYM® Cannabinoid Assay), only the Microgenics CEDIA DAU Multi-Level THC assay showed false-positive results. The other two assays provided true-negative results. The effects of SUSTIVA on cannabinoid screening tests other than these three are unknown. The manufacturers of cannabinoid assays should be contacted for additional information regarding the use of their assays with patients receiving efavirenz.

OVERDOSAGE

Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.

Treatment of overdose with SUSTIVA (efavirenz) should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal may be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with SUSTIVA. Since efavirenz is highly protein bound, dialysis is unlikely to significantly remove the drug from blood.

DOSAGE AND ADMINISTRATION

Adults

The recommended dosage of SUSTIVA is 600 mg orally, once daily, in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs). It is recommended that SUSTIVA be taken on an empty stomach, preferably at bedtime. The increased efavirenz concentrations observed following administration of SUSTIVA with food may lead to an increase in frequency of adverse events (see **CLINICAL PHARMACOLOGY: Effect of Food on Oral Absorption**). Dosing at bedtime may improve the tolerability of nervous system symptoms (see **WARNINGS: Nervous System Symptoms, PRECAUTIONS: Information for Patients,** and **ADVERSE REACTIONS**).

Concomitant Antiretroviral Therapy: SUSTIVA must be given in combination with other antiretroviral medications (see **CLINICAL PHARMACOLOGY: Drug Interactions** and **PRECAUTIONS: Drug Interactions** and **INDICATIONS AND USAGE**).

Pediatric Patients

It is recommended that SUSTIVA be taken on an empty stomach, preferably at bedtime. Table 10 describes the recommended dose of SUSTIVA for pediatric patients 3 years of age or older and weighing between 10 and 40 kg. The recommended dosage of SUSTIVA for pediatric patients weighing greater than 40 kg is 600 mg, once daily.

Table 10: Pediatric Dose to be Administered Once Daily

Body Weight		SUSTIVA Dose (mg)
kg	lbs	
10 to <15	22 to <33	200
15 to <20	33 to <44	250
20 to <25	44 to <55	300
25 to <32.5	55 to <71.5	350
32.5 to <40	71.5 to <88	400
≥40	≥88	600

HOW SUPPLIED

Capsules

SUSTIVA® capsules are available as follows:

Capsules 200 mg are gold color, reverse printed with "SUSTIVA" on the body and imprinted "200 mg" on the cap.

Bottles of 90 NDC 0056-0474-92

Capsules 100 mg are white, reverse printed with "SUSTIVA" on the body and imprinted "100 mg" on the cap.

Bottles of 30 NDC 0056-0473-30

Capsules 50 mg are gold color and white, printed with "SUSTIVA" on the gold color cap and reverse printed "50 mg" on the white body.

Bottles of 30 NDC 0056-0470-30

Tablets

SUSTIVA tablets are available as follows:

Tablets 600 mg are yellow, capsular-shaped, film-coated tablets, with "SUSTIVA" printed on both sides.

Bottles of 30 NDC 0056-0510-30

SUSTIVA capsules and SUSTIVA tablets should be stored at 25° C (77° F); excursions permitted to 15°–30° C (59°–86° F) [see USP Controlled Room Temperature].

Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

SUSTIVA® is a registered trademark of Bristol-Myers Squibb Pharma Company.

Other brands listed are the trademarks of their respective owners and are not trademarks of Bristol-Myers Squibb Company.

Printed in USA

XX-XXXXXX-XX

Revised xxxxx xxxx

Patient Information

Rx only

SUSTIVA® (sus-TEE-vah)

[efavirenz (eh-FAH-vih-rehnz)]

capsules and tablets

ALERT: Find out about medicines that should NOT be taken with SUSTIVA.

Please also read the section **"MEDICINES YOU SHOULD NOT TAKE WITH SUSTIVA."**

Read this information before you start taking SUSTIVA. Read it again each time you refill your prescription, in case there is any new information. This leaflet provides a summary about SUSTIVA and does not include everything there is to know about your medicine. This information is not meant to take the place of talking with your doctor.

WHAT IS SUSTIVA?

SUSTIVA is a medicine used in combination with other medicines to help treat infection with Human Immunodeficiency Virus type 1 (HIV-1), the virus that causes AIDS (acquired immune deficiency syndrome). SUSTIVA is a type of anti-HIV drug called a "non-nucleoside reverse transcriptase inhibitor" (NNRTI). NNRTIs are not used in the treatment of Human Immunodeficiency Virus type 2 (HIV-2) infection.

SUSTIVA works by lowering the amount of HIV-1 in the blood (viral load). SUSTIVA must be taken with other anti-HIV medicines. When taken with other anti-HIV medicines, SUSTIVA has been shown to reduce viral load and increase the number of CD4+ cells, a type of immune cell in blood. SUSTIVA may not have these effects in every patient.

SUSTIVA does not cure HIV or AIDS. People taking SUSTIVA may still develop other infections and complications. Therefore, it is very important that you stay under the care of your doctor.

SUSTIVA has not been shown to reduce the risk of passing HIV to others. Therefore, continue to practice safe sex, and do not use or share dirty needles.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF SUSTIVA?

Serious psychiatric problems. A small number of patients experience severe depression, strange thoughts, or angry behavior while taking SUSTIVA. Some patients have thoughts of suicide and a few have actually committed suicide. These problems tend to occur more often in patients who have had mental illness. Contact your doctor right away if you think you are having these psychiatric symptoms, so your doctor can decide if you should continue to take SUSTIVA.

Common side effects. Many patients have dizziness, trouble sleeping, drowsiness, trouble concentrating, and/or unusual dreams during treatment with SUSTIVA. These side effects may be reduced if you take SUSTIVA at bedtime on an empty stomach. They also tend to go away after you have taken the medicine for a few weeks. If you have these common side effects, such as dizziness, it does not mean that you will also have serious psychiatric problems, such as severe depression, strange thoughts, or angry behavior. Tell your doctor right away if any of these side effects continue or if they bother you. It is possible that these symptoms may be more severe if SUSTIVA is used with alcohol or mood altering (street) drugs.

If you are dizzy, have trouble concentrating, or are drowsy, avoid activities that may be dangerous, such as driving or operating machinery.

Rash is common. Rashes usually go away without any change in treatment. In a small number of patients, rash may be serious. If you develop a rash, call your doctor right away. **Rash may be a serious problem in some children.** Tell your child's doctor right away if you notice rash or any other side effects while your child is taking SUSTIVA.

Other common side effects include tiredness, upset stomach, vomiting, and diarrhea.

Changes in body fat. Changes in body fat develop in some patients taking anti-HIV medicine. These changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), in the breasts, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these fat changes are not known.

Tell your doctor or healthcare provider if you notice any side effects while taking SUSTIVA.

Contact your doctor before stopping SUSTIVA because of side effects or for any other reason.

This is not a complete list of side effects possible with SUSTIVA. Ask your doctor or pharmacist for a more complete list of side effects of SUSTIVA and all the medicines you will take.

HOW SHOULD I TAKE SUSTIVA?

General Information

- You should take SUSTIVA on an empty stomach, preferably at bedtime.
- Swallow SUSTIVA with water.
- Taking SUSTIVA with food increases the amount of medicine in your body, which may increase the frequency of side effects.
- Taking SUSTIVA at bedtime may make some side effects less bothersome.
- SUSTIVA must be taken in combination with other anti-HIV medicines. If you take only SUSTIVA, the medicine may stop working.
- Do not miss a dose of SUSTIVA. If you forget to take SUSTIVA, take the missed dose right away, unless it is almost time for your next dose. Do not double the next dose. Carry on with your regular dosing schedule. If you need help in planning the best times to take your medicine, ask your doctor or pharmacist.
- Take the exact amount of SUSTIVA your doctor prescribes. Never change the dose on your own. Do not stop this medicine unless your doctor tells you to stop.
- If you believe you took more than the prescribed amount of SUSTIVA, contact your local Poison Control Center or emergency room right away.
- Tell your doctor if you start any new medicine or change how you take old ones. Your doses may need adjustment.
- When your SUSTIVA supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to SUSTIVA and become harder to treat.
- Your doctor may want to do blood tests to check for certain side effects while you take SUSTIVA (efavirenz).

Capsules

- The dose of SUSTIVA capsules for adults is 600 mg (three 200-mg capsules, taken together) once a day by mouth. The dose of SUSTIVA for children may be lower (see **Can children take SUSTIVA?**).

Tablets

- The dose of SUSTIVA tablets for adults is 600 mg (one tablet) once a day by mouth.

CAN CHILDREN TAKE SUSTIVA?

Yes, children who are able to swallow capsules can take SUSTIVA. Rash may be a serious problem in some children. Tell your child's doctor right away if you notice rash or any other side effects while your child is taking SUSTIVA. The dose of SUSTIVA for children may be lower than the dose for

adults. Capsules containing lower doses of SUSTIVA are available. Your child's doctor will determine the right dose based on your child's weight.

WHO SHOULD NOT TAKE SUSTIVA?

Do not take SUSTIVA if you are allergic to the active ingredient, efavirenz, or to any of the inactive ingredients. Your doctor and pharmacist have a list of the inactive ingredients.

WHAT SHOULD I AVOID WHILE TAKING SUSTIVA?

- **Women taking SUSTIVA should not become pregnant.** Serious birth defects have been seen in animals treated with SUSTIVA. It is not known whether this could happen in humans. **Tell your doctor right away if you are pregnant.** Also talk with your doctor if you want to become pregnant.
- Women should not rely only on hormone-based birth control, such as pills, injections, or implants, because SUSTIVA may make these contraceptives ineffective. Women must use a reliable form of barrier contraception, such as a condom or diaphragm, even if they also use other methods of birth control.
- **Do not breast-feed if you are taking SUSTIVA.** The Centers for Disease Control and Prevention recommend that mothers with HIV not breast-feed because they can pass the HIV through their milk to the baby. Also, SUSTIVA may pass through breast milk and cause serious harm to the baby. Talk with your doctor if you are breast-feeding. You may need to stop breast-feeding or use a different medicine.
- Taking SUSTIVA with alcohol or other medicines causing similar side effects as SUSTIVA, such as drowsiness, may increase those side effects.
- Do not take any other medicines without checking with your doctor. These medicines include prescription and nonprescription medicines and herbal products, especially St. John's wort.

Before using SUSTIVA, tell your doctor if you

- **have problems with your liver, or have hepatitis.** Your doctor may want to do tests to check your liver while you take SUSTIVA.
- **have ever had mental illness or are using drugs or alcohol.**
- **have ever had seizures or are taking medicine for seizures** [for example, Dilantin® (phenytoin), Tegretol® (carbamazepine), or phenobarbital]. Your doctor may want to check drug levels in your blood from time to time.

WHAT IMPORTANT INFORMATION SHOULD I KNOW ABOUT TAKING OTHER MEDICINES WITH SUSTIVA?

SUSTIVA may change the effect of other medicines, including ones for HIV, and cause serious side effects. Your doctor may change your other medicines or change their doses. Other medicines, including herbal products, may affect SUSTIVA. For this reason, **it is very important to:**

- let all your doctors and pharmacists know that you take SUSTIVA.
- tell your doctors and pharmacists about all medicines you take. This includes those you buy over-the-counter and herbal or natural remedies.

Bring all your prescription and nonprescription medicines as well as any herbal remedies that you are taking when you see a doctor, or make a list of their names, how much you take, and how often you take them. This will give your doctor a complete picture of the medicines you use. Then he or she can decide the best approach for your situation.

Taking SUSTIVA with St. John's wort (*Hypericum perforatum*), an herbal product sold as a dietary supplement, or products containing St. John's wort is not recommended. Talk with your doctor if you are taking or are planning to take St. John's wort. Taking St. John's wort may decrease SUSTIVA levels and lead to increased viral load and possible resistance to SUSTIVA or cross-resistance to other anti-HIV drugs.

MEDICINES YOU SHOULD NOT TAKE WITH SUSTIVA

The following medicines may cause serious and life-threatening side effects when taken with SUSTIVA. You should not take any of these medicines while taking SUSTIVA:

- Hismanal® (astemizole)
- Propulsid® (cisapride)
- Versed® (midazolam)
- Halcion® (triazolam)
- Ergot medications (for example, Wigraine® and Cafergot®)

The following medicine should not be taken with SUSTIVA since it may lose its effect or may increase the chance of having side effects from SUSTIVA.

- Vfend® (voriconazole)

The following medicines may need to be replaced with another medicine when taken with SUSTIVA:

- Fortovase®, Invirase® (saquinavir)
- Biaxin® (clarithromycin)

The following medicines may need to have their dose changed when taken with SUSTIVA:

- Crixivan® (indinavir)
- Kaletra® (lopinavir/ritonavir)
- Methadone
- Mycobutin® (rifabutin)

- REYATAZ® (atazanavir). If you are taking SUSTIVA and REYATAZ, you should also be taking Norvir® (ritonavir).
- Zoloft® (sertraline)

These are not all the medicines that may cause problems if you take SUSTIVA. Be sure to tell your doctor about all medicines that you take.

General advice about SUSTIVA:

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use SUSTIVA for a condition for which it was not prescribed. Do not give SUSTIVA to other people, even if they have the same symptoms you have. It may harm them.

Keep SUSTIVA at room temperature (77° F) in the bottle given to you by your pharmacist. The temperature can range from 59° to 86° F.

Keep SUSTIVA out of the reach of children.

This leaflet summarizes the most important information about SUSTIVA. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for the full prescribing information about SUSTIVA, or you can visit the SUSTIVA website at http://www.sustiva.com or call 1-800-426-7644.

Distributed by:

Bristol-Myers Squibb Company

Princeton, NJ 08543 USA

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-972 / S-022
21-360 / S-006

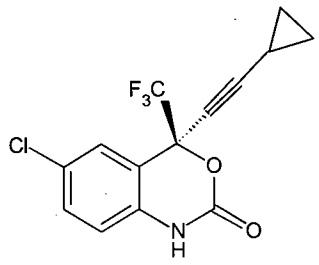
MEDICAL REVIEW

Medical Officer Review
sNDA 20-972 & 21-360
Labeling Supplement

Date of Submission:	October 10, 2003
Date received:	October 15, 2003
Draft review completed:	July 13, 2004
Final review completed:	August 4, 2004

Reviewed by:	Harry W. Haverkos, M.D. Medical Officer, HFD-530
Applicant:	Bristol-Myers Squibb Pharmaceutical Research Institute 5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7600
Drug Name:	Sustiva® capsules, 200 mg Sustiva® tablets, 600 mg
Indication:	Treatment of HIV-1 infection in combination with other antiretroviral agents

Chemical structure:



Medical Officer Review
sNDA 20-972 & 21-360

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Executive Summary

1. Recommendations

A. Recommendations on Approvability

This supplemental application contains data from a single, open-label randomized trial (DMP266 006) demonstrating virologic suppression and safety of efavirenz in combination with other antiretroviral agents through 168 weeks of therapy. We recommend that this submission fulfills phase 4 commitment # 4 agreed to in February 2000 – Submit efficacy data from 006 until at least all treatment arms reach the median time-to-treatment failure and present such median results for inclusion in the label. The efficacy and safety data presented will be included in a revised label. Although no new safety concerns were identified in the safety data through 168 weeks of therapy, the long term follow-up on efavirenz-treated patients did clarify the frequency and risk factors for serious psychiatric adverse events and liver enzyme abnormalities among patients co-infected with hepatitis viruses.

B. Recommendations on Phase 4 Studies and/or Risk Management Steps

No new phase 4 commitments are recommended at this time. The sponsor is encouraged to pursue fulfilling remaining phase 4 commitments agreed to in February 2000.

2. Summary of Clinical Findings

A. Brief Overview of Clinical Program

This submission reports data from a single multicenter study, DMP266-006. This open-label, randomized trial compared efavirenz (EFV)/zidovudine (ZDV)/lamivudine (3TC) and efavirenz/indinavir (IDV) to indinavir/zidovudine/lamivudine in 1,266 HIV-infected patients who were naïve to efavirenz, lamivudine, other non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors. The primary endpoint was the proportion of subjects with HIV RNA less than 400 copies/ml at Week 168. Patients were enrolled and followed through 168 weeks of therapy.

B. Efficacy

Forty-eight percent of patients in the EFV/ZDV/3TC arm and 40% of patients in the EFV/IDV arm compared to 30% of patients in the IDV/ZDV/3TC arm achieved and maintained HIV RNA < 400 copies per milliliter at week 168 of treatment. More patients (18%) in the IDV/ZDV/3TC arm discontinued study treatment due to adverse events compared to the EFV/ZDV/3TC arm (8%) or the EFV/IDV arm (7%). There was no significant difference in the mean CD4 cell counts among the treatment arms for those patients who completed 168 weeks of therapy; the overall mean increase was approximately 300 cells per milliliter. The efavirenz-containing arms demonstrated efficacy statistically superior to the control arm in this open-label study.

C. Safety

Nervous system symptoms, such as dizziness, headache, paresthesia, hypoesthesia, confusion, stupor, agitation, insomnia, depression, amnesia, depersonalization, euphoria, hallucination, somnolence, abnormal thinking, impaired concentration, and abnormal dreams, were common. Approximately 63% of EFV-treated patients experienced at least one such nervous system symptom on EFV compared to 47% in the comparison arm (IDV+ZDV+3TC). The nervous system symptoms associated with efavirenz use occurred sooner than those attributed to the IDV+ZDV+3Tc arm. The median time to onset of nervous system symptoms was two days in each of the EFV-containing arms and 38 days in the control group. The median duration of nervous system symptoms was 36 days in the EFV-containing arms and 58 days in the control group. Beyond 24 weeks of therapy, the incidence of new-onset nervous system symptoms among efavirenz-treated patients was generally similar to those in the indinavir-containing control arm.

Serious and potentially life-threatening psychiatric/nervous system adverse events were reported during the study, including aggressive reaction, depression (grade 3 or 4), psychotic depression, manic reaction, paranoid reaction, psychosis, suicide attempt, aggravated depression, and manic-depressive psychosis. One or more such events were reported in 8% of patients treated with EFV+ZDV+3TC, 5% treated with EFV+IDV, and 3% treated with IDV+ZDV+3TC. These events occurred later than the nervous system symptoms; the median time to onset of psychiatric system symptoms was approximately 9 months in all three treatment groups. The frequency of specific serious psychiatric events among patients who received efavirenz or control regimens, respectively, were: suicide attempt/ideation (1.6%, none), grade 3-4 depression (2.7%, 1.5%), aggravated depression (1.2%, 0.25%), aggressive reaction (0.5%, 0.5%), paranoid reaction (0.5%. none), and psychosis (0.4%, 0.25%).

Rash was more commonly reported in each of the efavirenz-containing arms than in the IDV+ZDV+3TC arm (37% vs. 22%). Three hundred four of 827 patients receiving efavirenz developed rash; over 97% of the rashes were Grade 1 or 2. The median time to onset of rash in the efavirenz-containing arms was four weeks and the median duration of days with > Grade 1 rash was 16-18 days.

Among patients co-infected with hepatitis B and/or hepatitis C virus, elevations in ALT to greater than five times upper limit of normal (ULN) developed in 20% of patients in the efavirenz arms and 7% in the control arm. Elevations in AST to greater than five times ULN developed in 13% of co-infected patients in the efavirenz arms and 7% in the control arm.

There were 15 pregnancies in 13 different subjects reported while on study treatment, eight pregnancies in 6 subjects treated with EFV+IDV, three pregnancies in 3 subjects treated with EFV+ZDV+3TC, and four treated with IDV+ZDV+3TC. All but two pregnancies were terminated. One 39 year old woman treated with EFV+ZDV+3TC throughout the first trimester, and nelfinavir + Combivir later in the pregnancy, delivered a full-term male with hydronephrosis and low birth weight. A 22 year old woman

delivered female twins at 31 weeks gestation after first trimester exposure to EFV+ZDV+3TC, and additional exposure to nelfinavir + Combivir. No defects were reported in either twin at birth, however no further follow-up is available.

D. Dosing

The study results demonstrate the safety and efficacy of efavirenz in combination with other antiretroviral agents through 168 weeks of therapy for the treatment of HIV-1 infection. The recommend dose of efavirenz is 600 mg orally, once daily, in combination with other antiretroviral agents. It is recommended that efavirenz be taken on an empty stomach, preferably at bedtime.

E. Special Populations

Pregnancy should be avoided in women receiving efavirenz. Serious birth defects have been seen in animals and humans treated with efavirenz. Women of childbearing potential should undergo pregnancy testing prior to initiation of and during treatment with efavirenz. Labeling reflects that efavirenz is a teratogen.

Pediatric patients, geriatric patients, patients with hepatic and/or renal impairment were not studied in DMP266-006.

Clinical Review

1. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Sustiva® (efavirenz) is a non-nucleoside reverse transcriptase (RT) inhibitor of human immunodeficiency virus type 1 (HIV-1). Efavirenz is available as capsules containing 50 mg, 100 mg or 200 mg of efavirenz or as 600 mg film-coated tablets. Efavirenz in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. Safety and efficacy of efavirenz have been established in men and women at least 18 years of age. The pharmacokinetics of efavirenz in pediatric patients was similar to the pharmacokinetics in adults who received 600 mg daily doses. The recommended dosage of efavirenz for pediatric patients 3 years of age or older and weighing between 10 and 40 kg is based on body weight. The recommended dose for children weighing between 10 and 15 kilograms is 200 mg once daily and the recommended dosage of efavirenz increases approximately 50 mg for each 5 kilogram increase in body weight over 15 kilograms. The recommended dosage of efavirenz for pediatric patients weighing greater than 40 kg is 600 mg once daily.

The current application seeks to incorporate 168-week efficacy and safety data from a completed study, AI266-006, into the label. The application also seeks to satisfy Phase 4 Commitment No. 4 (see letter of February 9, 2000) to submit efficacy data from trial 006

until at least all treatment arms reach the median time to treatment failure and present such median results for inclusion in the label.

B. State of Armamentarium for Indication(s)

There are now 21 FDA approved agents for the treatment of HIV-1 infection. These agents include nucleoside and non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and a fusion inhibitor. Combinations of 3 or 4 antiretroviral drugs are now standard therapy in North America and Europe and are gradually being adopted in more resource-poor countries as cost containment strategies are implemented. The development of resistance to these agents continues and the need for new drugs with improved resistance profiles remains critical. Many of the currently available antiretroviral drugs also have significant adverse effects and drugs and better tolerability and toxicity profiles are needed.

Three non-nucleoside reverse transcriptase inhibitors (NNRTIs), namely, delavirdine, efavirenz, and nevirapine, are currently marketed for use. Delavirdine is the least potent of these agents and is generally not recommended for use as part of an initial antiretroviral regimen. On the other hand, a special panel convened by the Department of Health and Human Services recommends efavirenz in combination with lamivudine and zidovudine, tenofovir, or stavudine as the preferred first-line NNRTI-containing regimen in antiretroviral-naïve patients.

C. Important Milestones in Product Development

for DMP 266, also known as efavirenz, was submitted by DuPont Merck Pharmaceutical Company on December 21, 1995. A discussion of the results of phase 1 and 2 trials was conducted with FDA on December 9, 1996. The applicant met with the Division of Antiviral Drug Products Advisory Committee in closed session on July 9, 1997 to discuss adequacy of overall drug development. 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. Fast Track designation was assigned to the IND on May 29, 1998. On June 11, 1998, NDA 20-972 (Sustiva® capsules) 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 20, 2001, NDA 21-360 (Sustiva® tablets) was submitted and was approved on February 1, 2002. The traditional approval letter contained Phase 4 commitment #4: "Submit efficacy data from trial 006 until at least all treatment arms reach the median to time treatment failure and present such median results for inclusion in the label." On March 30, 2001, an efficacy supplement for efavirenz tablets was submitted and was approved on February 1, 2002. On October 10, 2003, Bristol-Myers Squibb Pharmaceutical Company, the current sponsor of the drug, submitted this supplemental NDA for FDA review.

D. Other Relevant Information

No pediatric data was submitted with this supplemental NDA package. On June 29, 2000,
12, 2001. Pediatric Written Request was issued to DuPont Pharmaceuticals Company on September 17, 1998 to develop an appropriate liquid formulation for HIV-infected pediatric population between the ages of 3 months and 16 years. The sponsor agreed to conduct a 48-week, open-label, concentration-controlled, multicenter study in order determine the dosing regimen based on pharmacokinetic profile of efavirenz and tolerability in the pediatric population. The original Written Request called for submitting reports of studies on or before August 1, 1999. The Written Request was amended twice to extend the deadline and currently calls for submitting reports on or before October 31, 2005.

E. Important Issues with Pharmacologically Related Agents

None noted.

F. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews.

There were no new clinically relevant findings from chemistry, pharmacology/toxicology or biopharmaceutics pertinent to this supplement. These data were reviewed in detail in conjunction with the original NDAs (20-972 and 21-360). The current submission contains virology data reviewed by the Microbiology Reviewer, Dr. Lisa Naeger. The efficacy data was reviewed by the Statistical Reviewer, Dr. Suktae Choi. Dr. Harry Haverkos, the Medical Reviewer, evaluated efficacy and safety data.

3. Human Pharmacokinetics and Pharmacodynamics

Pharmacokinetics and Pharmacodynamics data were reviewed in conjunction with the original NDAs (20-972 and 21-360). No new data were presented in this submission.

4. Description of Clinical Data and Sources

A. Overall Data

This submission contains data from a single, randomized, open-label trial, Study 006, conducted by 110 investigators at 88 sites; 61 in North America, and 27 in Europe. One thousand sixty-six subjects were randomized; 422 subjects to receive EFV + ZDV + 3TC, 429 subjects to receive EFV + IDV, and 415 to receive IDV + ZDV + 3TC. Study 006 was originally designed as a 24-week study involving 330 randomized subjects. The protocol was amended nine times; major changes included modification of EFV and IDV doses in the EFV + IDV arm, increases in sample size to 1200 subjects, increase in treatment observation period to 168 weeks, addition of updated HIV RNA analyses, ie,

Amplicor Monitor Ultrasensitive method (lower limit of quantification of 50 copies per ml. Study visits occurred at weeks 2 and 4, then every 4 weeks until week 60, then quarterly thereafter. At study visits, subjects were provided study medications, had blood drawn for HIV-RNA levels and CD4 cell counts, and were evaluated for safety.

B. Tables Listing the Clinical Trials

There is only one clinical trial Study 006 in this submission, but the sample size and study duration was increased with several protocol amendments, as noted above. The first subject was enrolled on January 28, 1997; the last subject was randomized on September 16, 1998.

C. Postmarketing Experience

Periodic Adverse Drug Experience Reports for Sustiva® submitted through May 25, 2004 were reviewed. None of those reports suggested new safety data for inclusion in the label.

D. Literature Review

A listing of publications resulting from Study DMP266-066 was submitted.

5. Clinical Review Methods

A. How the Review was Conducted

Study 006 was reviewed for both safety and efficacy. The sponsor's conclusions regarding safety and efficacy were confirmed by independent FDA analysis of the data. Dr. Suktae Choi performed the statistical analysis confirming the primary endpoint and selected secondary endpoints. Dr. Choi also performed a detailed analysis evaluating subjects recruited in the initial study and those recruited in the amended protocol. This MO reviewed study design, efficacy results, adverse events and laboratory safety monitoring data. Dr. Lisa Naeger reviewed the virology methods and data.

B. Overview of Materials Consulted in Review

An electronic submission documenting the study results and Bristol-Myers Squibb Company's conclusions regarding Study DMP266-006, 168-week data were used as the primary data source in this review. On June 10, 2004, the sponsor provided updated efficacy and safety data responding to comments from the review team.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The Good Clinical Practice Branch, Division of Scientific Investigations, FDA conducted clinical inspections of 4 study sites; Dallas, TX, Providence, RI, San Francisco, CA, and San Juan, PR. No major deficiencies were noted in the three sites inspected that could

compromise the integrity of the data. See Clinical Inspection Summary, September 2, 1998 by Antoine El-Hage, Ph.D.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor states that the study was conducted according to accepted ethical standards based on the precepts established by the Declaration of Helsinki.

E. Evaluation of Financial Disclosure

The sponsor submitted financial disclosure information. There were no conflicts identified that would impact the study results.

6. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The results of Study DMP 266-006 support efavirenz as effective therapy for HIV-1 infection through three years when used in combination with other antiretroviral agents. The median time to treatment failure was 40 weeks for the control arm, 72 weeks for the EFV + IDV arm, and 132 weeks for the EFV + ZDV + 3TC arm. Forty-eight percent of patients treated with EFV + ZDV + 3TC achieved and maintained confirmed HIV RNA < 400 copies per milliliter through Week 168, 40% of those treated with EFV + IDV, and 30% treated with IDV + ZDV + 3TC. For all three treatment regimens, CD4 cell counts continued to increase with continued therapy with mean increases of approximately 300 cells per cubic millimeter. No statistically significant differences in CD4 count changes among treatment groups were noted.

B. General Approach to Review of the Efficacy of the Drug

The primary endpoint was the proportion of subjects with HIV RNA less than 400 copies/ml at Week 168 comparing each of the efavirenz-containing arms (efavirenz + zidovudine + lamivudine; efavirenz + indinavir) with the control arm (indinavir + zidovudine + lamivudine). Other analyses included response to therapy with HIV RNA less than 50 copies/ml at Week 168, comparison of the magnitude and duration of CD4 cell count changes on the three treatment regimens, safety profiles of the three regimens, and comparisons of long-term duration of HIV RNA suppression and response to therapy based on time to loss of virologic response, time to treatment failure and virologic response.

C. Detailed Review of Trials by Indication

The following table lists the primary analysis, treatment outcomes of randomized subjects on initial therapy at Week 168 with treatment response measured as HIV RNA less than 400 copies per ml.

Table 1. Percentage of patients by treatment outcome by primary analysis (HIV RNA less than 400 copies/ml) at Week 168

Outcome	EFV + ZDV + 3TC (N=422)	EFV + IDV (N=429)	IDV + ZDV + 3TC (N=415)
Responder (< 400 copies/ml)	47%	39%	29%
Virologic Failure	12%	19%	17%
Discontinued for adverse events	8%	8%	20%
Discontinued for other reasons*	32%	34%	34%

* Includes consent withdrawn, lost to follow-up, noncompliance, never treated, missing data, protocol, and those with HIV RNA < 400 copies/ml. who chose not to continue in the voluntary extension phases of the study.
Source: Dr. Suktae Choi analysis, June 25, 2004.

The following table lists the reasons for the 210 patients who discontinued therapy before achieving viral suppression.

Table 2. Reasons for discontinuations before achieving viral suppression

Discontinuations before achieving viral suppression	EFV + ZDV + 3TC (N=47)	EFV + IDV (N=70)	IDV + ZDV + 3TC (N=93)
Adverse event	22	17	43
Loss to follow up	17	23	20
Non-compliant	2	17	14
Withdrew consent	2	4	11
Death/CDC event	3	3	1
Other*	1	6	4

* Other includes protocol violation and missing data.
Source: Table 10.1.2, page 97.

Secondary Analyses

Secondary efficacy measures included comparisons of the proportion of patients in response (HIV RNA < 50 copies/ml.) at week 168, the magnitude and duration of CD4 cell count changes, and response to treatment based on time to loss of virologic response, time to treatment failure, and time to virologic response. The following table lists the results of selected secondary analyses.

Table 3. Percentage of patients by treatment outcome (HIV RNA less than 50 copies/ml) and mean increase in CD4 count from baseline of completers at 168 weeks

	EFV + ZDV + 3TC (N = 422)	EFV + IDV (N = 429)	IDV + ZDV + 3TC (N = 415)
Responder (< 50 copies/ml.)	42%	31%	23%
Mean change in CD4 count (cell/ml.) at 168 weeks	329	319	329
Number of patients observed at 168 weeks	207	161	129

Source: Table 10.2.1, page 109, and Dr. Suktae Choi analysis, June 25, 2004.

Table 4. Percentage of patients by treatment outcome (HIV RNA less than 400 copies/ml) by gender and race.

Responders	EFV + ZDV + 3TC	EFV + IDV	IDV + ZDV + 3TC
Total	200/422 (47%)	169/429 (39%)	122/415 (29%)
Male	170/347 (49%)	148/368 (40%)	99/333 (30%)
Female	30/75 (40%)	21/61 (34%)	23/82 (28%)
White	133/251 (53%)	109/256 (43%)	83/256 (32%)
Black	36/90 (40%)	25/86 (29%)	16/80 (20%)
Other Race	31/81 (38%)	35/87 (40%)	23/79 (29%)

Source: Dr. Suktae Choi analysis, July 13, 2004.

Resistance

Clinical isolates with reduced susceptibility *in vitro* to efavirenz were obtained in Study 006. One or more reverse transcriptase mutations at amino acid positions 98, 100, 101, 103, 106, 108, 188, 190, 225, and 227 were observed in patients treated with EFV + ZDV + 3TC or with EFV + IDV. The mutation K103N was the most frequently observed. Long-term resistance surveillance (average 52 weeks, range 4-106 weeks) analyzed 28 matching baseline and virologic failure isolates. Sixty-one percent of these failure isolates had decreased EFV susceptibility *in vitro*.

D. Efficacy Conclusions

The results demonstrated that EFV was not inferior to IDV at 168 weeks. Although testing for EFV superiority was not called for in the original study design, both EFV-containing regimens were superior to the control arm at week 168; EFV + ZDV + 3TC vs. IDV + ZDV + 3TC ($p< 0.0001$), EFV + IDV vs. IDV + ZDV + 3TC ($p=0.0023$).

There was no significant difference in mean increase in CD4 cell count among the treatment groups at 168 weeks. The overall mean increase was 325 cells/ml among patients who continued on study treatment; 329 cells/ml. for completers randomized to

EFV +ZDV+3TC and IDV+ZDV+3TC, and 319 cells/ml. for completers randomized to EFV+IDV.

7. Integrated Review of Safety

A. Brief Statement of Conclusions

The sponsor demonstrated no new or unexpected toxicity with the use of efavirenz during the 168 week study. Efavirenz has a known toxicity profile demonstrated in the safety data sets for the original NDA and its supplemental applications. As noted in the Warnings section of the 2000 efavirenz label, serious psychiatric adverse experiences have been previously reported among patients treated with efavirenz, and include aggressive reactions, paranoid reactions, psychosis, severe depression, and suicide attempts. The frequency of such events in Study 006 among patients treated with efavirenz was 6% compared to 3% in the control group. All 13 adverse events reported as suicide attempt/ideation occurred among efavirenz-treated patients. Approximately 60% of patients treated with efavirenz reported nervous system symptoms. Among patients treated with efavirenz, these symptoms included, but were not limited to dizziness, headache, insomnia, impaired concentration and abnormal dreams. Approximately 25% of patients treated with efavirenz reported rash. Fifteen pregnancies were reported during the study. Thirteen of the pregnancies were terminated; one mother gave birth to twins, another to a male child, diagnosed at birth with hydronephrosis.

B. Description of Patient Exposure

One thousand two hundred sixty six subjects were randomized; 38 (3%) did not receive study therapy. Of the 1,228 subject who started therapy, 483 (38%) completed the study – 46% in the EFV + ZDV + 3TC arm, 37% in the EFV + IDV arm, and 31% in the IDV +ZDV +3TC arm. A subject was defined as completing study by continuing until the sponsor terminated the study or by electing not to continue into an optional extension. The median time on study therapy was longest for the EFV + ZDV + 3TC arm (180 weeks); EFV + IDV arm (102 weeks), and IDV + ZDV + 3TC arm (76 weeks). The range of time subjects were on drug was less than a day to 264 weeks. Dose adjustments and missed doses of study medication were similar across study arms (ranging from 6% to 16%) for each study drug.

C. Methods and Specific Findings of Safety Review

The safety results presented are based on data for the 1,228 treated subjects, except for data on Serious Adverse Events, which includes all randomized subjects. Study visits occurred at weeks 2 and 4, then every 4 weeks until week 60, then quarterly for the duration of the study. At study visits, subjects were evaluated for safety, provided study medications, and blood was drawn for HIV-RNA levels, CD4 cell counts, hematology, and chemistry. Pregnancy testing was performed monthly for women of childbearing potential. Adverse events were coded and grouped by body system using a modified version of the WHOART dictionary. Serious adverse events were initially defined as

those that were immediately life-threatening, cancers, overdoses, and those events that resulted in death, permanent or substantial temporary disability, congenital anomaly, clinically significant end-organ toxicity, hospitalization, or prolongation of hospitalization. During the course of the study, the definition was modified; cancers and overdoses were not routinely designated as serious. Clinical narratives were provided for deaths and serious adverse events. At the request of the FDA during the review, narratives for all pregnancies were developed and submitted.

The following table lists safety results, including rates of deaths and adverse events.

Table 5. Safety results: Deaths, Serious Adverse Events

	EFV + ZDV + 3TC (N=412)	EFV + IDV (N=415)	IDV + ZDV + 3TC (N=401)
Median follow-up	180 weeks	102 weeks	76 weeks
Deaths (Deaths/100 subject-years of follow-up)	8 (0.72)	5 (0.54)	3 (0.38)
Adverse Events leading to discontinuations	52 (13%)	50 (12%)	104 (26%)
Serious Adverse Events	94 (23%)	79 (19%)	67 (17%)
Number of Serious Adverse Event narratives submitted	33	33	38
Pregnant and treated	3	6	4

There were sixteen deaths in the study, eight deaths in the EFV + ZDV + 3TC group (A), five deaths in the EFV + IDV group (B), and three in the IDV +ZDV + 3TC group (C). The following table lists the deaths by treatment group.

Table 6. Deaths

Subject ID/Group	Gender/Age	Study Day	Date of Death	Cause of Death
72204 A*	M/52	115	8/23/98	Myocardial infarction (history of sinus bradycardia, LVH, and PVCs pre-study; pre-study cholesterol=135 mg/dl., HDL=30 mg/dl. – latest on-study cholesterol=126 mg/dl., HDL=28 mg/dl.)
31211 A*	M/60	652	6/17/99	Abdominal aortic aneurysm rupture
23237 A*	M/53	843	10/6/00	Heart Failure (few details provided)
52206 A*	M/50	1055	4/4/01	M. xenopi and P. aeruginosa

				pneumonia, sepsis
38229 A*	F/38	978	5/1/01	Lung cancer, right hemispheric CVA
15219 A*	M/36	1382	6/10/01	Overdose (Darvon® and Xanax®); possible suicide – deemed unlikely related to study drugs
17213 A*	M/50	1054	8/11/01	Hepatocellular carcinoma (history of HBV, HCV, and alcohol abuse)
33206 A*	M/37	1367	11/3/01	Unknown – unknown if treatment related – history of suicide attempts, IV heroin abuse
15227 B	M/31	54	1/5/98	Kaposi's sarcoma of lung
31203 B*	M/38	332	7/3/98	Myocardial infarction (no pre-study lipid studies available – latest on-study cholesterol = 266 mg/dl., HDL = 32 mg/dl.)
35251 B *	M/50	230	12/30/98	Myocardial infarction (history of high lipids, obesity – no autopsy, no records
43205 B *	M/32	321	3/4/99	Coronary artery disease, pneumonia (borderline hypertension, pre-study cholesterol = 229, HDL = 27; latest on-study cholesterol = 328, HDL =39)
84204 B *	M/44	326	5/30/99	Heart failure (history of systolic ejection murmur, ?MI – pre-study cholesterol =139, HDL 48; latest on-study cholesterol = 129, HDL = 47)
12104 C	M/51	232	9/2/98	Liver failure – possibly treatment associated
35267 C*	M/29	202	2/16/99	Astrocytoma (grade 2), seizures, pneumonia
60203 C*	M/39	996	2/10/01	Unknown – myocardial infarction – IV drug abuser (? Cocaine and heroin)

Source: Table 12.2, text in 12.2, Supplement Table S.12.2A, and Appendix 12.9A
* Brief narrative provided.

The sponsor reported an additional 104 narratives for serious adverse events, discontinuations due to serious adverse events, and psychiatric events of special interest. Thirty-three such reports were reported for patients treated with efavirenz, zidovudine, and lamivudine (Group A); 33 with efavirenz and indinavir (Group B); and 38 with

indinavir, zidovudine, and lamivudine (Group C). The following table lists these serious adverse events by treatment group and event type.

Table 7. Serious adverse events reported in narratives by event type and treatment group.

	EFV + ZDV +3TC (N=412)	EFV + IDV (N=415)	IDV + ZDV + IDV (N=401)
Total	33	33	38
Psychiatric events Suicide attempt Depression Other	 2 13[1] 3	 2 12 0	 0 0 1
Nervous system Seizures CVA Other	 1 0 2 (agitation, decreased concentration)	 2 2 2 (insomnia, weakness)	 0 0 3 (peripheral neuropathy)
Renal Nephrolithiasis Pain (stone not documented) Other	 1 0 0	 0 0 1	 13 3 0
Gastointestinal Hepatitis Pancreatitis Nausea/vomiting or pain	 3 2[1] 2	 4 0 0	 4 0 5
Metabolic Lipodystrophy New onset diabetes	 0 0	 5 1	 2 1
Rash	1	1	1
Other	4 anemia, KS, wt loss, pneumonia	1, Cardiomyopathy	5 PCP, Alopecia, Anemia, pancytopenia, EFV mistake

Footnote: One patient reported with both pancreatitis and depression

Similar percentages of patients in all groups reported new-onset adverse events. Several frequently occurring adverse events are listed in the following table.

Table 8. Selected New-onset Clinical Adverse Event (All Grades)

Adverse event	EFV + ZDV + 3TC (N=412)	EFV + IDV (N=415)	IDV + ZDV + 3TC (N=401)
Nausea	165 (40%)	139 (33%)	237 (59%)
Upper Respiratory infection	201 (49)	169 (41)	151 (38)

Rash[1]	158 (38)	172 (41)	105 (26)
Headache	149 (36)	127 (31)	115 (29)
Fatigue	133 (32)	102 (25)	135 (34)
Diarrhea	152 (37)	154 (37)	111 (28)
Dizziness	135 (33)	129 (31)	42 (10)
Vomiting	105 (25)	80 (19)	134 (33)
Flu-like symptoms	101 (25)	89 (21)	78 (19)
Insomnia	101 (25)	103 (25)	65 (16)
Dyspepsia	101 (25)	68 (16)	74 (18)
Pain	108 (26)	84 (20)	113 (28)
Depression	104 (25)	82 (20)	86 (21)
Concentration impaired	51 (12)	35 (8)	7 (2)
Dreaming abnormal	40 (10)	31 (7)	4 (1)
Anxiety	65 (16)	60 (14)	45 (11)

Footnote: Rash includes maculopapular rash, erythematous rash, and rash.

Source: Table 12.1: pp 120-125.

Laboratory Abnormalities
Adverse events due to laboratory abnormalities were reported among all three treatment groups. Hyperbilirubinemia and hematuria were reported more frequently among the control arm. The results of laboratory abnormalities are shown in the following table.

Table 9. Clinical Adverse Events, New-onset Laboratory abnormalities (All Grades - at least 5% in any treatment group).

	EFV + ZDV + 3TC (N=412)	EFV + IDV (N=415)	IDV + ZDV + 3TC (N=401)
Hypercholesterolemia	43 (10%)	65 (16%)	28 (7%)
Hypertriglyceridemia	43 (10)	35 (8)	34 (8)
SGPT increased	29 (7)	34 (8)	20 (5)
SGOT increased	30 (7)	30 (7)	22 (5)
Gamma-GT increased	38 (9)	28 (7)	15 (4)
Hyperbilirubinemia[1]	3 (1)	6 (1)	70 (17)
Granulocytopenia	38 (9)	17 (4)	22 (5)
Hyperglycemia	26 (6)	18 (4)	16 (4)
Hematuria[1]	9 (2)	10 (2)	33 (8)
Hyperlipemia	14 (3)	21 (5)	9 (2)
Amylase increased	15 (4)	24 (6)	5 (1)
Anemia	22 (5)	7 (2)	24 (6)

Footnote: Statistical differences noted between EFV-containing arms and control, $p < 0.05$. Source: Table 12.1: pp 120-125.

Table 10. Laboratory abnormalities (Grades 3-4) Related to Study Therapy (at least 1% of patients in any treatment group).

	EFV + ZDV + 3TC (N=412)	EFV + IDV (N=415)	IDV + ZDV + 3TC (N=401)
Hypertriglyceridemia	10	9	10
SGPT increased	8	11	7
SGOT increased	6	6	7
Gamma-GT increased	15	9	7
Hyperbilirubinemia	1	1	32
Granulocytopenia	19	7	10
Amylase increased	5	5	1
Anemia	7	0	5

Source: Table S.12.1.2, S2 pages 515-520.

Analysis of Selected Adverse Events

Nervous system and psychiatric adverse events

Fifty-nine percent of patients receiving efavirenz reported central nervous system symptoms compared to 29% of control patients. Among patients treated with efavirenz, these symptoms included, but were not limited to dizziness (32%), insomnia (25%), impaired concentration (10%), and abnormal dreams (9%). These symptoms were severe (i.e., grade 3) in 2.2% of patients and led to dose interruptions or discontinuations of efavirenz in 4.7% of patients. These nervous system symptoms usually began in the first two days of therapy with efavirenz and persisted for a median of approximately five weeks. On the other hand, onset of first nervous system symptoms for the control patients generally began at a median of 38 days after starting therapy and lasted a median of 58 days. Headache, with or without central nervous system symptoms, was reported in 33% of patients treated with efavirenz and 29% of control patients. If headache, paresthesia and hypoesthesia are also considered nervous system adverse events, then 64% of patients treated with efavirenz-containing regimens had at least one nervous system adverse event, and 47% of control patients (Source Tables 12.1, pages 120-124, and Table 12.1.4.1, page 132).

Serious and potentially life-threatening psychiatric adverse experiences have been previously reported among patients treated with efavirenz, including aggressive reactions, depression (Grades 3 and 4), psychotic depression, manic reaction, paranoid reaction, psychosis, suicide attempt, aggravated depression, and psychosis manic-depressive. The frequency of such adverse events among patients treated with efavirenz was 6% compared to 3% in the control group. The onset of first psychiatric symptoms was significantly later in the treatment course (days 250-300) for both efavirenz and control arms than for nervous system symptoms. The frequency of specific serious psychiatric events among patients who received efavirenz or control regimens, respectively, were: suicide attempt/ideation (1.6%, none), grade 3-4 depression (2.7%, 1.5%), aggravated depression (1.2%, 0.25%), aggressive reaction (0.5%, 0.5%), paranoid reaction (0.5%, none), and psychosis (0.4%, 0.25%). Logistic regression analysis disclosed that treatment with efavirenz, history of injecting drug use, psychiatric history, and receipt of psychiatric medication at study entry were significantly associated with severe depression

(See Table S.12.1.4.2, page 523). Patients with serious psychiatric adverse experiences should seek immediate medical evaluation.

Rash

Adverse event of the skin and appendage were commonly reported during the study. The frequency of adverse events depends on how one defines such abnormalities as shown in the following table.

Table 11. Rash

Adverse event of skin and appendages	EFV + ZDV + 3TC (N=412)	EFV + IDV (N=415)	IDV + ZDV + 3TC (N=401)
New onset Rash*, grade 1-4	142 (34)	162 (39)	88 (22)
Any such event, grade 3-4	8 (2)	5 (1)	5 (1)
Rash*, grade 3-4	3 (1)	4 (1)	1 (<1)
Urticaria, grade 3-4	1 (<1)	3 (<1)	0
Erythema multiforme, grade 3-4	0	1 (<1)	0

* Rash defined as maculopapular rash, generalized rash, localized rash, urticaria, erythema multiforme, follicular rash, pustular rash, or petechial rash.
Source: Tables S.12.1.3, S2 pages 515-20, 12.1.4.1-Revised Submitted June 11, 2004.

Median onset of first symptom of rash began on day 36 for the EFV+ZDV+3TC group and persisted a median duration of 27 days; rash began on day 19 and persisted 18 days for the EFV+IDV group. Median onset of rash was 104 days for the control arm which persisted for a median of 42 days. Fourteen patients (2%) discontinued efavirenz due to rash, 45 (5%) attributed efavirenz dose interruptions to rash (see June 11, 2004 submission).

Patients co-infected with hepatitis B and/or hepatitis C virus

There were 137 subjects treated with efavirenz and 84 treated with IDV+ZDV+3TC who were seropositive for hepatitis B (surface antigen positive) and/or hepatitis C (antibody positive) viral infection at baseline. Characteristic of patients co-infected with HBV/HCV are shown in the next table.

Table 12. Liver function abnormalities among patients co-infected with HBV/HCV

	EFV+ZDV+3TC (N=69)	EFV + IDV (N=68)	IDV+ZDV+3TC (N=84)
Both HBV/HCV	1	3	4

HBV, not HCV	11	15	16
HCV, not HBV	57	50	64
Normal AST at baseline	39 (57%)	41 (60%)	53 (63%)
Normal ALT at baseline	47 (68%)	48 (71%)	59 (71%)
AST rise when normal at baseline	17/39 (44%)	21/41 (51%)	22/53 (42%)
AST rise when abnormal at baseline	13/30 (43%)	15/27 (56%)	7/30 (23%)
ALT rise when normal at baseline	23/47 (49%)	23/48 (48%)	22/59 (37%)
ALT rise when abnormal at baseline	13/22 (59%)	13/20 (65%)	7/25 (28%)
AST to grade 3-4 (>5xULN)	8/69 (12%)	10/68 (15%)	6/84 (7%)
ALT to grade 3-4 (>5xULN)	13/69 (19%)	14/68 (21%)	6/84 (7%)

Source: Table 12.6.4, pages 184-7, Appendix 12.6.4B, pages 14490-502.

Among those co-infected patients, elevations in AST and ALT to greater than five times ULN developed in a greater number of patients treated with efavirenz than those in the control arm.

Lipodystrophy

Lipodystrophy was reported as abdomen enlarged, breast enlargement, cachexia, gynecomastia, lipidosis, lipoma, and/or obesity for adverse event reporting. Lipodystrophy of any severity was reported as an adverse event in 3%, 4%, and 5% of subjects treated with EFV + ZDV + 3TC, EFV + IDV, and IDV + ZDV + 3TC. Obesity was the most frequently reported AE in the grouping and was evenly distributed across the three treatment groups.

The protocol specified that a lipodystrophy survey was to be performed for all subjects at Week 24 or retrospectively at any visit beyond week 24. The initial question on the questionnaire asked if the subject had experienced any buffalo hump, truncal obesity, or fat distribution symptoms. If the answer was "yes" to that question, then three pages of questions was to be completed. This included information on specific types, features, and evolution of lipodystrophy-related signs and symptoms. A waist-to-hip ratio was to be recorded for those who responded "yes" to the initial question. If the answer to the initial question was "no," then no further evaluation was completed. The initial question was completed for only 666 subjects, 33 replied "yes' to the initial question. Lipodystrophy was reported by 9 (2%) of those treated with EFV + ZDV + 3TC, 10 (2%) with EFV + IDV, and 14 (3%) with IDV + ZDV + 3TC. Central obesity was the most frequent positive response to the questionnaire.

A substudy was proposed to evaluate body composition by DEXA, BIA, and CT scanning. Of note, at least one CT scan is available for 378 subjects, 144 treated with EFV + ZDV + 3TC, 124 with EFV + IDV, and 110 with IDV + ZDV +3TC. However, complete data are available for only 4 subjects at Week 48 and for 6 different subjects at Week 112. These data are not interpretable according to the sponsor.

Lipids

Measurement of serum lipid levels were added as a protocol amendment, therefore, not all subjects have baseline and early visit lipid levels. In addition, data on serum lipid profiles are difficult to interpret because the protocol did not specify that samples were to be collected following overnight fast, thus invalidating serum triglyceride and LDL results. However, values for total cholesterol and HDL are measured directly and should be valid.

Table 13. Mean total cholesterol, mean HDL levels, and mean triglyceride levels at baseline, week 48 and week 156 by treatment arm.

	EFV + ZDV + 3TC	EFV + IDV	IDV + ZDV + 3TC
Baseline cholesterol (Number of subjects)	163.37 mg/dl (186)	170.08 mg/dl (178)	160.90 mg/dl (153)
Cholesterol at week 48 (n)	198.51 (280)	227.14 (258)	188.14 (221)
Cholesterol at week 156 (n)	203.87 (223)	231.55 (177)	197.03 (148)
Baseline HDL (n)	38.38 (186)	37.58 (178)	37.63 (153)
HDL at week 48 (n)	47.01 (280)	49.28 (258)	39.86 (221)
HDL at week156 (n)	43.69 (223)	48.65 (177)	37.84 (148)
Baseline Triglycerides (n)	156.89 (186)	155.12 (178)	154.99 (153)
Triglycerides at Week 48 (n)	204.76 (280)	209.50 (258)	183.85 (221)
Triglycerides at Week 156 (n)	240.30 (223)	191.81 (177)	215.81 (148)

Source: Table S.12.A, page 607-612.

A lipid sub-study was proposed to measure lipid studies at a central laboratory. Enrollment in the study was voluntary. Data are available for only 16 subjects, with follow-up data available for only 5 of the 16 volunteers.

Pregnancy

There were 15 pregnancies in 13 different subjects reported while on study treatment, eight pregnancies in 6 subjects treated with EFV+IDV, three pregnancies in 3 subjects treated with EFV+ZDV+3TC, and four treated with IDV+ZDV+3TC. All but two

pregnancies were terminated. One 39 year old woman treated during the first trimester with EFV+ZDV+3TC delivered a full-term male with hydronephrosis and low birth weight. A 22 year old woman with first trimester exposure to EFV+ZDV+3TC delivered female twins at 31 weeks gestation. No follow-up beyond delivery or HIV status was reported for any of the three live-born infants.

D. Adequacy of Safety Testing

Safety monitoring performed during this study was adequate.

E. Summary of Critical Safety Findings and Limitations of Data

The safety profile of efavirenz has been established by the experience of over one thousand subjects treated in the context of controlled clinical trials and from knowledge from widespread clinical use over the last several years. The long-term follow-up of efavirenz recipients in Study 006 provides some clearer understanding of two previously reported events, namely serious psychiatric adverse events and liver enzyme abnormalities among patients co-infected with hepatitis B and hepatitis C viruses.

Serious and potentially life-threatening psychiatric adverse events have been reported in patients treated with efavirenz, including aggressive reaction, depression (grade 3 or 4), psychotic depression, manic reaction, paranoid reaction, psychosis, suicide attempt, aggravated depression, and manic-depressive psychosis. In Study 006, a controlled trial of 827 patients treated with regimens containing efavirenz and 401 control patients, one or more such events were reported in 8% of patients treated with EFV+ZDV+3TC, 5% treated with EFV+IDV, and 3% treated with IDV+ZDV+3TC. These events occurred later than the nervous system symptoms; the median time to onset of psychiatric system symptoms was approximately 9 months in all three treatment groups. The frequency of specific serious psychiatric events among patients who received efavirenz or control regimens, respectively, were: suicide attempt/ideation (1.6%, none), grade 3-4 depression (2.7%, 1.5%), aggravated depression (1.2%, 0.25%), aggressive reaction (0.5%, 0.5%), paranoid reaction (0.5%. none), and psychosis (0.4%, 0.25%). Logistic regression analysis disclosed that treatment with efavirenz; history of injecting drug use, psychiatric history, and receipt of psychiatric medication at study entry were significantly associated with an increased likelihood of experiencing one or more psychiatric adverse events during the study. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risk of continued therapy outweigh the benefits.

Study 006 provides information on longer-term incidence of transaminase abnormalities with efavirenz among patients co-infected with hepatitis B and/or hepatitis C viruses. One hundred thirty seven patients treated with efavirenz regimens and 84 treated with indinavir, zidovudine and lamivudine were seropositive at screening for hepatitis B (surface antigen positive) and/or hepatitis C virus (hepatitis C antibody positive). Among patients co-infected with hepatitis B and/or hepatitis C virus, elevations in ALT to greater

than five times upper limit of normal (ULN) developed in 20% of patients in the efavirenz arms and 7% in the control arm. Elevations in AST to greater than five times ULN developed in 13% of co-infected patients in the efavirenz arms and 7% in the control arm. Liver function tests should be monitored in patients with a history of hepatitis B and/or C virus infections.

In addition, neurological symptoms, which occur early and are generally transient, are seen in approximately sixty percent of subjects. Rash is also a common adverse event occurring in about a third of efavirenz treated patients.

8. Dosing, Regimen, and Administration Issues

The recommended dosage of efavirenz is 600 mg orally, once daily, in combination with other antiretroviral agents. It is recommended that efavirenz be taken on an empty stomach, preferably at bedtime. The increased efavirenz concentrations observed following administration with food may lead to an increase in frequency of adverse events. Dosage at bedtime may improve the tolerability of nervous system symptoms.

9. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Although the studies were not powered to compare groups by gender, results generally favoring efavirenz-containing regimens over control regimens were maintained for males and females.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Although the studies were not powered to compare groups by race, results generally favoring efavirenz-containing regimens over control regimens were maintained for Whites, Blacks, and Other Races.

C. Evaluation of Pediatric Program

There were no studies involving pediatric patients included in the sNDA package.

D. Comments on Data Available or Needed in Other Populations

All subjects in study 006 were to be HIV-infected with measurable viral load greater than 10,000 copies/ml and CD4 count greater than or equal to 50 cells per ml. All subjects were naïve to NNRTIs, PIs, and lamivudine at entry. Fifteen percent of subjects had prior exposure to NRTIs, most commonly zidovudine. Recruited subjects were between the ages of 13 and 60 years of age in most parts of the world, and between 18-60 years of age in Europe. Pregnant or lactating females were excluded.

The sponsor is encouraged to continue with the development of a pediatric program, with emphasis on developing a liquid formulation along with obtaining safety, tolerability, pharmacokinetic and antiviral activity data on children.

10. Conclusions and Recommendations

A. Conclusions

One large open-label randomized trial of 1,228 patients of 168-week duration demonstrated virologic suppression and safety of efavirenz-containing regimens compared to an indinavir-containing control regimen. Overall, 48% of patients in the EFV + ZDV + 3TC arm and 40% in the EFV + IDV arm achieved and maintained HIV RNA < 400 copies/ml at Week 168 of treatment compared to 30% of patients in the IDV + ZDV + 3TC arm. At 48 weeks of therapy, 69% of patients in the EFV + ZDV + 3TC arm, 57% in the EFV + IDV arm and 48% in the IDV + ZDV + 3TC arm achieved RNA < 400 copies/ml. A similar decrease in proportion of treatment responders was observed for all three treatment groups between 48 and 168 weeks. The decline in outcome over time could not be attributed to any one reason, but reflected a number of patients in each treatment group who experienced virologic rebound, withdrawn consent, loss to follow up, and other reasons for discontinuing study therapies. Several secondary endpoints, including proportion of patients < 50 copies/ml and time to treatment failure, also produced statistically significant results favoring the efavirenz-treated groups. There was no significant difference in mean CD4 cell count among treatment arms; the mean increase from baseline was approximately 325 cells/ml for each treatment arm.

No new safety concerns with use of efavirenz were identified during the review. The longer term follow-up of efavirenz recipients in Study 006 provides a better understanding of the incidence and risk factors for serious psychiatric adverse events and liver enzyme abnormalities among patients co-infected with one or more hepatitis viruses.

Several issues remain to be explored as articulated in the 2000 post-marketing commitments. The sponsor will continue with the development of the pediatric program, continue to study and define the resistance profile of efavirenz, and investigate lipid metabolic pathways.

B. Recommendations

The Medical Officer recommends that the supplemental application of efavirenz to treat HIV-1 infection in combination with other antiretroviral therapies be approved. The efficacy and safety data generated by this 168-week study should be included in the label.

C. Labeling Review

Labeling discussions focused on presentation of efficacy data through 168 weeks of therapy and provision of updated safety data regarding liver function abnormalities among patients co-infected with HIV and hepatitis B or C viruses, and psychiatric adverse events. Viral resistance data was also updated in the label.

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

Concurrence:
HFD-530/TL/Marcus
HFD-530/DivDir/Birnkrant
CC:
HFD-530/NDA 20-972
HFD-530/NDA 21-360
HFD-530/Div File
HFD-530/CSO/Patel
HFD-530/Chem/Miller
HFD-530/Pharm/Farrelly
HFD-530/Micro/Naeger
HFD-530/Biopharm/Reynolds
HFZ-725/Stats/Choi
HFD-530/MO/Haverkos

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